Differences and common ground in 177Lu-PSMA radioligand therapy practice patterns: International survey of 95 theranostic centers

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Purpose

Lutetium-177 labeled prostate-specific membrane antigen (Lu-PSMA) radioligand therapy effectively treats metastatic castration-resistant prostate cancer. Patients requiring treatment, and consequently the number of theranostic centers, are expected to increase significantly after Food and Drug Administration and European Medicines Agency approval. This requires standardization/harmonization among theranostic centers. The aim of this study was to assess operational differences and similarities between Lu-PSMA treatment centers.

Methodology

The survey comprised 62 questions including multiple choice and free text format answers and was prepared using Qualtrics XM (Qualtrics, Provo, UT, United States) in a web-based design. The questions were drafted by UCLA investigators and externally reviewed by five international experts in the field of PSMA theranostics (WPF, ME, MH, MR, BH). Once the final version of the questionnaire was outlined, an official e-mail invitation for study participation was sent in June 2022. E-mail recipients included: 1) all centers involved in patient recruitment for the TheraP and VISION trials, 2) PubMed screening for corresponding authors on clinical Lu-PSMA publications, and 3) international contacts of the investigators. Duplicates were removed in order to allow for only one valid response per center. The survey was closed in late September 2022.

Survey structure
The questionnaire involved: 1) general physician and center specific questions, questions on 2) patient selection, 3) radiopharmaceuticals, 4) clinical assessment before and following Lu-PSMA treatments, 5) laboratory values, 6) treatment discontinuation, 7) post-treatment imaging, and 8) general questions.

Data analysis
Survey answers were exported in an Excel spreadsheet and data analyzed. Descriptive analysis was performed using SPSS software (IBM SPSS Statistics. Armonk, NY: IBM Corp).

Results

Geographic location of participating centers

A total of 95 out of 211 (45%) contacted centers completed the questionnaire (Figure 1). Most participating centers were in Europe (48/95, 51%), followed by North- and South-America (21/95, 22%), Asia (21/95, 22%), Oceania (3/95, 3%), and Africa (2/95, 2%). On a national level, Germany (22%), France (12%), Brazil (8%), the United States (7%), India (6%), and China (5%) provided the highest number of participating sites (Figure 2a).

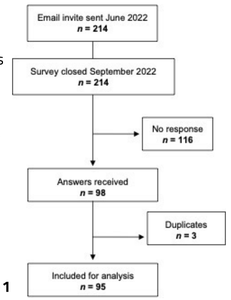
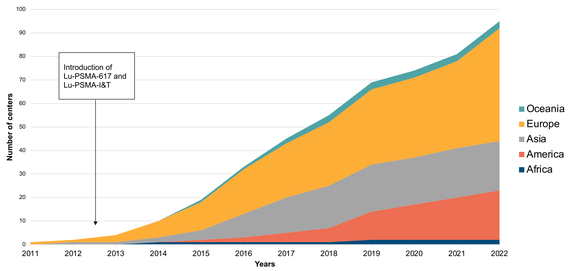


Figure 1

Population characteristics
During the 12 months prior to this study, a total of 5906 patients received Lu-PSMA therapy in the 95 participating centers. Most patients were treated in Europe (2840/5906; 48%), followed by Asia (1313/5906; 22%) and Oceania (1225/5906; 21%) (Figure 2b). Most centers were actively involved in Lu-PSMA through different model of care: Lu-PSMA was given in 84/95 (88%) centers as standard-of-care (SOC) treatment and/or compassionate care access (CCA), in 42/95 (44%) centers as part of industry sponsored clinical trials, and in 21/95 (22%) centers as part of locally approved research protocols (LARP) not sponsored by industry (multiple options of care possible per center, therefore number exceeds 100%. 46/95 (48%) centers only treated patients with mCRPC, whