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Safety and Efficacy of Lu-177 PSMA-617 Versus Established Therapies in mCRPC: Pooled Evidence from Randomized Phase II/III Trials

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Purpose/Objective(s): Lu-177 PSMA-617 delivers targeted β-radiation to prostate cancer cells, offering a distinct mechanism beyond androgen-signaling inhibition in metastatic castration-resistant prostate cancer (mCRPC). Pivotal trials have shown improved progression-free survival with favorable tolerability. As its clinical use expands, comparative evidence with established systemic therapies remains limited. This meta-analysis evaluates the pooled efficacy and safety outcomes.

Materials/Methods: A systematic review and meta-analysis were performed according to PRISMA guidelines to evaluate Lu-177 PSMA-617 in mCRPC. Of 456 studies screened, seven met eligibility criteria and were included in the final analysis. Data on progression-free survival (PFS), overall survival (OS), and grade ≥3 adverse events (AEs) were extracted and pooled using a random-effects model (REML method). Hazard ratios (HRs) and risk ratios (RRs) with 95% confidence intervals (CIs) were calculated, and heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated using both Egger's regression and Begg's rank correlation.

Results: A total of 2,526 patients from seven randomized trials were analyzed, including 1,365 in the Lu-177 PSMA-617 arms and 1,161 in the standard-of-care arms. Lu-177 PSMA-617 significantly improved PFS compared with control (pooled HR = 0.64; 95% CI 0.50−0.81; $p < 0.001$). No significant difference was observed in OS (HR = 0.91; 95% CI 0.66 −1.25; $p = 0.55$). The pooled RR for grade ≥ 3 AEs was 0.98 (95% CI 0.83 −1.14; $p = 0.75$).

Conclusion: Across contemporary randomized trials, Lu-177 PSMA-617 consistently prolongs PFS with no significant difference in AEs. OS benefit remains unconfirmed, likely reflecting post-progression and salvage use of Lu-177 PSMA-617 in control arms in some trials, as well as disease and trial heterogeneity. The data collectively reinforce Lu-177 PSMA-617 as a well-tolerated, effective radioligand option for advanced mCRPC, warranting continued integration into earlier disease settings and combination strategies.

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Quantitative Ra-223 SPECT/CT for Tumor Dosimetry in Combined SBRT−RPT: Retrospective Analysis from a Phase II Trial

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Purpose/Objective(s): Outside of standard of care (SoC) body scaled administered activities, Ra-223 has historically relied on model-based or 2D planar imaging approaches for dosimetry. Advances in quantitative SPECT/CT reconstruction now allow improved estimation of Ra-223 activity distributions for organ and lesion dosimetry and combining quantifiable SPECT/CT- alpha-based RPT with SBRT may enable synergistic tumor dose escalation while mitigating toxicities of SBRT alone. Here, we retrospectively analyzed combined SBRT and Ra-223 RPT dosimetry in oligometastatic prostate cancer patients from a Phase II clinical trial using SPECT/CT-derived dose estimates for multiple cycles.

Materials/Methods: Five patients received SoC Ra-223 (55 kBq/kg) under an IRB-approved Phase II protocol. Quantitative SPECT/CT scans were acquired ∼2−4, 24, and 48 hours after injection during the first and final treatment cycles using a novel reconstruction method incorporating forward-projection modeling and multiple-energy−range corrections. SoC photon SBRT plans were created in RayStation, and voxelwise Ra-223 dose-rate maps were registered in 3D Slicer to the SBRT CT and integrated; the resultant absorbed dose was then imported and registered to the SBRT CT into the TPS for voxelized summation. An alpha-particle RBE factor of 5 was applied to the Ra-223 dose contribution.

Results: Case studies are presented for multiple patients in both the early and last cycles. 0.08 Gy/MBq, 0.42 Gy/cycle, a cumulative 2.52 Gy, and 12.6 RBE-Gy was calculated for one patient's lesion from Ra-223, resulting in a combined mean 45.4 RBE-Gy. While the dose was combined at the voxel level, there are assumed to be large uncertainties associated with Ra-223

voxelized activity distributions and resultant dosimetry, therefore mean absorbed dose was the preferred quantity.

Conclusion: This work demonstrates the feasibility of multi−time point, patient-specific Ra-223 dosimetry using quantitative SPECT/CT and its potential integration with external beam radiotherapy (EBRT) dosimetry. These results highlight the potential of alpha-RPT imaging to inform combined SBRT+RPT treatment strategies and to support future optimization of EBRT planning. Due to uncertainties, subsequent efforts should investigate the potential and feasibility of incorporating small scale alpha dosimetry with image-based SPECT/CT dosimetry.

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Phase I Trial Combining Radiopharmaceutical Therapy (RPT) with Total Marrow and Lymphoid Irradiation (TMLI) in Relapsed or Refractory (R/R) AML

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Purpose/Objective(s): Patients with R/R acute leukemia who undergo allogeneic hematopoietic cell transplantation (alloHCT) have a dismal prognosis. To improve outcomes, innovative conditioning using organ sparing targeted radiotherapy, such as RPT and TMLI, are needed to dose escalate with acceptable toxicities, including in older patients who cannot tolerate myeloablative TBI. In R/R acute leukemia, conditioning with TMLI 12 Gy, fludarabine (F), and melphalan (M) resulted in a 5-year overall survival (OS) of 42% and event-free survival of 41%. In this trial (NCT05139004) we evaluated adding radiolabeled ^{90}Y-DOTA-anti-CD25 Mab (monoclonal antibody) to TMLI 12 Gy, F / M in this same population.

Materials/Methods: The primary objective of this 3+3 design phase I trial was to determine the maximum tolerated dose (MTD) of ^{90}Y-anti-CD25 Mab (Basiliximab) (Day -15) combined 1 week later with 12 Gy TMLI (1.5 Gy twice daily, days -8 to -5), F (30 mg/m^2/d days -5 to -2), and M (100 mg/m^2, day -2) in patients with R/R AML scheduled for alloHCT with a matched donor. TMLI target structures were bone, major lymph node chains and spleen. Planned dose levels of RPT were 0.3, 0.4, and 0.5 mCi/kg (10 mg Mab). ^{111}In-anti-CD25 Mab was co-infused followed by serial nuclear scans to assess dosimetry and pharmacokinetics.

Results: 7 patients with R/R AML were treated at the dose levels of 0.3 mCi/kg (n=3) and 0.4 mCi/kg (n=4). Median age was 60 years old (31-74). All patients had detectable bone marrow (BM) blasts (10-36%) and 5 had detectable circulating blasts (0.1-1.8 K/uL; 9-91%). In 4 patients, RPT decreased circulating blast count to undetectable levels prior to TMLI. ^{111}In-anti-CD25 Mab scans demonstrated uptake in bone marrow and spleen out to 144 hours. All patients completed TMLI 12 Gy, F/M. Mean doses (Gy) from combined RPT and TMLI to lungs were 6.6, kidneys 8.5, liver 10.8 and lower GI 6.6. All patients achieved complete remission on day +30 bone marrow biopsies. Toxicities were grade 3 nausea (n=1), diarrhea (n=2), and anorexia (n=3). At 0.3 mCi/kg, one patient remained in CR for 923 days but died from complications of thrombotic microangiopathy. One remained in CR for 442 days but died of an unrelated cerebral vascular accident and one died from disease at 10 months. At 0.4 mCi/kg, two patients expired from GVHD at 54 and 177 days; and two expired from infection at 64 and 110 days. Although no dose-limiting toxicities (DLT) were observed, there was no further dose escalation due to non-relapse mortality (NRM) developing in all 4 patients within 6 months at the 0.4 mCi/kg dose level.

Conclusion: ^{90}Y-anti-CD25 Mab at 0.3 mCi/kg combined with 12 Gy TMLI /F/M appears feasible with no DLTs observed. Combined radiation doses to organs from RPT and TMLI were less compared to standard 12 Gy TBI. Using RPT in a combined modality approach, targeting a radiosensitive disease and in a potentially curative setting warrants further evaluation. A successor trial evaluating ^{225}Ac-anti-CD38 combined with TMLI/F/M in R/R AML has been initiated (NCT06287944).

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Personalized Multi-Timepoint Voxel-Level Dosimetry in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with ^{177}Lu-PSMA-617 Therapy

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Purpose/Objective(s): Radiopharmaceutical therapy (RPT) has grown rapidly, though standard dosing across agents (e.g., 200 mCi) remains unchanged. Prior studies have shown correlations between absorbed dose, toxicity, and treatment response. We evaluated patient-specific dosimetry, its relationship to outcomes, and potential for treatment personalization using voxel-level dose parameters in patients treated with ^{177}Lu-PSMA-617 (Pluvicto) with dosimetry obtained as part of standard clinical care.

Materials/Methods: Nineteen patients were included in this series, treated between July 2023 and May 2025, who had evaluable post-cycle 1 dosimetry and received at least 1 cycle of therapy. Voxel-level Monte Carlo dosimetry was performed using the Torch RPT dosimetry platform (Voximetry). SPECT/CT imaging was acquired at three timepoints following the first treatment cycle: 3 ± 2 hours, 24 ± 4 hours, and 96 ± 24 hours. Mean

absorbed doses from cycle 1 were extrapolated across six cycles to approximate cumulative dose. Institutional organ-at-risk (OAR) constraints were defined as kidney mean dose (D_mean) < 24 Gy and salivary gland D_mean < 20 Gy for a full course of therapy. After cycle 1 dosimetry, physicians could continue therapy as planned, delay subsequent cycles, reduce injected activity by 20%, or discontinue treatment. Descriptive statistics summarized the findings.

Results: Reasons for obtaining patient dosimetry included prior external beam radiotherapy (n=11; 57.9%), bone marrow toxicity concerns (n=9; 47.4%), kidney dysfunction (n=6; 31.6%), prior RPT (n=2; 10.3%), or a combination of these (n=7; 36.8%). Compared with VISION phase III trial data, mean absorbed doses to key OARs (heart, kidneys, liver, lungs, salivary glands, spleen) were not substantially different. Assuming consistent dosimetry across six cycles, cumulative mean kidney and salivary gland doses were 17.7 Gy (range, 5.8-27.5) and 15.9 Gy (range, 3.0-32.2), respectively. Other OAR mean doses included bowel bag 7.9 Gy (range, 0.4-20.8) and bone marrow 9.4 Gy (range, 1.2-24.3). Tumor volumes received a mean absorbed dose of 91.3 Gy (range, 9.6-273.4). Personalized dosimetry, combined with clinical context, guided safe continuation of Pluvicto in most patients (n=13; 68.4%), while a smaller number of patients were recommended to discontinue treatment early (n=5; 26.3%) or delay cycle administration (n=1; 5.3%). Based on kidney dose limits after cycle 1, 15/19 patients (79.0%) could have safely received a seventh cycle; similarly, based on salivary gland limits, 8/15 patients (53.3%) could have received an additional cycle.

Conclusion: Multi-timepoint voxel-level dosimetry is feasible and provides actionable data to personalize RPT. Our institutional experience demonstrates the potential to safely extend therapy in select patients. Future work will focus on workflow optimization, standardized tumor segmentation, and integration of dosimetry as a clinical decision-support tool.

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Patient-Specific Dosimetry-Based Approaches of I-131 Therapy of Metastatic Cancer

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Purpose/Objective(s): Metastases in patients with differentiated thyroid cancer (DTC) often have reduced uptake of I-131 radioiodine, with less favorable outcomes. Personalized dosimetry-based approaches have been available for decades but have only been used on rare occasions, in part because no quantitative methods have been designed to determine which patients would benefit from personalized approaches. We present a method for early estimation of sub-optimal uptake using I-123 SPECT images, and present a further option for increasing absorbed dose (AD) to iodine-(partially)-refractory tumors: adjunctive dosimetry-based combination therapy with SBRT.

Materials/Methods: Lesion volumes of interest (VOIs) were contoured retrospective on ^{123}I SPECT/CT. SPECT counts were measured in lesion VOIs, whole-body regions, and background. Time-integrated activity coefficients (TIACs) were derived by applying pharmacokinetic curves from I-131 multi-timepoint SPECT/CT data to the retrospective I-123 24-hour uptake data. TIACs were input into MIRDCalc to estimate lesion AD coefficients. After dosimetrically-determined activity was administered, preselected patients, those with a low number of symptomatic metastases were imaged with SPECT/CT at three time points (24 h, 48 h, 72 h or 96 h) and the ADs to the different target lesions and normal organs were calculated. The data was then provided to dosimetrists for SBRT planning for toxicity constraints, with the goal of reaching 80 Gy of EQD2.

Results: Eighteen patients included 22 analyzable lesions in the retrospective I-123 study. Only a minority (n=2) were predicted to have achieved the tumoricidal threshold of 80 Gy. Median AD was 8.6 Gy (range 1.6 −313.6 Gy) for a conventional 150 mCi administration. Five patients with seven lesions were treated with combination radioiodine-SBRT. All but one lesions received more than the target AD, which would not have been achievable with a single modality. Only in one patient did the AD to the normal organs from the radioiodine limit the amount of SBRT delivered.

Conclusion: Most metastatic DTC lesions reviewed retrospectively were estimated to have received subtherapeutic ADs of radioiodine. The use of personalized dosimetry-based treatment for metastatic thyroid cancer would potentially improve outcomes and should be used more readily; use of diagnostic I-123 could help determine which patients would benefit. An additional boost of SBRT could also improve dosimetry and outcomes, by combining the dosimetry from both modalities for safety and maximum efficacy.

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^{64}Cu-anti-CEA M5A PET Imaging Pre and Post Neoadjuvant Radiotherapy in Advanced Rectal Cancer

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Purpose/Objective(s): Prior studies have demonstrated that radiolabeled anti-carcinoembryonic antigen (CEA) monoclonal antibody (M5A) can target CEA-expressing cancers. This pilot study (NCT05245786) evaluates the ability of ^{64}Cu-DOTA-M5A PET imaging to define disease extent before and after neoadjuvant radiotherapy in patients with locally advanced rectal cancer.

Materials/Methods: Patients with biopsy proven cT3-4, N0 or N+ rectal cancer scheduled for neoadjuvant chemoradiation prior to TME or total neoadjuvant therapy underwent 64Cu-M5A PET imaging within 4 weeks prior to start of neoadjuvant RT and 6-8 weeks after end of all neoadjuvant therapy and prior to planned surgery. A regional analysis (primary, pelvic nodes, and extra-pelvic) compared CEA scans to standard of care (SOC) CT and MRI imaging, FDG PET if available, biopsies and surgical findings.

Results: Thirteen patients have been imaged with ^{64}Cu-M5A PET (ages 38-76; CEA 1.8-21.1). CEA PET imaging prior to RT identified the primary tumor in 11 patients. For disease involving pelvic nodes, CEA PET imaging was in concordance with SOC imaging in 8 patients. In 6 patients CEA

scans identified suspicious lesions outside the pelvis, which in 2 patients were confirmed by SOC imaging and biopsy (lung metastases; and a single liver metastasis), while in 4 patients PET avid nodes detected (para-aortic, left supraclavicular, mediastinal, porta hepatis, and portacaval) were outside the regions imaged as part of SOC.

7 patients have also been imaged post RT and prior to surgery. 4 had radiologic complete response (CR) on CEA scans which correlated with pathologic CR at surgery or with clinical CR on follow-up sigmoidoscopy. Three had positive scans; 1 at the primary site confirmed as residual disease at surgery; and 1 at the primary site, in mediastinal, para-aortic, and pelvic lymph nodes, and a new focus near the hepatic surface with biopsy confirmation of disease at the primary site and liver; and 1 with progression of tumor at the primary site and an avid lung metastases confirmed by FDG PET.

Conclusion: ^{64}Cu-M5A PET imaging in patients with advanced rectal cancer shows promise in identifying sites of disease at the primary site and regional lymph nodes, as well as identifying extra pelvic sites of disease not seen by SOC imaging. It also shows promise in assessing response to neoadjuvant therapy and selection of patients for non-operative management. ^{64}Cu-M5A imaging warrants further evaluation to complement SOC imaging at initial staging, to select patients for local regional therapy and to select patients for non-operative management after neoadjuvant therapy. Given its targeting capabilities, M5A is also being evaluated radiolabeled with ^{225}Ac as a therapeutic radiopharmaceutical (NCT05204147) and as an anti-CEA-IL2 immunotherapy fusion agent (NCT06130826) in combination with EBRT in phase 1 trials.

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Hematologic toxicity outcomes of Lu-PSMA-617 in patients previously treated with EBRT for oligometastatic disease

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Purpose/Objective(s): Hematologic toxicities of Lu-PSMA-617 treatment occur in a plurality of patients and can limit further cycles. External beam radiation therapy (EBRT) can also cause radiation induced lymphopenia, anemia, and thrombocytopenia. As radiation therapy for oligometastatic disease becomes standard of care, more patients will have had multiple courses of EBRT directed at bony metastases prior to progressing to mCRPCa and Lu-PSMA-617 treatment. Here we evaluate if EBRT to bony oligometastases prior to delivery of Lu-PSMA-617 impacts hematologic toxicities and outcomes.

Materials/Methods: Patients who received Lu-PSMA-617 for mCRPCa at our institution and who received prior EBRT for bony oligometastases were identified via retrospective review. Hematologic adverse events were identified at pre-cycle blood draws according to the VISION trial, and CTCAE guidelines. Descriptive statistics and inferential statistics were calculated using PRISM software (Fisher's Exact Test).

Results: 70 patients received EBRT for bony mets prior to Lu-PSMA-617 administration with a median interval time of 31.5 mo (IQR 17.3-54.8 mo). The median number of EBRT courses prior to Lu-PSMA-617 was 2, with 39 patients receiving 2 or more prior courses. 24/70 patients (34.3%) did not receive the full 6 courses of Lu-PSMA-617 with 10 patients discontinuing due to disease progression and 2 patients due to adverse events (neither of which were due to hematologic toxicities). There were no grade 3 or greater hematologic toxicities in the cohort and grade 1 or 2 anemia was 16/70 (22.9%), thrombocytopenia 23/70 (32.9%), and leukopenia 17/70 (24.3%). Compared to the VISION trial, there were higher rates of thromobocytopenia and leukopenia in this cohort, but a lower rate of non-completion of 6 rounds of Lu-PSMA-617 (**Table 1**). The PSA50 response rate after Lu-PSMA-617 initiation for this patient cohort was 55.7% (39/70). Median survival from first Lu-PSMA-617 administration was 21 mo. When dichotomizing by 1 vs 2 or more prior courses of EBRT, there was no statistically significant difference regarding anemia (32.3% vs 15.4%, p =0.15), thrombocytopenia (32.3% vs 33.3%, p >0.99), leukopenia (22.6% vs 25.6%, p >0.99), PSA50 (58.1% vs 53.9%, p =0.81), or completion of all 6 cycles (70.1% vs 69.1%, p >0.99).

Conclusion: Patients who received prior EBRT for bony oligometastases did not have worse outcomes and had more frequent but milder hematologic toxicity compared to the VISION trial. More courses of EBRT did not increase toxicity or decrease efficacy. Studies of synchronous Lu-PSMA-617 and EBRT may be warranted.

Table 1. 1 Fisher's Exact Test

	Retrospective Review	Vision Trial	p[1]=
Patients n =	70	529	
Anemia %Gr 1-2 (Gr 3)	22.9 (0)	31.8 (12.9)	0.1674
Thrombocytopenia %Gr 1-2 (Gr 3)	32.9 (0)	17.2 (7.9)	0.0032
Leukopenia %Gr 1-2 (Gr 3)	24.3 (0)	12.5 (2.5)	0.0151
% < 6 cycles Lu-PSMA-617 treatment	34.3	52	0.0072

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Factors Influencing Lesion-Level Response after Lu-177 PSMA-Radioligand Therapy on Post-therapy SPECT/CT with AI-Annotation

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Purpose/Objective(s): Post-therapy SPECT/CT after treatment with Lu-177 PSMA-617 for metastatic prostate cancer (PC) enables a quantitative whole-body assessment of tumor burden and uptake; however, the relative prognostic value of lesion-level metrics for subsequent lesion response remains uncertain. The objective of this study is to determine which quantitative PSMA SPECT/CT metrics (e.g., $SUV_{mean/max/peak}$, lesion volume, total lesion activity, organ-normalized ratios, and spatial dispersion) at a particular treatment cycle, i.e., at time *t*, best predict the lesion-level outcome on a subsequent post-therapy SPECT/CT study at a later cycle, i.e., at time *t+1* (~6 weeks later) using multinomial modeling.

Materials/Methods: We retrospectively identified 43 patients with PC treated with at least 2 cycles of Lu-177 PSMA-617 who underwent quantitative post-therapy SPECT/CT at ~24 h (IRB-approved, consent waived). A state-of-the-art deep learning model segmented the lesion, liver, salivary

glands, and prostate; lesions were defined as 3D connected components within the tumor mask (≥10 voxels). For each time *t*, lesion-level metrics included volume, SUV_{mean}, SUV_{max}, SUV_{peak} (~1 mL spherical VOI), ratios to liver/salivary (mean/max), ratios to total-tumor (mean/max), and distance to the prostate centroid; subject-level metrics included PSMA total tumor volume (TTV) and total lesion activity (TLA = Σ SUV_{mean} × volume). Lesion outcomes at *t + 1* by volume were assigned by majority overlap with the subsequent study (1 = progression with volume increasing by >30%, 2 = stable, 3 = partial response with volume decreasing by). Primary modeling used penalized multinomial logistic regression (cross-validated L1/L2) for the 3-class outcome, with one-vs-rest ROC AUC (bootstrap 95% CIs) for class-wise discrimination.

Results: Using all lesion- and subject-level predictors jointly, the penalized multinomial model achieved AUCs (95% CI) of 0.67 (0.63−0.71) for progression (n=174), 0.82 (0.80−0.84) for stable (n=420), 0.88 (0.87−0.90) for complete response, and 0.79 (0.78−0.81) for partial response (n=1101). Bootstrap, FDR-controlled class-wise coefficients revealed outcome-specific signals: higher SUV_{peak} was associated with complete response, higher SUV_{max} was associated with stable and partially responding lesions, and higher SUV_{mean} significantly increased the odds of a subsequent lesion progression. Conversely, higher baseline lesion volume strongly reduced the odds of a complete response.

Conclusion: Quantitative post- Lu-177 PSMA-617 therapy SPECT/CT for a particular cycle (time *t)* provides an independent, clinically meaningful signal for predicting lesion-level outcomes at a subsequent treatment cycle (*t*+1), with class-wise discrimination ranging from 0.67−0.88. Core drivers are lesion uptake (SUV_{max}, SUV_{mean}, SUV_{peak}), and volume metrics, supporting prospective validation and integration with clinical covariates for individualized therapy response assessment.

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Clinical Outcomes Among Patients Treated with Lu-PSMA-617 and EBRT for Oligometastatic Prostate Cancer

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Purpose/Objective(s): Lu-PSMA-617 use is expanding for patients with metastatic prostate cancer, but little is known regarding the impact of metastatic burden on treatment response or the efficacy of Lu-PSMA-617 when delivered in combination with external beam radiation therapy (EBRT) for oligometastatic disease control.

Materials/Methods: An institutional registry comprising all patients receiving Lu-PSMA-617 was analyzed to identify patients who received EBRT with ablative intent to all known sites of active disease. Patient and treatment characteristics were abstracted from medical record and imaging review. Kaplan-Meier and Cox proportional hazards regression was used to analyze time-to-event endpoints. Logistic regression was used to analyze association between PSA response and covariates.

Results: From June 2022 to August 2025, 88 men were treated with Lu-PSMA-617 for metastatic prostate cancer and received EBRT for oligometastatic disease control. The median age at first Lu-PSMA-617 was 74 (range: 52-92). Race was predominantly white (84.1%), followed by Hispanic (6.8%), Black (5.7%), and Asian, American Indian/Alaskan Native, and other (all 1.1%). The anatomic distribution of PSMA-PET positive disease at time of Lu-PSMA-617 included the prostate (35.2%), pelvic lymph nodes (33%), abdominal/retroperitoneal nodes (38.6%), thoracic/mediastinal lymph nodes (33%), cervical/neck lymph nodes (23.9%), bone (94.3%), liver (12.5%), lung (18.2%), or other (12.5%). Most patients receiving Lu-PSMA-617 had polymetastatic disease with the total number of metastases at time of Lu-PSMA-617 initiation 6-20 (82.7%) and fewer than 5 active sites in 14.2%. The total number of bone metastases was 1-5 in 36.5%, 6-20 in 60% of patients. Most patients (40.9%) received 6 Lu-PSMA-617 cycles, 15.9% 4 or 5, 38.6% 2-3, and 4.5% 1 cycle. PSA at first Lu-PSMA-617 was <2 (22.7%), 2-10, (22.7%), and >10 (54.5%). The median time from initial diagnosis to metastatic diagnosis was 21.8 months (range 0-314.3). The median follow-up was 22.1 months among patients still alive and median overall survival (OS) was 20.1 months. PSA at first Lu-PSMA-617, number of bone metastases, and total number of bone metastases were not associated with OS on univariate analysis. Patients with fewer than 5 metastases at time of Lu-PSMA-617 had a trend towards increased survival than those with > 5 (HR = 4.00, p=0.06). PSA50 response was 55.7% with median time from first Lu-PSMA-617 to PSA50 1.6 months (range 1.1-6.9).

Conclusion: A diverse population of patients treated with both Lu-PSMA-617 and EBRT for oligometastatic disease control demonstrated favorable OS. Bone-only involvement, initial PSA, and total number of bone metastases were not associated with survival after Lu-PSMA-617 in our patient cohort. Selective use of ablative EBRT to metastatic or primary sites for patients with oligometastatic prostate cancer in combination with Lu-PSMA-617 may augment clinical outcomes. Further prospective study is warranted.

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Toward Consensus in Lu-177 RPT Dosimetry: Comparing Multi-Timepoint and Single-Timepoint Imaging in Clinical Implementation

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Objectives: To evaluate the dosimetric accuracy and operational implications of MTP versus STP imaging protocols for Lu-177−based radiopharmaceutical therapy across all treatment cycles. Radiopharmaceutical therapy (RPT) using Lutetium-177 (Lu-177) PSMA is a growing treatment modality in precision oncology. Patient-specific dosimetry is critical for optimizing therapeutic efficacy while minimizing toxicity to organs at risk. Multi-timepoint (MTP) imaging is considered the gold standard but presents practical challenges in routine clinical settings. This study compares MTP and single-timepoint (STP) dosimetry across all treatment cycles to evaluate their feasibility, accuracy, and impact on clinical workflow.

Activities/Methods: Patients undergoing Lu-177 PSMA therapy received both MTP and STP imaging during each treatment cycle.

- **MTP Protocol:** Quantitative SPECT/CT scans were performed at 4, 48, 72, and 96−106 hours post-infusion.
- **STP Protocol:** A single scan was acquired at either 72 or 96 hours, with separate dose estimates calculated.

Dosimetry was performed using MIM SurePlan MRT software. Time-activity curves were generated for each protocol, and absorbed doses were calculated for tumor volumes and critical organs. STP accuracy was evaluated against corresponding MTP results per cycle.

Outcomes: MTP dosimetry provided the most accurate and comprehensive dose assessments across all cycles. STP scans at 72 or 96 hours

produced dose estimates with more uncertainty than the MTP values. Add- ing a second time point (e.g., 4 + 96 hrs) reduced uncertainty to »14%, approaching the reference standard. STP protocols reduced patient burden and resource demands but introduced more variability, especially in lesions with atypical clearance kinetics. These findings align with previous model-

ing studies by Cole et al. (2022, MIM Software White Paper) and compara- tive dosimetry analyses by Peters et al. (2023, *EJNMMI*), and George et al. (2023, *Frontiers in Chemistry*, doi: 10.3389/fchem.2023.1218670).

Lessons Learned: MTP imaging remains the reference standard for Lu- 177 RPT dosimetry. However, imaging at carefully selected timepoints can provide acceptable accuracy and may be a viable alternative in resource- constrained settings. Routine dual-timepoint imaging offers a compromise, enabling broader implementation of patient-specific dosimetry without sig- nificant loss of precision. These results support recent recommendations for personalized RPT from St. James et al. (2021, *IJROBP*) and Hanscheid et al. (2018, *JNM*).

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Multispecialty Expansion in Radiopharmaceutical Therapy: National Trends in Medicare from 2013-2023

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Objectives: There has been rapid expansion in the use of radiopharmaceutical therapies (RPT) in recent years due to the emergence of evidence supporting FDA approval and clinical use of several novel IV therapies. In addition, there has been growing recognition that a multidisciplinary approach to delivering these treatments may be optimal, given the unique logistical, regulatory, and expertise-based demands these therapies require. The current landscape of RPT delivery in the US is poorly understood. We evaluated temporal and specialty-specific trends in intravenous (IV) RPT delivery among Medicare beneficiaries from 2013–2023.

Activities/Methods: We analyzed Medicare Provider Public Use Files (2013-2023) which describe Medicare Part B professional claims (and therefore may undercount hospital outpatient global-billed services). We identified administrations of IV RPT (CPT 79101). We grouped providers into specialty categories (Nuclear Medicine (NM), Diagnostic Radiology/Interventional Radiology (DR/IR), Radiation Oncology (RO), Medical Oncology/Hematology (MO), and Other) based on their reported taxonomy and analyzed changes in IV RPT administration over time in absolute counts and on specialty-specific shares. Temporal trends were assessed using Poisson regression with robust variance to estimate annual changes in specialty share.

Outcomes: From 2013–2023, annual IV RPT administrations (CPT 79101) increased from 529 to 12,395, representing a >20-fold increase and a 37% compound annual growth rate.

In 2023, DR/IR accounted for 45.2 % of all IV RPT services, NM 36.6 %, RO 15.3 %, and MO 2.5 %. All major specialties demonstrated substantial absolute growth in IV RPT participation, and relative participation patterns evolved over time (Poisson IRRs 0.97 [NM], 1.09 [DR/IR], 0.91 [RO], 1.65 [MedOnc/Heme]; all $p \leq 0.002$).

Lessons Learnt: IV RPT administrations in Medicare grew more than 20 fold from 2013-2023, reflecting rapid national clinical adoption. Growth occurred across all specialties, with evolving relative participation patterns over time. These findings highlight the expanding modern multidisciplinary footprint of RPT delivery in the US, characterized by substantial absolute growth across specialties and shifting participation patterns. This reinforces the importance of continued cross-disciplinary planning to address research, credentialing, regulatory, and workflow needs to advance the field of RPT moving forward.

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Withdrawn

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A Model of Parallel Radiopharmaceutical Therapy Delivery in One Large Academic Health System

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Objectives: To describe a model of parallel radiopharmaceutical therapy (RPT) delivery in a large, academically based health system serving the Washington metropolitan region.

Activities/Methods: Within a single health system, RPT is offered at four clinical locations spanning two hospital campuses – one in Maryland and one in Washington, D.C.. - and one freestanding ambulatory healthcare and surgical center. Of these four sites, three are managed and operated by the Department of Radiation Oncology, offering ^{177}Lu-PSMA-617, Radium-223 dichloride, ^{90}Y-microspheres and participation in clinical tri- als. The fourth site, an outpatient center within a hospital campus, is oper- ated by the Division of Nuclear Medicine and Molecular Imaging in Radiology, and offers ^{177}Lu-PSMA-617, ^{177}Lu-DOTATATE, radioactive iodine-131 and participation in clinical trials. For each location, patients are initially screened for clinical eligibility including imaging, then undergo consultation and financial clearance either through Radiation Oncology or Nuclear Medicine. If appropriate, treatments are scheduled and ordered from the vendor, with RPT administration overseen by an authorized user (AU) in the consulting department. Nuclear medicine technologists admin- ister therapies in Radiology, whereas trained nurses and qualified medical physicists assist the AUs in delivering therapies in Radiation Oncology. Patient education, safety precautions, and coordination of follow-up are all managed by the provider team.

Outcomes: Under this parallel delivery model, patients have access to high quality standard of care and novel RPT agents across hospital and ambula- tory settings in two different departments. This academic medical center was the first to provide Lu-DOTATATE in the state and has successfully treated several thousand patients with RPT to date. The diversity of offer- ings has expanded the health system's geographic reach and access to RPT care, resulting in an increased annual total volume of patients treated with RPT. The departments have collaborated on patient and staff education and radiation safety initiatives. However, the parallel model has also

resulted in duplication of infrastructure and staff efforts within the Departments of Radiation Oncology and Radiology.

Lessons Learned: This parallel RPT delivery model provides an example of two departments providing RPT services in separate geographic locations across a large health system, broadening patient access to therapy and clinical research. Each department has streamlined RPT processes and standard operating procedures. However, by operating within separate channels of supply and workflow, this approach may not be taking advantage of potential economies of scale, shared infrastructure, shared staffing or other operational synergies.

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A Multidisciplinary Care Process Model for Radiopharmaceutical Therapy including Both Radiation Oncologists and Nuclear Medicine Physicians as Authorized Users

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Objectives: Radiopharmaceutical Therapy (RPT) is a growing field in oncology requiring an authorized user (AU) for administration. Both radiation oncologists (RO) and nuclear medicine physicians (NM) can fulfill the role as an AU. We developed a multidisciplinary clinical RPT care process model (mRPT) to incorporate both RO and NM in a community-based RPT program.

Activities/Methods: A focus group including RO, NM, and medical oncology evaluated multiple mRPT models for a cohort of patients receiving 177Lu-PSMA therapy (LuPSMA) for metastatic castrate-resistant prostate cancer. The goal was to create a mRPT model that resulted in equitable distribution of AU duties, while improving access to RPT throughout a large geographic area without compromising quality.

Outcomes: It was determined that the AU role would be dependent on volume of disease of the patient at presentation and the potential need for external beam radiation. Radiation oncology was AU for patients who either had low volume/oligometastatic disease or could benefit from EBRT. Nuclear medicine treated all other patients. Prior to mRPT implementation, all LuPSMA cases were covered by RO. An RPT tumor board was created to discuss cases and divide AU responsibilities. As more rural RPT sites of care were added to the system, more RO than NM physicians were available to deliver RPT, though additional NM physicians are being actively recruited.

Lessons Learned: Community-based mRPT models can be developed to incorporate both RO and NM as AUs in RPT delivery.

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Using Virtual Phantoms to Commission the Fitting, Integration, and Dose Calculation for Lu177 Radiopharmaceutical Therapy Dose Calculations

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Purpose/Objective(s): There are numerous steps in calculating absorbed doses for RPT including quantitative SPECT/CT imaging, segmentation, image registration, fitting functions to time activity curves (TAC), integrating fit functions, partial volume corrections (PVC), and the final radiation transport step. There is currently no guidance from professional societies on commissioning RPT Dose calculation systems (RPT-DCS). Our objective is to describe a process using virtually generated phantoms for commissioning RPT-DCS.

Materials/Methods: To test the fitting, integration, and dose calculation, 4 spheres (=10mm, 15mm, 28.8, and 62 mm) filled with Lu177 in a cold background were virtually generated in matched high resolution SPECT/CT (0.98mm x 0.98mm x 1.25mm) at multiple time points ranging from 1 to 168 h. Different TACs were simulated including physical decay, 50 h effective half-life, bi-exponential fit with slow 10 h uptake and 80 h clearance, as well as another bi-exponential assuming instant uptake with 20% of the activity clearing with a 5 h half-life and the other 80% clearing with a 50 h half-life. In addition to confirming fitting and integration, extrapolation rules for trapezoidal integration were also tested. RPT-DCS calculated time integrated activities (TIA) were compared against the true number of disintegrations. Reported mean absorbed dose results were compared against MIRDCalc and local deposition estimates. To test heterogeneity dose calculation, a virtual phantom was created with HU mapped to 1.92 g/cc mineral bone; for a single uniform sphere with a 50 h effective half-life, multi-time point SPECT/CT was generated and the RPT-DCS calculated dose to the sphere was compared to MIRDCalc.

Results: For physical decay of spheres using original VOIs, for the smallest to largest sphere, respectively. Agreement with local deposition followed a similar trend. The RPT-DCS resamples SPECT/CT to match the Voxel-S-Value geometry (2.33 to 3 mm isotropic) before convolution; this displaces activity outside the original VOIs. Rerunning MIRDCalc with updated activity contained with the resampled VOIs demonstrated improved agreement: 4%, 1%, 2%, 2% for the smallest to largest sphere, respectively. RPT-DCS agreed within 4% for local deposition as well. When testing integration and extrapolation rules all RPT-DCS TIAs and absorbed doses agreed within 4% of expected values when accounting for the software's resampling. For biexponential kinetics with 5 time points out to 168 h, RPT-DCS was able to recover pre-specified half-lives to better than 1%. For material heterogeneity with mineral bone, the RPT-DCS agreement with MIRDcalc was within 5%.

Conclusion: Using virtual phantoms lets users confirm and understand limitations of RPT-DCS. Confirming fitting and integration capabilities is important as the results characterize the source strength which directly affects reported absorbed doses.

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From Concept to Clinic: Development and Prototype Implementation of the Intelligent Radiotherapy Collaboration System for Integrated Radiopharmaceutical Workflows

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Objectives: Radiopharmaceutical therapy (RPT) has become a key pillar of precision oncology. As clinical programs scale to higher patient volumes and multiple isotopes, workflow and data integration challenges—spanning scheduling, documentation, dosimetry, and multidisciplinary coordination—have become increasingly evident. This study describes the design and prototype evaluation of an integrated digital collaboration system, developed through a research partnership between our institution and an industry collaborator, to provide a scalable, interoperable framework for end-to-end theranostic workflows.

Activities/Methods: At MCI, RPT is implemented within Radiation Oncology (RO) under an APEx-accredited framework, following an RO-led multidisciplinary model with Nuclear Medicine (NM) and Medical Oncology (MO). The current RPT portfolio includes iodine-131 (I-131), lutetium-177 (Lu-177), radium-223 (Ra-223), and emerging actinium-225 (Ac-225) and lead-212 (Pb-212) therapies. A process audit identified inefficiencies such as manual scheduling, fragmented documentation, and non-automated dosimetry workflows. The software prototype was developed with modular functionality for registration, consultation, authorization, radiopharmaceutical ordering, infusion coordination, laboratory trending, and follow-up. The system communicates bidirectionally with institutional electronic medical record and oncology information systems via Health Level Seven (HL7) standards to synchronize patient, order, and appointment data. Integration with the institutional Picture Archiving and Communication System (PACS) and quantitative imaging/dosimetry platforms enables automated retrieval of radiologic studies, including post-therapy single-photon emission computed tomography/computed tomography (SPECT/CT) data, for lesion identification, voxel-based dosimetry, and treatment-response analysis. The modular design, customizable to both RO and NM led models, supports scalability to combination therapies.

Outcomes: Prototype testing demonstrated stable interoperability and reliable bidirectional data exchange. Automated image retrieval, dosimetric analysis, and structured documentation improved workflow efficiency, data integrity, and regulatory traceability across multidisciplinary teams.

Lessons Learned: The integrated collaboration system establishes a validated, adaptable digital framework for RPT workflows. While in prototype evaluation, its demonstrated functionality supports development of an artificial intelligence (AI)—ready, interoperable platform unifying imaging, dosimetry, laboratory, and documentation data—enabling safe, efficient, and scalable expansion of RPT programs.

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Challenges Establishing a Radiopharmaceutical Therapy Clinic within a Radiation Oncology Department in a Community-Based Hospital

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Objectives: To describe the challenges and strategies to implement a radiopharmaceutical therapy (RPT) clinic managed within a radiation oncology department in an academic-affiliated, community-based hospital.

Activities/Methods: One of the most challenging aspects of implementing RPT was finding a location to satisfy radiation safety regulations and an efficient workflow. The clinic offers 177Lu-PSMA-617 and Radium-223 dichloride. Due to a gamma decay component and higher activity, 177Lu-PSMA-617 posed additional constraints, such as a dedicated bathroom. Workflow required the use of three main spaces: a hot lab, a procedure room and a dedicated bathroom in proximity to each other. The hot lab was used to safely store and calibrate doses, storage of radioactive waste for decay, and to measure wipe test to check for potential surfaces contamination. Proximity of these spaces was required for efficient workflow and to limit radiation exposure. Final location was decided with the assistance of the radiation safety officer (RSO) based on occupancy for contiguous areas and areas on the floor immediately below. RSO also completed the NRC license amendment. A vital signs room was converted into the hot lab, contiguous to the procedure room. The closest bathroom, just a few feet across from the procedure room, was assigned for use only to 177Lu-PSMA-617 patients. The hot lab location planning, set up and final NRC approval occurred from 9/2023 to 6/2024. Workflow consisted of receiving the dose in the hot lab, calibrating it and storing it until application. Immediately after infusion, residual dose was measured in the hot lab to better assess the dose the patient had effectively received. Patients were offered the opportunity to void in the designated bathroom before departing to minimize potential use of public restroom until arrival at home. Discarded radioactive waste (syringes, tubbing, pads, bathroom toilet wrapping, etc.) was collected in a wheeled shielded container and eventually stored in hot lab on a dedicated shielded drum. Physics was also responsible for dose calibration, delivered dose calculation, radiation safety and contamination monitoring during procedures.

Outcomes: The careful selection of spaces needed for RPT implementation resulted in an efficient workflow while minimizing radiation exposure. Over a 16-month period, from 06/2024 to 10/2025, we have treated 12 patients with Radium-223 dichloride and 28 patients with 177Lu-PSMA-617, respectively. Our workflow enables us to meet current demand by treating up to 3 patients in a half-day session, twice weekly.

Lessons Learned: Establishing RPT in a clinical area designed for other purposes, required thoughtful selection of spaces and redefining functions for some rooms to accommodate regulations and safe practices e improve workflow while minimizing costly remodeling.

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Radiopharmaceutical Retreatment

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Objectives: The response rates for Lu-177 dotatate in the management of advanced neuroendocrine cancer and Lu-177 PSMA 617 in the management of advanced prostate cancer have been very good objectively as measured by repeat dotatate PET imaging and serum PSA determination respectively. In addition, patients have frequently seen symptoms related to their advanced disease improve. Unfortunately, their disease frequently progresses subsequently, and additional treatment options are limited. Patients and their referring physicians are therefore interested in retreatment, given their previous good responses.

Activities/Methods: Our center initiated Lu-177 dotatate therapy in 2018 upon FDA approval and has treated 45 patients through October of 2025. We initiated Lu-177 PSMA 617 in 2022 upon FDA approval and has treated 150 patients through October of 2025. We have retreated 11 patients with radiopharmaceutical therapy, 4 with Lu-177 dotatate and 7 with Lu-177 PSMA 617, representing approximately 6% of our patient population.

Outcomes: For the Lu-177 dotatate patients retreated, there was a range of 30-48 months interval between completion of the first course of treatment and initiation of the second course. Age range was 50-81. All patients were able to complete a full 4 cycle course of retreatment. Three patients had mild to moderate improvement of disease on followup dotatate PET imaging, and one had stable disease. There was Grade 1 and 2 hematologic toxicity but no renal toxicity and all adverse effects were temporary. For the Lu-177 PSMA 617 patients retreated, there was a range of 8-20 months interval between completion of the first course of treatment and initiation of the second course. Age range was 49-81. Four patients received the entire 6 cycle course and had objective improvement in disease status. One received 5 cycles with initial PSA response and subsequent progression. Two received 2 cycles and had rapid disease progression. Grade 1 and 2 hematologic toxicity was noted, but the treatment was generally well tolerated.

Lessons Learned: Retreatment is feasible, is generally well tolerated, and is effective in resulting in responses in many patients treated. Selection criteria for retreatment include good response to first course of treatment, avidity of known disease on appropriately targeted PET imaging. and longer interval between courses. We have not seen major barriers to insurance approval for this therapy. Further research will likely result in the development of other biomarkers to help advise retreatment consideration.

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2000

A Single Institution 177Lu-DOTATATE Retreatment Dosimetry Experience

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Purpose/Objective(s): Dosimetry has been shown to predict efficacy and toxicity with the treatment of 177Lu-DOTATE in neuroendocrine tumors. However, the dosimetry of retreatment with 177Lu-DOTATATE has yet to be reported.

Materials/Methods: Patients retreated with a second course of 177Lu-DOTATATE were offered dosimetry at clinician discretion. Serial SPECT/CT were utilized and kidneys were segmented on CT using a deep learning algorithm and tumors via a SPECT gradient-based tool guided by radiologist defined contours on CT/MRI. An automated workflow using contour intensity-based SPECT-SPECT registration, generation of Monte Carlo dose-rate maps, and dose-rate fitting was used to perform dosimetry. Comparison of tumor kidney ratio (TKR) from cycle 1 to cycle 3 was performed with the Wilcoxon signed-rank test. Kidney toxicity was evaluated based on estimated glomerular filtration rate based on chart review.

Results: Dosimetry was performed on 10 patients who underwent retreatment. Median age was 67 (range 46-76) and 50% of the patients identified as men. The median time since first course of treatment was 28.7 months (range 5.3-67.8). In the retreatment course, 8 patients completed 4 cycles while 2 patients only received 3 cycles (one had an additional cycle planned at time of analysis). Dosimetry was performed at cycle 1 for all 10 patients, cycles 2 and 3 for 9 patients, and cycle 4 for 5 patients. After cycle 1 the median absorbed dose (AD) to kidneys was 3.5Gy (range 2.1-6.7) and to segmented tumors was 7.5Gy (range 4.4-31.0). The median TKR was 2.0 (range 1.0-10.7). Among the 9 patients with dosimetry after the third cycle, the median TKR decreased to 1.6 (range 0.9-10.1) at cycle 3 from median 1.9 (range 1.0-10.7) after the first cycle ($p = 0.008$). Two patients had dosimetry obtained with the first course of treatment and for both the TKR was lower with retreatment (pt 1: 2.8>1.5; pt 2: 8.3>2.1). For all patients the reported TKR is lower than previously published rates. At baseline one patient had grade 2 kidney dysfunction and 5 additional patients developed grade 2 kidney dysfunction after treatment. For 4 patients this was transient while for 2 it was not (including the patient with baseline dysfunction).

Conclusion: Dosimetry after retreatment with 177Lu-DOTATATE suggests there may be a decrease in TKR with each cycle as has been previously reported for the initial treatment course. There may be reduced TKR in the second course of treatment compared to initial treatment, but further work is needed to better evaluate this. Overall, retreatment appears safe with no severe kidney toxicity.

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2001

Lesion-Level Pharmacokinetic Modeling to Characterize Treatment Response Patterns in ^{177}Lu-PSMA-617 Therapy

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Purpose/Objective(s): ^{177}Lu-PSMA-617 radioligand therapy exhibits variable efficacy across metastatic lesions in castration-resistant prostate cancer (mCRPC). Quantitative modeling of lesion-level absorbed dose kinetics may elucidate treatment response heterogeneity and support the development of personalized therapeutic strategies.

Materials/Methods: We retrospectively analyzed 5 mCRPC patients treated with standard ^{177}Lu-PSMA-617 therapy (7.4 GBq every 6 weeks). A total of 21 individual metastatic lesions were contoured and tracked across 4−6 treatment cycles using quantitative single-point dosimetry, following the Hanscheid Method. Temporal uptake dynamics were modeled using exponential decay kinetics:

D(t)=D0 ·e−λt+D_baseline . Where (D*0*) represents initial PSMA-avid tumor burden, (*λ*) denotes the response rate constant, and (D_baseline) indicates residual uptake. Model parameters were extracted via non-linear regression.

Results: Among 21 evaluable metastases (median 5 imaging timepoints, range 4−6), exponential decay modeling yielded excellent fit quality (median (R^2 = 0.89), IQR: 0.78−0.95). Initial uptake amplitudes varied widely ((D0 = 0.96−5.53 Gy/ GBq, median 2.40), reflecting substantial inter-lesion variability in baseline PSMA expression. Response rate constants showed marked heterogeneity ($\lambda = 2.86 - 79.05 \times 10^{-3}$ day^{-1}, median 14.88×10^{-3} day^{-1}). Overall tumor dose reduction ranged from 40.4% to 100% (median 79.4%) over a median follow-up of 126 days. Rapid responders ($\lambda > 20 \times 10^{-3}$ day^{-1}, n = 8, 38%) achieved >80% reduction within 126 days, while slow responders ($\lambda < 10 \times 10^{-3}$) day^{-1}, n = 5, 24%) showed <70% reduction. Complete responses (≥99% reduction) were observed in 3 lesions (14%), characterized by high initial uptake (D0 > 2.5 Gy/GBq) and rapid decay ($\lambda > 30 \times 10^{-3}$ day^{-1}). Residual uptake ranged from 0.01 to 1.08 Gy/ GBq, potentially indicating the presence of resistant subclones.

Conclusion: Lesion-level kinetic modeling reveals significant inter- and intra-patient heterogeneity in response to ^{177}Lu-PSMA-617. The decay rate constant (*λ*) serves as a quantitative biomarker of radiosensitivity, enabling classification into distinct phenotypes: rapid responders (potential candidates for treatment de-escalation), moderate responders (standard continuation), and slow responders (candidates for intensification). Lesions with high baseline PSMA expression and rapid decay demonstrate superior responses. This framework supports lesion-adapted strategies and may inform cycle planning, early treatment modification, and integration of local therapies for resistant lesions. Prospective validation in larger cohorts with anatomical stratification is warranted.

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2002

Evaluation of [18F]-FDG PET-CT Imaging Performance in a Biology-Guided Radiotherapy Platform: Final Results from a Prospective Pilot Study

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Purpose/Objective(s): The RefleXion X1 is a biology-guided radiotherapy system which is currently cleared by the FDA to deliver radiation to lung and bone lesions with real-time FDG positron-emission tomography (PET) guidance. The purpose of this single-institution study is to evaluate the performance of its PET imaging subsystem for patients with various 18F-FDG avid non-lung and non-bone malignancies.
Materials/Methods: Patients scheduled for a standard-of-care (SOC) 18F-FDG PET/CT scan were enrolled. Upon completion of the SOC PET/CT scan on a diagnostic (non-X1) PET/CT system, images were transferred to a radiotherapy planning system for PET-avid tumor target contouring. If at least one non-bone or non-lung PET-avid lesion was identified, the patient was then scanned on the X1 unit. The target volume, activity concentration (AC) and normalized target signal (NTS) were determined and BgRT planning was performed. A gross target volume (GTV) was drawn on the SOC PET/CT images for the PET-avid lesion, a planning target volume (PTV) was defined as a 5-mm isotropic expansion of the GTV, and a biology tracking zone (BTZ) was defined as a 5-mm isotropic expansion of the PTV. To ensure sufficient PET signal strength from the tumor to guide BgRT delivery, AC must be at least 5 kBq/ ml and NTS must be at least 2.7.
Results: Seventeen patients completed both SOC PET/CT scans and X1 PET scans. The anatomical sites included the head & neck region, esophagus, mediastinum, abdomen, and pelvis. BgRT planning was unsuccessful for eight patients due to either low activity concentration in the PTV or high FDG uptake in the PTV vicinity. BgRT plans were successfully generated for nine patients with an average GTV volume of 18.3±13.6 cm3 (range: 2.3 − 43.4 cm3) and an average PTV volume of 46.9±25.2 cm3 (range: 9.7 − 90.8 cm3). The BgRT plans had an average AC of 10.2±2.9 kBq/ ml (range: 8.2 − 16.6 kBq/ml) and an average NTS of 9.7±5.4 (range: 3.4 − 18.0). The average estimated treatment time was 29.5±7.8 minutes (range: 13.4 − 41.2 minutes).
Conclusion: X1 PET scans on the BgRT machine allowed visualization of tumor metabolic activity at a variety of anatomical sites for treatment planning purposes. BgRT could potentially be delivered to non-bone and non-lung anatomical sites provided that sufficient FDG metabolic activity is demonstrated in the tumor.

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2003

Fluorine 18-labeled Fluorodeoxyglucose versus Gallium 68-labeld Fibroblast Activation Protein Inhibitor as a Bio-guide in Biology-guided Radiotherapy for Multiple Anatomical Sites: a Dosimetric Comparison

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Purpose/Objective(s): A medical linac (X1, RefleXion Medical Systems, Hayward, CA) uses real-time PET signals from the tumor to guide beam delivery in biology-guided radiotherapy (BgRT). This study aims to evaluate variations in target volumes and plan dosimetry when the Fluorine 18-labeled Fluorodeoxyglucose (FDG) or Gallium 68-labeld fibroblast activation protein inhibitor (FAPI) is used as a bio-guide in BgRT to treat tumors in different anatomical sites.
Materials/Methods: Imaging data was retrieved for patients who received sequential FDG and FAPI PET/CT scans in an imaging study at a single institution. Patients with malignancies in the pancreas, cervix, and lung were selected and ten patients were included for each anatomical site. The gross tumor volume (GTV) was drawn based on a standard uptake value (SUV) threshold of 40% of the maximum SUV for the lesion in both FDG and FAPI scans. The planning target volume (PTV) was created by adding a site-specific margin to the GTV. A biology tracking zone (BTZ) was created by adding a margin to the PTV to encompass the range of tumor motion. The diagnostic FDG/FAPI PET images were first converted to simulated PET images on the X1 machine before BgRT treatment planning. The BgRT plans used a jaw width of 2 cm and a prescription dose of 8 to 10 Gy per fraction for 3 to 5 fractions. The activity concentration (AC) and normalized target signal (NTS) were calculated to evaluate BgRT feasibility on the X1.
Results: With an average weight of 55.5±10.5 kg (range: 39 − 78 kg), patients received an average injected FDG dose of 8.4±1.6 mCi (range: 6.1 − 12.9 mCi) and an average injected FAPI dose of 3.2±0.8 mCi (range: 2.0 − 5.2 mCi) prior to FDG/FAPI PET/CT scans. BgRT planning failed for thirteen and seven cases when FDG PET and FAPI PET images were used, respectively, due to GTV size, low PET signal in the GTV, and/or high FAPI uptake surrounding the target volume. In the BgRT plans based on FDG PET images, the average GTV volume was 16.1±10.9 cm^3; the average AC, NTS, conformity index (CI), and homogeneity index (HI) were 37.3± 63.3 kBq/ ml (range: 6.5 − 260.1 kBq/ml), 5.3±3.1 (range: 3.0 - 15.7), 1.19±0.1, and 1.34±0.1, respectively. In the BgRT plans based on FAPI PET images, the average GTV volume and was 28.7±24.2 cm^3; the average AC, NTS, CI, and HI were 20.7± 27.8 kBq/ ml (range: 5.1 - 129.5 kBq/ml), 10.3±5.2 (range: 3.2 - 20.7), 1.27±0.2, and 1.35±0.1, respectively.
Conclusion: The target volume size and location with high radiotracer uptake depends on whether FDG or FAPI was used. Both FDG and Gallium 68-labeled FAPI could be potentially used as a bio-guide for BgRT on the X1 for various disease sites, although suitable thresholds for AC and NTS to ensure delivery accuracy have not yet been established for the Gallium 68-labeled FAPI radiotracer.

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2004

Pilot Study: Detection of Metastatic Colorectal Liver Disease Preoperatively Using ^{124}I-Labeled M5A Monoclonal Antibody to Carcinoembryonic Antigen (CEA)

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Purpose/Objective(s): Metastatic Colorectal cancer (mCRC) frequently spreads to the liver, and accurate detection of disease is essential for treatment planning. Standard imaging may miss small or extra-hepatic lesions. I-124 M5A is a radiolabeled monoclonal antibody targeting carcinoembryonic antigen (CEA), a tumor marker widely expressed in mCRC. This study evaluates the feasibility of I-124 M5A PET imaging for detecting CEA-positive liver metastases.

Materials/Methods: Patients with CEA-positive mCRC liver metastases observed on conventional imaging received I-124 M5A with PET imaging at days 2 and 6 post-infusion. Potassium iodide (SSKI) drops were administered to provide thyroid blockade. The first 2 patients received 10 drops daily starting 24 hours prior to infusion until 48 hours post injection. Due to significant thyroid uptake of I-124 expression subsequent patients received protracted courses of SSKI (i.e. 15 days) to reduce I-124 thyroid uptake. The primary study endpoint was localization of I-124 M5A to CEA-positive metastases in the liver. Secondary endpoints were safety and detection of additional hepatic or extra-hepatic lesions not identified on standard imaging.

Results: Four patients (median age 59 [range, 51-69] years) received I-124 M5A at a planned dose of 5 mCi/ 5mg (median administered dose, 5.45 mCi/ 5 mg). I-124 M5A PET demonstrated uptake in aortocaval lymph nodes in one patient, which was confirmed as metastatic disease at surgery; this nodal disease was also evident on standard imaging thus, a true positive for our novel I-124 M5A pet tracer. The other three patients unfortunately had negative I-124 M5A PET scans. However, conventional imaging and surgical evaluation revealed malignant disease (i.e. liver metastases) in these false negative scans. Thyroid uptake was observed in three patients but decreased as the number & length of SSKI administration increased. The best blockade of thyroid gland uptake occurred when 20 drops of SSKI were given for 15 days. Overall toxicity was minimal; grade 2 pruritus (n=1) and grade 2 subclinical hypothyroidism (n=1). Median follow-up was 12 months (range, 5.8 − 13.8).

Conclusion: I-124 M5A PET demonstrated feasibility but limited ability to detect mCRC liver metastases. Larger studies are warranted to determine its role in mCRC imaging and unexpected thyroid uptake underscores the need for improved blockade strategies. We are currently exploring other radiolabeled CEA antibodies to detect mCRC.

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2005

In Silico Optimization of Novel PSMA-Targeted Ligands for Actinium-225 Radiotheranostic Therapy

P. Suryadevara; *Ayutara, Frisco, TX*

Purpose/Objective(s): To design and evaluate next-generation prostate-specific membrane antigen (PSMA) ligands optimized for Actinium-225 radiotheranostic applications. Current PSMA ligands demonstrate suboptimal binding stability, limited tumor retention, and variable chelation behaviors when paired with alpha-emitting isotopes. This study hypothesized that structure-guided modifications combined with quantum mechanical modeling could identify new ligand architectures with improved PSMA affinity, radiometal coordination efficiency, and predicted tumor retention properties.

Materials/Methods: Ligand candidates were generated by systematically modifying three regions of the PSMA pharmacophore: (1) urea-based binding core, (2) linker composition, and (3) chelator-proximal groups. Computational docking was performed using validated PSMA structures, followed by density functional theory (DFT) optimization of metal-ligand geometry. Molecular dynamics (MD) simulations (100 ns) were used to quantify conformational stability and root-mean-square deviation (RMSD). ADMET prediction models evaluated solubility, plasma stability, and predicted clearance. Comparative scoring metrics included docking score, binding free energy, chelator strain energy, and solvent-exposed surface area.

Results: Two ligand candidates demonstrated superior in silico performance relative to reference PSMA scaffolds. Lead candidate L-3a showed a 22−28% improvement in docking score and a 16% reduction in chelator strain energy, indicating more favorable coordination geometry for alpha-emitter complexation. MD analysis showed sustained PSMA pocket engagement with a mean RMSD < 2.1 Å across the simulation window. Lead candidate L-3b demonstrated enhanced predicted plasma stability and lower hydrophobic penalty, resulting in improved ADMET composite score. Both ligands exhibited reduced off-target interaction profiles and improved ligand−metal binding energy favorable for Actinium-225 conjugation. These characteristics collectively suggest potential gains in tumor retention and radiopharmaceutical stability

Conclusion: Computational design integrating docking, DFT geometry refinement, and MD simulations enabled identification of two novel PSMA-targeted ligands with improved predicted performance for Actinium-225 radiotheranostic applications. The results support advancement of these candidates into preclinical radionuclide labeling, in vitro PSMA binding assays, and in vivo biodistribution studies. This framework demonstrates the value of computational screening in accelerating optimization of targeted alpha-therapy agents.

Author Disclosure: **P. Suryadevara**: None.

2006

Clinical Practice Patterns in a Prospective Registry of Patients with Metastatic Prostate Cancer Treated with Lutetium-177 Vipivotide Tetraxetan and External Beam Radiation Therapy at an Academic Tertiary Center

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Purpose/Objective(s): Optimal integration of radioligand therapy (RLT) with external beam radiation therapy (EBRT) requires a multidisciplinary understanding of the patient and treatment factors influencing treatment outcomes. We hypothesized that a longitudinal registry of patients treated with lutetium Lu 177 vipivotide tetraxetan (Lu-PSMA-617) and EBRT for metastatic prostate cancer would capture current patterns of clinical practice and opportunities for longitudinal assessment of factors associated with clinical outcomes and toxicity.

Materials/Methods: A prospective registry of patients receiving Lu-PSMA-617 was established at our institution comprising patients consecutively approved for treatment following discussion at a multidisciplinary theranostics tumor board, including medical oncology, nuclear medicine,

and radiation oncology. Clinical and treatment factors were abstracted based on medical record review including prior courses of systemic therapies, external beam radiotherapy, and radiologic imaging at time of first Lu-PSMA-617 or EBRT. Lesion level characteristics were based on imaging and medical record review.

Results: From June 2022 to July 2025, 372 patients received Lu-PSMA-617 at our institution. Indications for 479 courses of EBRT received among this cohort included oligometastatic disease control, with 43% (n= 206) courses of metastatic-directed therapy and 5.6% (n=27) to control the prostate primary, 30% (n=146) palliative EBRT for polymetastatic disease, 15% (n=72) for definitive primary treatment, and 4.2% (n=20) to control a polymetastatic primary. Among 298 patients with complete systemic therapy information, 90% (n=268) had prior docetaxel, 38% (n=113) cabazitaxel, 66% (n=196) abiraterone, 51% (n=153) enzalutamide, 12% (n=35) apalutamide, 34% (n=102) darolutamide, 14% (n=42) radium-223. Among 269 with complete LuPSMA information, the median number of LuPSMA cycles was 4 and range 1-7. LuPSMA was most commonly discontinued for disease progression.

Conclusion: All patients receiving Lu-PSMA-617 at our institution had received prior EBRT and systemic therapy with Lu-PSMA-617 typically delivered for treatment of polymetastatic disease following progression after multiple lines of systemic therapy. Most patients receiving Lu-PSMA-617 had received prior EBRT for prostate cancer, most commonly to treat metastases with either ablative or palliative intent. To our knowledge, this is one of the first prospective registries to characterize the clinical indications for combining Lu-PSMA-617, EBRT, and systemic therapy and contemporary patterns of practice at an academic tertiary center.

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2007

Real-World Outcomes of ^{177}Lu-PSMA-617 Radioligand Therapy Delivered at Scale for Metastatic Castration-Resistant Prostate Cancer in a Community-Based Theranostics Center

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Purpose/Objective(s): Radioligand therapy with ^{177}Lu-PSMA-617 (Pluvicto®, Novartis; henceforth, LuPSMA) has demonstrated progression-free and overall survival benefit in metastatic castration-resistant prostate cancer (mCRPC). However, real-world outcomes at scale and the impact of adaptive strategies such as using post-therapy SPECT/CT remain less well defined.

Materials/Methods: We retrospectively evaluated 272 consecutive patients with PSMA PET−positive mCRPC treated with LuPSMA between August 2022 and July 2025 at a single community-based theranostics center. LuPSMA was administered every 6−10 weeks. Routine 24-hour post-therapy SPECT/CT imaging informed adaptive decisions. Outcomes included PSA response (PSA50, PSA90), PSA progression-free survival (PSA-PFS), overall survival (OS), and toxicity.

Results: Median cycles delivered was 3 (range 1−9). Seventy-two patients (26.5%) completed all 6 cycles. Treatment was adapted: 30.5% paused/held for strong response and 22.4% discontinued for progression. PSA50 was achieved in 129/272 (47.4%) and PSA90 in 68/272 (25.0%) patients. Median PSA-PFS was 140 days (4.60 months), and median OS was 448 days (14.73 months). Hematologic grade ≥3 toxicities included anemia (15.0%), thrombocytopenia (4.8%), and neutropenia (5.1%). No significant renal or unexpected toxicities were observed. Mild, transient xerostomia was infrequently documented.

Conclusion: Large-scale real-world LuPSMA treatment demonstrated efficacy and safety consistent with pivotal trials while highlighting the utility of post-therapy SPECT/CT to personalize treatment course. Adaptive strategies—pausing in exceptional responders and discontinuing early in non-responders—were feasible without compromising survival. Prospective validation of imaging-guided response adaptation is warranted.

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2008

Lesion-Level Outcomes Among Patients Treated with Lu-PSMA-617 and EBRT for Oligometastatic Prostate Cancer

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Purpose/Objective(s): The treatment landscape for metastatic prostate cancer is rapidly changing and little is known about the clinical impact of the combination of Lu-PSMA-617 and external beam radiation therapy (EBRT) for achieving oligometastatic disease control.

Materials/Methods: A registry database comprising all patients receiving Lu-PSMA-617 at our institution was analyzed to identify patients who received EBRT (including stereotactic body radiotherapy or fractionated RT) for purpose of oligometastatic disease control, where ablative radiation delivered to all active sites of disease. Patient and radiation treatment characteristics were abstracted from medical record review. Lesion-level outcomes were assessed with imaging and medical record review. Kaplan-Meier and Cox proportional hazards regression was used to analyze time-to-event endpoints.

Results: From June 2022 to August 2025, 88 men were treated with Lu-PSMA-617 for metastatic prostate cancer and received prior, concurrent, or subsequent EBRT to 202 lesions for the purpose of oligometastatic disease control. 35.6% of patients had 1-3, 10.9% had 4-5, and 2.5% had greater than 6 lesions treated with EBRT. Staging scans at time of EBRT included bone scan (49.5%), PSMA-PET (39.1%) or both (4%). The number of metastases at time of SBRT at a lesion-level was 1-3 (79.7%), 4-5 (10.9%), or > 5(9.4%). At lesion-level, Lu-PSMA-617 began > 6 months after EBRT in 70.1%, within 6 months of EBRT in 14.8%, and > 6 months prior to EBRT in 13.4% of courses. The anatomic distribution of metastases treated with EBRT included the pelvic lymph nodes (13.4%), abdominal/retroperitoneal lymph nodes (5.9%), thoracic/mediastinal lymph nodes (1.5%), cervical/neck lymph nodes (3.5%), bone (82.2%), lung (2%), or other (8.9%). 59.9% of patients receiving SBRT received concurrent systemic treatment. Lu-PSMA-617 was given prior to SBRT in 16.3%, within 12 months (20.8%), > 12 and less than 24 months (17.8%), > 24 months and ≤36 months (17.8%), or > 36 months (27.2%). There was a 53.4% rate of local failure after EBRT, with a median time to local failure 21.1 months (95% Confidence Interval: 17.3, 40.5). 95% of lesions treated with EBRT also had further systemic therapy with a median time to next treatment of 10.3 months (95% CI: 8.5, 11.8).

Conclusion: EBRT for the purpose of oligometastatic disease control can be integrated at multiple timepoints relative to Lu-PSMA-617 for treatment of metastatic prostate cancer and was commonly delivered to ablate a limited number of bone lesions. Most patients received Lu-PSMA-617 more than 12 months after prior EBRT. Selective EBRT for oligometastatic disease control may help delay time to next therapy among patients receiving Lu-PSMA-617. Further prospective study is warranted.

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2009

Pharmacovigilance of Lutetium Lu-177 PSMA-617 Versus PARP Inhibitors in metastatic Castration Resistant Prostate Cancer: A FAERS-Based Analysis

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Purpose/Objective(s): Lutetium-177 vipivotide tetraxetan (Lu-177 PSMA-617) represents a novel radioligand therapy for metastatic castration-resistant prostate cancer (mCRPC), while PARP inhibitors (PARPi) are established agents in patients with homologous recombination repair tumor mutations. However, comparative post-marketing safety data between these therapeutic classes are limited. We conducted a pharmacovigilance analysis using the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) to evaluate hematologic, renal, and musculoskeletal adverse events (AEs) associated with Lu-177 PSMA-617 and PARPi.

Materials/Methods: FAERS case reports up to 2025 of Lu-177 PSMA-617 (Pluvicto) or PARPi (Olaparib, Rucaparib, Niraparib, Talazoparib) were retrieved and harmonized. AEs were categorized using standardized MedDRA terminology. A 2 × 2 contingency framework was applied to estimate Reporting Odds Ratios (RORs) and 95% confidence intervals (CIs) using Fisher's exact method, comparing Lu-177 PSMA-617 (exposed group) versus PARPi (reference group).

Results: A total of 797 AE reports were identified, including 312 associated with Lu-177 PSMA-617 and 485 with PARP inhibitors. Compared with PARP inhibitors, Lu-177 PSMA-617 demonstrated significantly higher reporting odds of thrombocytopenia (ROR 2.01, 95% CI 1.34−3.03; p=0.0003), dry mouth (ROR 9.19, 95% CI 3.96−24.69; p<0.001), and bone pain (ROR 2.73, 95% CI 0.98−8.27; p=0.30). In contrast, lower reporting odds were observed for anemia (ROR 0.63, 95% CI 0.46−0.86; p=0.0029) and arthralgia (ROR 0.34, 95% CI 0.10−0.94; p=0.026). No statistically significant differences were noted between treatments for renal, neurologic, or gastrointestinal adverse events.

Conclusion: Lu-177 PSMA-617 demonstrates a distinct toxicity pattern, driven primarily by xerostomia and thrombocytopenia, reinforcing the need for proactive monitoring and targeted supportive care. At the same time, Lu-177 PSMA-617 shows lower relative reporting of anemia and arthralgia, alongside higher reporting of bone pain, compared with PARP inhibitors, recognizing that these treatment populations are not directly comparable. Overall, these findings support a favorable and manageable safety profile for Lu-177 PSMA-617 as it moves toward broader and earlier use in the mCRPC treatment landscape.

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2010

Utilization of Radiopharmaceutical Therapies in Animals with Naturally Occurring Disease

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Purpose/Objective(s): Define advantages and disadvantages of veterinary patients as animal models, evaluate novel drugs and devices for radiopharmaceutical therapies (RPTs) using specific case illustrations.

Hypothesis: the use of veterinary patients significantly improves the employment of RPTs for human use.

Materials/Methods: 20+ case studies will be researched to demonstrate the utility of using animals for the translation of RPTs for humans. Some of these examples will include a a) New Zealand White rabbit cancer model for the evaluation of a novel Y^{90} hydrogel therapy; b) the approved usage of the same Y^{90} hydrogel therapy in the application of pet dog cancers, and c) the use of a newly approved veterinary device with tin^{117m} for the treatment of canine synovitis. RPT research development will also be reviewed to include discussing proof-of-concept data on specific RPT studies.

Results: Veterinary patients demonstrate unparalleled roles in the world of RPT development. Choosing whether to use a lab animal model or veterinary patient will depend on the specific questions being explored. Developing a research plan with a relevant list of questions and statistically appropriate methods for answering these questions is crucial prior to implementing a veterinary patient animal study. Spontaneous disease in companion animals offer unique models for evaluating human disease biology and advancing translational therapeutics, including RPT drugs and devices. RPT drug and device development requires special setup and evaluation; learning from the structure of each study produces crucial and increasing value for future studies.

Conclusion: Historically, mice and rats have been used as lab animal models for RPT development. However, given the complexity of a disease and the need to reduce reliance on lab animals, there is incentive for evaluating models that do not rely on mice, rabbits, pigs and other laboratory animals. Veterinary patients serve a unique and valuable role in helping the advancement of RPTs as there are dozens of illnesses that occur in veterinary patients, that cannot be mimicked in lab animal models but have direct translation potential for human disease. The inclusion of naturally occurring diseases in veterinary animals in the RPT research world can aid in the understanding of the biology, treatment, and relief of human disease. The goal is not to change how biomedical RPT research is conducted but rather demonstrate the utility in complementing traditional animal models with naturally occurring disease in pets.

Author Disclosure: **R.A. Krimins**: I am presently serving a 3-year position as the Secretary for EAS.; Eastern Apiculture Society.

2011

PROMPT-R: a Phase II Study evaluating POSLUMA-PSMA PET Response after Oligo-Metastatic/Progressive-directed Treatment with Radiotherapy

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Background/Rationale: The availability of prostate-specific membrane antigen (PSMA)-PET has advanced metastatic prostate cancer (PCa) detection and enables response assessment to PSMA-directed radioligand therapy, yet there is limited data to guide the use of PSMA-PET for response assessment after external beam radiotherapy (RT). A better understanding of early radiographic progression is needed to guide treatment intensification and surveillance strategies in patients receiving metastasis-directed RT (MDRT). Flotufolastat F-18, with reduced urinary excretion, improves visualization of disease near the bladder and ureters and has demonstrated high detection rates in recent multicenter studies. This trial evaluates whether serial flotufolastat F-18 PSMA-PET can identify metastatic progression before PSA rise and characterizes relationships between PET response, PSA kinetics, and circulating tumor DNA (ctDNA) using tumor-informed whole-genome sequencing technology.

Objectives: The primary objective is to determine the frequency of early progression on PSMA-PET prior to PSA progression, measured by Peak-SUL in existing or new lesions after MDRT. Secondary objectives include evaluation of ctDNA dynamics and radiographic response following MDRT.

Trial Design: Phase II, single-center, non-randomized study enrolling 50 patients. Patients undergo baseline PSMA-PET pre-MDRT and at follow up (6, 12, and 24 months, then yearly up to 3 years or until progression). Serial ctDNA is collected at baseline, post-RT, and at each imaging timepoint.

Patient Population: Adults with castration-sensitive PCa and ≤5 metastatic sites outside the pelvis. Patients with brain and liver metastases are excluded. There are 3 groups: Cohort 1 (n=20): De novo oligometastatic, treated with MDRT+ADT+ARSI. Cohort 2 (n=20): Oligoprogressive after prior local therapy, treated with MDRT+ADT. Cohort 3 (≤10): Oligoprogressive, MDRT alone.

Treatment/Intervention: MDRT will be delivered using ablative regimens meeting a biological equivalent dose (BED)>100 Gy, α/β=2. MDRT will begin 8−12 weeks after ADT±ARSI (Cohorts 1−2) or after enrollment (Cohort 3). Primary tumors must be controlled or treated with curative intent.

Endpoints: The primary endpoint is progression on PSMA-PET before PSA rise. The secondary endpoints are quantitative ctDNA change, ctDNA −PET correlation, and durability of PET-defined response.

Statistical Methods: Early PET-detected progression will be estimated with 95%CIs and PET−ctDNA associations assessed with mixed-effects and correlation models. Time-to-event outcomes will be analyzed with Kaplan−Meier.

Status of Trial: Enrollment began Nov 2025 and is ongoing.

Conclusion: PROMPT-R integrates high-sensitivity PSMA-PET imaging with molecular monitoring to evaluate early metastatic progression in oligometastatic/oligoprogressive PCa after MDRT. Findings can refine PSMA-PET response assessment after MDRT and enable adaptive treatment strategies in future trials.

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2012

Progressive/ Recurrent Intracranial Meningioma treated with SSTR-Targeted Alpha emitter RYZ101 (PRIMe-STAR)

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Background/Rationale: Progressive and/or recurrent meningiomas are aggressive tumors with poor prognosis. SSTR2 expression has been seen in 79−100% of meningiomas and the expression is retained at progression. ^{177}Lu-DOTATATE has been evaluated in advanced meningiomas with encouraging results. Interim results of a phase II study evaluating the therapeutic efficacy of ^{177}Lu-DOTATATE in patients with advanced intracranial meningioma showed a PFS-6 rate of 50%. In a meta-analysis evaluating 76 patients with advanced meningiomas receiving SSTR2-targeting PRRT, the PFS-6 rate was 94%, 48%, and 0% for WHO grade I, II, and III meningiomas, respectively. RYZ101 (^{225}Ac-DOTATATE), shares the same targeting moiety as ^{177}Lu-DOTATATE, but is labeled with the alpha-emitting radionuclide ^{225}Ac. Alpha particles have a much higher linear energy transfer, causing more frequent DNA double-strand breaks, leading to cell death with higher efficiency. In addition, alpha particles have a much shorter range (40-100 μm), allowing for more selective killing of cancer cells and sparing of surrounding healthy tissue. Clinical evidence suggests potentially improved efficacy and therapeutic index with ^{225}Ac compared with ^{177}Lu. Recent ongoing studies have shown the utility of SSTR2 targeted therapies in patients with solid tumors such as NETs and lung cancers. Alpha-particle therapy holds promise in the treatment of recurrent meningiomas which are often relatively radio-resistant. In this study, we plan to evaluate the efficacy and safety of RYZ101 (^{225}Ac-DOTATATE) in patients with progressive/recurrent meningiomas after first line therapy.

Objectives: To evaluate the efficacy and safety of alpha-emitter RYZ101 (^{225}Ac-DOTATATE) in patients with progressive/recurrent meningiomas after first line therapy.

Trial Design: Seamless Phase I/II

Patient Population: Progressive Grade 1-3 meningioma s/p prior radiation treatment

Treatment/Intervention: RYZ101 intravenous administration (10.2 MBq) every 8 weeks for 4 cycles.

Endpoints: To establish safety of ^{225}Ac-DOTATATE (RYZ101). To estimate the efficacy of ^{225}Ac-DOTATATE (RYZ101) therapy in the treatment of patients with progressive or recurrent grade 1-3 intracranial meningioma as measured by the progression free survival at 6 months.

Statistical Methods: Sample size calculation was based on the historical PFS-6 of 26% in patients with progressive / recurrent meningiomas. The study uses a Simon two-stage design to enroll 30 patients. The null hypothesis of a true response rate of 0.26 (H0) is tested against a one-sided alternative response rate of 0.5. This yields a power of 80% at one-sided significance level of 0.05.

A preplanned interim analysis will be conducted after 14 patients (Phase I), with an early stopping rule of >33% dose limiting toxicity (DLT), with DLT defined as grade 3 or higher non-hematological toxicity or grade 4 or higher hematological toxicity.

Status of Trial: Open, Recruiting

Author Disclosure: **J.D. Palmer**: Grant/research funding; Genentech. Honoraria; ICOTEC, Varian Medical Systems, Carbofix, Servier. Travel expenses; Servier. Develop educational curriculum, yearly national meeting and research goals; Spine Therapy Society. **R. Upadhyay**: Honoraria; Varian Medical Systems. **R. Raval**: Honoraria; Varian Medical Systems. Program Director; The Ohio State University Wexner Medical Center. **R. Singh**: None. **E.M. Thomas**: Partner; Renaissance Institute of Precision Oncology & Radiosurgery. Grant/research funding; Varian Medical Systems. Honoraria; Varian Medical Systems. Travel expenses; Varian Medical Systems. Compensation/Payment; Varian Medical Systems. **S. Beyer**: None. **J.B. Elder**: None. **D. Prevedello**: None. **K. Wu**: None. **P. Giglio**: None. **P. Singh**: None. **J. Ivanidze**: None. **B. Tang**: None.

2013

CLARIFY Phase 3 Trial: Positron Emission Tomography using ^{64}Cu-SAR-bisPSMA in Patients with High-Risk Prostate Cancer Prior to Radical Prostatectomy

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Background/Rationale: High-risk localized prostate cancer (PC) most often spreads to the pelvic lymph nodes (LNs) before becoming widely metastatic. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is strongly overexpressed in PC, making it an ideal target for imaging and therapy. ^{64}Cu-SAR-bisPSMA may offer several advantages over the currently approved PSMA positron emission tomography (PET) agents due to its bivalent structure (SAR-bisPSMA) and longer half-life of ^{64}Cu (12.7h vs. <2h for ^{18}F and ^{68}Ga). ^{64}Cu-SAR-bisPSMA has demonstrated higher tumor uptake (2-3x), prolonged retention, and detection of additional PC lesions compared to approved PSMA agents.
Objectives: This Phase 3 diagnostic trial aims to establish the diagnostic performance of ^{64}Cu-SAR-bisPSMA PET to detect regional nodal metastases in men with high-risk PC.
Trial Design: CLARIFY (NCT06056830) is a multi-center, single-arm, open-label Phase 3 diagnostic study of ^{64}Cu-SAR-bisPSMA.
Patient Population: The target population is patients with untreated, histopathology-confirmed prostate adenocarcinoma with high-risk features, who are proceeding to radical prostatectomy (RP) with pelvic lymph node dissection (PLND).
Treatment/Intervention: Eligible patients will receive a single administration of ^{64}Cu-SAR-bisPSMA (200 MBq) followed by a PET/CT scan on Day 1 (1-4h post-dose) and Day 2 (24±6h post-dose). Patients will then proceed to RP with PLND.
Endpoints: The co-primary endpoints are sensitivity and specificity of ^{64}Cu-SAR-bisPSMA PET to detect PC within pelvic lymph nodes as matched against the SOT at each imaging timepoint (Day 1 and Day 2). Secondary objectives include assessment of safety and determining the positive and negative predictive value of ^{64}Cu-SAR-bisPSMA PET.
Statistical Methods: The ^{64}Cu-SAR-bisPSMA PET/CT scans will be interpreted locally and by 3 independent, blinded, central readers. Each reader will assess the scans for the presence of abnormal ^{64}Cu-SAR-bisPSMA uptake in the pelvic LNs, prostate gland, extra-pelvic LNs, visceral/soft tissue, and bone. The specimens from surgery will be processed and analyzed locally to derive the standard of truth (SOT). A total of 383 patients will be enrolled.
Status of Trial: The study is open for recruitment in sites in the United States and Australia.

Author Disclosure: **M. Gorin**: None. **E. Lengyelova**: Stock; Clarity Pharmaceuticals. Stock options; Clarity Pharmaceuticals. **L. Nordquist**: Stock; Clarity Pharmaceuticals. **G. Morrish**: Independent Contractor; Clarity Pharmaceuticals. Stock; Clarity Pharmaceuticals. Stock options; Clarity Pharmaceuticals. **O. Gervasio**: Stock; Clarity Pharmaceuticals. Stock options; Clarity Pharmaceuticals. **R. Miller**: Independent Contractor; Clarity Pharmaceuticals. **N. Shore**: Grant/research funding; Clarity. Compensation/Payment; Astellas, Dendreon, Janssen, Bayer, Myriad, MDxHealth, Tolmar, Myovant, Pfizer, emdSerono, AstraZeneca, Genentech, Urogen, Guardant, Abbvie, Amgen, Bristol Myers Squibb, Boston Scientific, Exact Imaging, FerGene, Foundation Medicine, Invitae, Nymox, Propella, Sanofi Genzyme, Pacific Ed. **D.L. Boothe**: Honoraria; Novartis, AllyGPO, Prostate Cancer Foundation, GE Healthcare, Society of Utah Medical Oncology. Travel expenses; Cellectar Biosciences, AllyGPO, Prostate Cancer Foundation, GE Healthcare, Society of Utah Medical Oncology, ASTRO. Compensation/Payment; Cellectar Biosciences, RadOnc Questions, Novartis, Mirion Medical. Ownership eq.

2014

AMPLIFY: A Phase 3 Study of ^{64}Cu-SAR-bisPSMA Positron Emission Tomography in Participants with Biochemical Recurrence of Prostate Cancer

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Background/Rationale: Prostate cancer (PC) is the second most prevalent cancer in men globally. The need for improved PC imaging is reflected in a biochemical recurrence (BCR) rate of 20 to 40% after initial definitive therapy. Despite advances in technology, many patients will fail to have their recurrence accurately localized by imaging, especially at low PSA levels. Imaging modalities that are widely available and can accurately detect, monitor, and restage residual / recurrent loco-regional and metastatic disease are therefore highly desirable. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is strongly overexpressed in PC, making it an ideal target for imaging and therapy. ^{64}Cu-SAR-bisPSMA may offer several advantages over the currently approved PSMA positron emission tomography (PET) agents for PC due to the bivalent structure of SAR-bisPSMA and longer half-life of ^{64}Cu ($t_{1/2}$ = 12.7h), compared to the approved monovalent PSMA agents utilizing ^{18}F and ^{68}Ga ($t_{1/2}$ < 2h). Evidence has demonstrated prolonged tumor retention and 2-3x higher tumor uptake with detection of additional PC lesions using ^{64}Cu-SAR-bisPSMA compared to approved PSMA PET agents.
Objectives: The primary objective is to investigate the ability of ^{64}Cu-SAR-bisPSMA PET/CT to detect recurrence of PC, with co-primary endpoints of participant-level correct detection rate (CDR) and region-level positive predictive value (PPV) assessed independently for Day 1 and Day 2.
Trial Design: AMPLIFY (NCT06970847) is a multi-center, single arm, open-label Phase 3 diagnostic performance study of ^{64}CuSAR-bisPSMA PET/CT.
Patient Population: Participants with a history of prostate adenocarcinoma and rising or detectable PSA after initial definitive treatment.
Treatment/Intervention: All participants are required to have baseline conventional imaging. Eligible patients will receive a single administration of ^{64}Cu-SAR-bisPSMA (200 MBq) followed by a PET/CT scan on Day 1 (1-4h post-dose) and on Day 2 (24±6h post-dose). Participants will then continue into the follow-up period to verify the ^{64}Cu-SAR-bisPSMA PET/CT findings.
Endpoints: The primary objective is to investigate the ability of ^{64}Cu-SAR-bisPSMA PET/CT to detect recurrence of PC, with co-primary endpoints of participant-level correct detection rate (CDR) and region-level positive predictive value (PPV) assessed independently for Day 1 and Day 2. Key secondary objectives include assessment of safety, participant-level PPV, and participant-level detection rate (DR).
Statistical Methods: A total of 220 patients will be enrolled. The Day 1 and Day 2 scans will be interpreted individually by a qualified local reader and 3 independent, blinded, central readers for the presence of abnormal ^{64}Cu-SAR-bisPSMA uptake. ^{64}Cu-SAR-bisPSMA PET/CT results on Day 1 and Day 2 will then be assessed against a composite Reference Standard by a central expert panel.
Status of Trial: The study is open for recruitment in the United States and Australia.

Author Disclosure: **N. Shore**: Compensation/Payment; astellas, dendreon, janssen, bayer, myriad, mdxhealth, tolmar, myovant, pfizer, emdserono, astrazeneca, genentech, urogen, guardant, abbvie, bristol myers squibb, exact imaging, fergene, foundation medicine, nymox, propella, sanofi genzyme, pacific edge, cold genes, genesis care, alessa, immunitybio, LANTHEUS, lilly, . **E. Lengyelova**: Stock; Clarity Pharmaceuticals. Stock options; Clarity Pharmaceuticals. **J.A. Efstathiou**: Honoraria; Blue Earth

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2015

Phase 1 Dose Escalation and Expansion of AB001 in Patients with Metastatic Castration Resistant Prostate Cancer (mCRPC): The ARTISAN Trial

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Background/Rationale: Treatment options for patients with mCRPC have been improved by radioligand therapies such as beta-emitting ^{177}Lu-PSMA-617. However, prostate cancer remains the fifth leading cause of cancer mortality, with the lives of more than 250,000 men shorted by mCRPC each year. New therapies with differentiated mechanisms of action that could extend survival while retaining quality of life are needed. Alpha-particle emitting radioisotopes offer significant advantages compared with beta-emitters. Alpha particles have higher atomic mass (4), charge (2+), and linear energy transfer. Furthermore, the short particle range (<100 μm) is expected to minimise damage to surrounding normal tissue. ^{212}Pb is attractive for alpha radiotherapeutics due to its short 10.6 hour half-life which fits well with the rapid tumour uptake achievable with PSMA-targeting small molecules. The ARTISAN study will evaluate the safety and tolerability of AB001, a ^{212}Pb-labelled, PSMA-targeted small molecule alpha-radiotherapeutic, in participants with advanced PSMA positive mCRPC.
Objectives: The objective of this study is to evaluate the safety and tolerability of AB001 in two populations: participants with mCRPC who have not received prior treatment with ^{177}Lu-PSMA radioligand therapy and participants who have been treated with at least one dose ^{177}Lu-PSMA therapy.
Trial Design: The ARTISAN study is a Phase 1, open-label, multicentre, dose escalation expansion study of AB001.
Patient Population: Patients with advanced PSMA-positive mCRPC. Participants must have received previous treatment with at least one androgen receptor pathway inhibitor and at least one prior taxane.
Treatment/Intervention: Dose Escalation will be initiated with the first cohort of participants receiving a starting dose of 100 MBq, on a 6-week cycle. Four cycles of AB001 are planned; however, individual participants may continue up to a maximum of six treatment cycles provided they derive clinical benefit. In Dose Escalation, subsequent cohorts of participants will be opened at different dose and treatment schedules, to determine the recommended dose and schedule for Dose Expansion.
Endpoints: The primary endpoint in Dose Escalation will be to identify the recommended dose and schedule for each population for Dose Expansion. The primary endpoint in Dose Expansion will further evaluate safety, tolerability, and preliminary activity of AB001 in the two populations. Assessment of AB001 biodistribution and dosimetry estimation by ^{212}Pb SPECT imaging will be used in addition with radioactive and ligand PK evaluation to enable efficient dosage optimisation of AB001 in this Phase 1 trial.
Statistical Methods: A Time-to-Event Bayesian Optimal Interval (TITE BOIN) design is employed to allow dosage optimisation by both escalation of the ^{212}Pb radioactive dose (MBq) and assessment of optimal cycle duration.
Status of Trial: Trial is open for recruitment. Research Sponsor: ARTBIO

Author Disclosure: **B.R. Mancini**: Honoraria; GE HealthCare, Lantheus, Decipher (Veracyte). Travel expenses; GE HealthCare, Lantheus. Compensation/Payment; MCG Health, GoodRx Health. Ownership equity; BAMF Health, Inc.. Serve as Medical Director in addition to primary role as a physician providing patient care.; BAMF Health. **L. Nordquist**: None. **M. Stein**: Grant/research funding; Bristol-Myers Squibb, Lilly, Xencor, Regeneron, Bicycle Therapeutics, AstraZeneca, Telix Pharmaceuticals, Exelixis, ARTBIO. Compensation/Payment; Exelixis, Johnson & Johnson/Janssen, GI Innovation. Ownership equity; Rafael Holdings. Stock; Rafael Holdings. **J.M. Floberg**: None. **M. Ghesani**: Compensation/Payment; Siemens, Telix, Lantheus, ITM, Serac Life Sciences, Novartis, Blue Earth, Bayer, Cardinal. **V. Paulus**: None. **M. Suppiah-Coll**: None. **R. Greasley**: None. **J. Needham-Clark**: None. **T. Aarvak**: None. **J. Sullivan**: None. **M. Yu**: None. **O. Sartor**: Compensation/Payment; Astellas Pharma, Progenics, Swiss Rockets, Abdera, Actinium Pharma, AdvanCell, Alpha9, ArtBio, AstraZeneca, Bayer, Clarity, Convergent, Curium, ITM, JNJ, Merck, Modex, Norroy, NorthStar, Novartis, Nucleus Biopharma, Precede, Telix, Wren Laboratories. Ownership equity; Cardinal Health, AbbVie, United Health Group, Cura.

2016

A PHAse 1/2a Study of ^{64}Cu-LNTH-1363S FAPi PET/CT Imaging AgeNT in Patients with SarcOMa or Gastrointestinal Tract Cancer (PHANTOM Trial)

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Background/Rationale: Fibroblast activation protein (FAP) is highly expressed in the microenvironment of multiple tumor types. The differential expression of FAP in tumor versus normal tissue has made it a promising agent for imaging and potentially a target for therapeutic applications. ^{64}Cu-LNTH-1363S is a high affinity FAP inhibitor (FAPi) radiolabeled with Copper-64 (^{64}Cu) that is being assessed in the PHANTOM trial for biodistribution, dosimetry, dosing, and optimal imaging timing in metastatic sarcoma (Part 1) and non-metastatic sarcoma of gastrointestinal tract (GIT) cancers (Part 2).
Objectives: For part 1, the primary objective is to assess the biodistribution, radiation dosimetry, optimal dose, and imaging time window of ^{64}Cu-LNTH-1363S in patients with metastatic sarcoma. The secondary objectives are to evaluate the safety, tolerability and FAP expression profile of ^{64}Cu-LNTH-1363S and monitor cardiac safety. For part 2, the primary objective is to evaluate the correlation of 64Cu-LNTH-1363S biodistribution with FAP expression. The secondary objectives are to validate the optimal dose of the reagent, evaluate the safety and tolerability profile of ^{64}Cu-LNTH-1363S, and monitor cardiac safety.
Trial Design: The trial is a multicenter, open-label, prospective phase 1/2a study.
Patient Population: For part 1, 6 patients $\geq$ 15 years of age with metastatic sarcoma will be enrolled. For part 2, 20 patients $\geq$ 15 years of age with non-metastatic sarcoma or GIT cancers (esophageal, gastric, pancreatic, colorectal cancer) planned for surgery within 60 days will be enrolled.
Treatment/Intervention: In part 1, patients will receive 8 $\pm$ 1 mCi (~90 μg mass dose) of the ^{64}Cu-LNTH-1363S reagent with PET/CT imaging performed 0.5 hr, 1hr, 2 hrs, 4-6 hrs, and 24 hrs post administration. In part 2, patients will receive the optimal radioactivity of the ^{64}Cu-LNTH-

1363S reagent as determined in part 1 and 2 PET/ CT scans will be performed between 0.5 hr and 3 hrs post administration based on the optimal timing determined in part 1.

Endpoints: In part 1, endpoints are Time Activity Curves (TACs), describing percentage of the injected activity versus time for selected organs and tumor lesions and absorbed radiation doses of ^{64}Cu-LNTH-1363S in critical organs, image quality score, optimal dose, and imaging time window, frequency and severity of adverse events, and changes in ECG parameters. In part 2, endpoints are correlation of ^{64}Cu-LNTH-1363S biodistribution with FAP expression by IHC, image quality score, frequency and severity of adverse events, and changes in ECG parameters.

Statistical Methods: Analysis will be descriptive and correlate image quality score with dose and timing of imaging in part 1 and correlation of ^{64}Cu-LNTH-1363S biodistribution with FAP expression by IHC in part 2 with assessment by Spearman's correlation coefficient. Adverse event data will be summarized by the number and percent of patients reporting each event.

Status of Trial: Open for enrollment at 5 centers in the United States.

Author Disclosure: **Y. Liu**: None. **S. Srinivas**: None. **F. Moradi**: None. **H. R. Kulkarni**: None. **B. Turpin**: None. **G. Chand**: None.

2017

Creating a Hospital Based Mulitdisciplinary Radiopharmaceutical Center of Excellence

A.L. Salner,[1] P. Karak,[2] and M. Hungerford[2]; [1]*Hartford HealthCare Cancer Institute, Hartford, CT,* [2]*Hartford Hospital, Hartford, CT*

Objectives: The creation of a hospital based radiopharmaceutical program "takes a village" of team members from radiation oncology, nuclear medicine, radiology, nursing, hospital administration, hospital finance, radiation safety, and pharmacy, amongst others. The complexity of this therapeutic approach requires a collaborative effort in order to ensure a high quality, safe, and fiscally sound program.

Activities/Methods: Radiation oncology took the initiative of initiating our program in 2018 at the time of FDA approval of Lu-177 dotatate, and nuclear medicine was intimately involved in the imaging and radiopharmaceutical handling component. Theranostics as a field certainly requires a closely coordinated marriage of both the diagnostic and therapeutic components. We therefore elected to have co-directors of our theranostic program from Radiation Oncology and Nuclear Medicine.

Outcomes: The operational aspects of delivering care for Lu-177 dotatate require 2 IVs, 1 in each arm, and the utilization of IV amino acid solution and a mix of anti-emetics. We involved our infusion oncology nurses to help with IVs and patient care, our pharmacy team for the amino acid solution and anti-emetics supply and Epic health record "build", and nuclear medicine technology to receive, calibrate, transport, and assist in administration of the radioligand. Radiation safety's active involvement is essential in: program and standard operating procedure development, licensures, radiation safety committee approvals, waste monitoring and release, and in the monitoring of and counseling of each patient. Hospital administration provides business planning and review, space designation, strategic planning, and ultimately program approval. Hospital financial services provide pre-authorization, billing, and other revenue cycle services.

Lessons Learned: After treating a high volume of neuroendocrine cancer patients for several years, we were able to initiate the use of Lu-177 PSMA promptly in 2022 for a large volume of patients. We have participated in many research trials involving new and exciting radioligands and uses. We have learned that the use of these agents represents a "program" not a "treatment". With much effort by our team, we are proud to have been designated by SNMMI as a Clinical Radiopharmaceutical Therapy Center of Excellence.

Author Disclosure: **A.L. Salner**: Compensation/Payment; Teladoc. I oversee Cancer Center activities; Hartford Hospital. **P. Karak**: Directs clinical activities in department; Hartford Hospital. **M. Hungerford**: Compensation/Payment; GE Health, Cardinal Health. mnages clinical activities in nuclear medicine; Hartford Hospital.

2018

The Role of an Advanced Practice Provider as a Theranostics Program Coordinator: Navigating Barriers to Achieve Program Success and Optimal Patient Outcomes

J.E. Ligorski,[1] D. Huffman,[1] A. Abel,[2] A.C. Mueller,[3] N. Vasil,[1] K. Bennet,[4] T. Flannery,[1] K. Zia,[4] and R.B. Patel[4]; [1]*University of Pittsburgh Medical Center, Pittsburgh, PA,* [2]*Department of Radiation Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA,* [3]*Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA,* [4]*UPMC Hillman Cancer Center, Pittsburgh, PA*

Objectives: The emergence of theranostics as a precision medicine approach in oncology has necessitated multidisciplinary coordination across multiple fields including radiation oncology, nuclear medicine, radiology, oncology, and laboratory testing. Patient and program success have many barriers and facits that need prompt attention. This abstract aims to define the role of an Advanced Practice Provider (APP) as a Theranostics Program Coordinator (TPC), as well as to identify systemic, operational, and clinical barriers that must be navigated to implement a successful theranostics program with the ultimate goal of improving patient access and outcomes

Activities/Methods: A retrospective review was conducted at a single institution with an active theranostics program over a 10-month period. Data was collected on 63 patients undergoing theranostic treatment with lutetium Lu 177 vipivotide tetraxetan for the treatment of castration-resistant prostate cancer through a centralized spreadsheet. Data points included laboratory values, SPECT/CT results, treatment timelines, and documented reasons for delays in care. Additionally, coordination of care with nuclear medicine, oncology, scheduling were noted to assess workflow challenges. Qualitative comparative analysis was performed on program efficiency before and after the APPs involvement as TCP.

Outcomes: The data revealed multiple categories of delay in care, with the most common being insurance approval, coordination of diagnostic imaging, and patient centered issues. The APP plays a critical role in real-time tracking of these variables, escalating urgent cases, rescheduling missed appointments efficiently, and facilitating communication between clinical and administrative teams. Since the implementation of the APPs role as the TPC, the program has become more efficient and improves patient outcomes. Use of a centralized spreadsheet allowed proactive identification of at-risk patients, improving continuity of care, and helps the entire team. Since the APPs integration, anecdotal and informal assessments indicated improved clarity in workflow, reduced scheduling bottlenecks, and navigate patient delays to improve patient outcomes.

Lessons Learned: The APP as the TPC is a pivotal role in managing the complex, evolving landscape of radiopharmaceutical therapy. The APP along with the physician as the authorized user can increase the capabilities of a theranostic program. The APP has direct involvement in data collection, workflow oversight, and interdisciplinary coordination allowing for rapid identification and mitigation of care delays. These contributions lead to measurable improvements in treatment timelines, operational efficiency, and patient treatment success, while allowing the authorized user/physician to continue to assess and treat new patients. Investment in this role is essential for any institution aiming to build a scalable and sustainable theranostics program.

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2019

Developing a Quantitative SPECT/CT Standards for Reliable RPT Dosimetry: A Practical Approach.

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Objectives: Quantitative SPECT/CT is central to accurate dosimetry for Lu-177 radiopharmaceutical therapy (RPT), yet clinical implementation remains highly variable. As our institution expanded its RPT program, we identified inconsistencies in quantitative SPECT/CT performance that impacted absorbed-dose calculations. This work reports a single-institution experience in optimizing the Lu-177 workflow and qualifying SPECT/CT for robust, reproducible dosimetry, guided by the quantitative imaging principles described by the publications. (1)https://doi.org/10.3389/fonc.2024.1331266 and (2) https://doi.org/10.1186/s40658-025-00764-1

Activities/Methods: A comprehensive end-to-end review of our Lu-177 therapy workflow was performed in a Radiation Oncology department. SPECT/CT systems were evaluated for quantitative readiness using phantom-based calibration, stability testing, and adherence to recommended protocols for sensitivity, scatter correction, energy-window selection, CT-based attenuation correction, and partial-volume recovery. Reconstruction parameters (iterations, subsets, filters, and compensation methods) were standardized across technologists and clinical sessions. Failure modes specific to dosimetry acquisition—such as inconsistent calibration coefficients, suboptimal VOI definition, and unverified reconstruction settings—were cataloged and assigned risk priority numbers (RPNs). Mitigation strategies were implemented through protocol unification, quantitative QC scheduling, and cross-department training.

Outcomes: Before standardization, volumetric sensitivity drift, reconstruction variability, and inconsistent partial-volume handling contributed to significant uncertainty in absorbed-dose estimates. After implementing harmonized calibration and reconstruction workflows, scanner sensitivity variation decreased to <5%, quantitative repeatability improved, and adherence to standardized VOI protocols increased. The qualified SPECT/CT platform supported reliable multi-time-point Lu-177 dosimetry with consistent quantification across therapy cycles, enabling a shift from semi-quantitative to standardized absorbed-dose reporting.

Lessons Learned: A structured qualification process can reliably "tame" SPECT/CT for quantitative Lu-177 dosimetry in a single-institution RPT program. Standardizing calibration, reconstruction, and QC procedures—combined with a formalized workflow review—significantly reduces imaging-related variability and strengthens dosimetry reproducibility. As RPT volume increases, establishing quantitative SPECT/CT as a controlled clinical process is essential for safe, consistent therapy delivery and future personalized dosing.

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2020

Two years of Lu177 DOTATATE Release Exposure Rate Measurements and Implications of the Proposed Revision to NRC Lu177 Release Criteria

J. Mikell, A. Guta, J.L. Garcia-Ramirez, and J.E. Zoberi; *WashU Medicine, Department of Radiation Oncology, St. Louis, MO*

Objectives: The occupancy factor for patient release calculations is increased from 0.25 to 1.0 in a proposed revision to the NRC Regulatory Guide 8.39 (NRC-2023-0086). This results in a reduction in acceptable exposure rate measurements for patients receiving lutetium-177 (Lu177) radionuclide treatments from a previously estimated value of 8.6 mR/ h to 2.2 mR/ h at 1 meter. This work examines patient exposure rate measurements collected after Lu177 DOTATATE and assesses compliance and activity escalation limitations with the proposed NRC release calculation rule change.

Activities/Methods: An IRB-approved retrospective chart review was performed for all Lu177 DOTATATE treatments within our department from 2023 to 2025. Nominal prescribed activity for all treatments was 7.4 GBq. The number of treatments satisfying the current release criteria as well as the proposed release criteria revision were assessed at two time points in the Lu177 DOTATATE administration process: immediately following Lu177 DOTATATE infusion (post-Lu177) and immediately following amino acid infusion (post-AA). Activity escalation was estimated by scaling the administered activity by 2.2 mR/ h divided by the post-Lu177 or post-AA exposure rate measurement.

Outcomes: Patient exposure rate measurements at 1 meter immediately following post-Lu177 had mean ± standard deviation [min, max] of 2.10 ± 0.33 [1.26, 3.20] mR/h. For post-AA, mean patient exposure rate was reduced to 1.20 ± 0.36 [0.58, 2.50] mR/h. Measurements post-AA were on average 59% ± 17% of the post-Lu177 exposure rate. Mean time between these two measurements was (3.89 ± 0.52) h. Of the 192 measurements observed, 54 (28%) did not satisfy the proposed release rule change for post-Lu177. Three (1.5%) exposure rate measurements at post-AA did not satisfy the proposed rule change. The maximum activity that could be delivered with for post-Lu177 was 8.02 ± 1.29 GBq; this increases to 14.90 ± 4.38 GBq when release exposure measurements are post-AA.

Lessons Learned: The proposed NRC guidance change is likely to affect clinics using exposure rate measurements immediately following Lu177 DOTATATE infusion. Due to additional biological clearance via voiding, clinics using exposure rate measurements after completion of the amino acid infusion may not need to change their workflows. Meaningful activity escalation would require clinics to use release exposure measurements after amino acids to comply with the proposed guidance.

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2021

Building a Safer Lu-177 RPT Program: A Multi-Institutional, Multi-Disciplinary FMEA_ FTA Analysis.

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Objectives: As the clinical use of Lu-177-based radiopharmaceutical therapies (RPTs) expands, integrating radiation oncology (RO) and nuclear medicine (NM) workflows poses novel delivery and safety challenges. This abstract reports on five years of operational experience from a busy RO and NM clinic network. It leverages the findings of a recent multi-institutional failure−mode and fault−tree analysis of Lu-177 therapies (George et al., JApplClinMedPhys 26(1):e14550) to propose a structured delivery strategy aimed at reducing radiation-related incidents when patients depart the facility.
Activities/Methods: Over five years, our network of RO and NM departments administered Lu-177 therapies under routine clinical conditions. In parallel, we conducted a prospective process review informed by the George et al. study (https://doi.org/10.1002/acm2.14550), which surveyed multiple centers and identified high-risk points, including patient excretion monitoring, contamination control, dose tracking, and inter-departmental handoffs. We mapped our workflow, identified failure modes, assigned risk priority numbers (RPNs), and developed a composite quality management (QM) program tailored for combined RO/NM settings.
Outcomes: Key failure modes with elevated RPNs included discharge instructions for radioactive patients, inadequate isolation/segregation of excreta, lack of cross-department training, and manual handoffs during dose administration. The implementation of targeted mitigation strategies —such as standardized patient discharge checklists, dual-department training sessions, real-time contamination surveys, and unified dose−tracking logs—yielded measurable improvements in endpoint metrics: zero radiation-related incidents for departing patients, improved documentation completion rates, and increased staff confidence in safety protocols across departments.
Lessons Learned: The five-year real-world experience of a combined RO/NM clinic(s) demonstrates that delivering Lu-177-based RPTs at scale can be achieved safely when underpinned by a structured QM framework informed by multi-institutional failure analysis data. This model emphasizes not only shielding and physical protection, but also process design, inter-departmental coordination, and patient discharge safety. As RPT volumes grow, programs should look beyond basic shielding requirements and adopt a risk-aware, cross-functional operational model to safeguard patients, staff, and facilities.

Author Disclosure: **S.C. George**: None. **A. Gutierrez**: Honoraria; IBA, AB, Elekta, AB, Zap Surgical. Travel expenses; IBA, AB, Elekta, AB. **A. Kaiser**: Honoraria; HMP Education, Accuray. **M.D. Chuong**: Grant/research funding; ViewRay, Novocure, StratPharma. Honoraria; ViewRay, Sirtex. Travel expenses; ViewRay. In-kind donations; ViewRay. Compensation/Payment; ViewRay. GI section editor; International Journal of Radiation Oncology Biology Physics. Board of Directors member; Proton Collaborative Group. **A.C. Botero**: None. **J.E. Zoberi**: Waiving of annual meeting registration fees; ASTRO. Chair of ASTRO Safety WP on Rph; ASTRO. Chair of Radiopharms Session at Annual ABS Mtg; ABS. Chair of ETC; AAPM. **N.M. Maughan**: None. **R.P. Tolakanahalli**: Honoraria; MIM Software Inc.

2022

Implementing Radiopharmaceutical Therapy in Community Radiation Oncology: A Scalable Model with Preliminary Program Insights

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Objectives: Radiopharmaceutical therapy (RPT) with agents containing Lu-177 for metastatic prostate-specific membrane antigen (PSMA) positive cancer, represents a major advancement in this cohort by delivering targeted radiation to help extend survival while minimizing systemic toxicity. Traditionally performed in nuclear medicine, integrating RPT into outpatient radiation oncology departments can expand patient access and optimize workflows in community settings. However, successful adoption requires a structured, programmatic approach.
Activities/Methods: This initiative combined a phased implementation strategy with a multi-step operational framework across three community hospitals within a large health system. Phase one focused on regulatory compliance, financial analysis, equipment procurement, staff training, workflow modifications, and reimbursement planning. Concurrently, leadership engagement was achieved through SBAR documentation, proforma development for financial modeling, and executive alignment. Policy and procedure development, stakeholder integration, and infrastructure planning were completed, followed by equipment installation and workflow validation through manufacturer-supported dry runs. Implementation meetings increased in frequency as launch approached, ensuring readiness.
Outcomes: Preliminary outcomes demonstrate that RPT services were successfully established simultaneously across all three sites, meeting regulatory standards and financial viability while minimizing operational disruption. Key success factors included early leadership engagement, detailed financial planning, and systematic stakeholder involvement. Planning for subsequent phases is underway, including patient-specific dosimetry correlation with tumor and organ-at-risk dose from prior radiation or concurrent with RPT delivery.
Lessons Learned: This combined approach provides a scalable roadmap for community hospitals seeking to integrate RPT within radiation oncology. By emphasizing phased planning, financial strategy, and structured stakeholder engagement, this model ensures sustainability and broadens access to advanced oncologic therapies beyond academic centers.

Author Disclosure: **K.W. Brooks**: None. **C. Stone**: None.

2023

Assessment of Healthcare Access Following Implementation of Lutetium-177 Vipivotide Tetraxetan Radioligand Therapy for Patients with Castration-Resistant, Metastatic PSMA-Positive Prostate Cancer in a Rural Cancer Center Serving a 100 mile Catchment Area

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Purpose/Objectives: To investigate the feasibility, safety, and impact of Lutetium-177 vipivotide tetraxetan (Lu 177) program implementation on healthcare access for advanced prostate cancer patients at a rural community cancer center (Center).
Activities/Methods: The APEx-accredited Center initiated Lu 177 for prostate cancer in 2025. A retrospective review was conducted utilizing institutional policies, protocols, patient data, treatment outcomes, and care needs. Adverse events were graded according to CTCAE V6. Barriers and facilitators to implementation and patient access were identified through clinical records and staff interviews.
Outcomes: The treatment team at the Center comprised a board certified radiation oncologist authorized user (AU), in contrast to the University where a nuclear medicine physician is the AU. The team included a registered nurse and two certified nuclear medicine technologists. Medical physics and radiation safety services were provided through an external contractor, who additionally coordinated Lu 177 delivery. Treatment protocols and operations were developed with input from the University and the drug manufacturer. Patients underwent consultation, lab evaluation prior to administration, and follow up at the time of injection. All treatment patients met standard eligibility criteria. One contraindication to treatment was urinary incontinence. Due to the risk of radioactive contamination and the limited isolation area within the Center, such cases posed a threat to diagnostic and therapeutic operations. These patients were referred to the University. Seven patients started Lu 177, median ECOG 1 (0-1), median age 77, (63-86). Median number of treatments was 3 (2-5). Initial PSA ranged from 0.5 to >5000. Five patients remain on therapy, while 2 stopped due to new malignancy (1) and progression

(1). Two patients had marked responses after 2 doses. One had complete symptomatic recovery from spinal cord compression, previously refractory to radiation, surgery, and steroids. The other one had PSA >5000 reduced to 259. Adherence to scheduled appointments was 100%, The farthest distance traveled to the Center was 2 hours. The three patients who traveled 2 hours all expressed preference for the ease of access at the Center, in contrast to logistical challenges of a larger urban facility. Two patients had Grade 2 nausea. Four patients had grade 3 anemia. All patients received doses on schedule without dose reductions. No injection related contamination was observed. Key facilitators included historical use of Ra223, a modern PET scanner, and University radiologists reading all films. The University Nuclear Medicine Physician trained the radiation oncologist for AU status.

Lessons Learned: The program proved to be feasible and safe, and enhanced access to essential healthcare for patients in rural areas. Urinary incontinence posed a contamination issue within the Center. These results can serve as a model for other rural centers to improve access to theranostics.

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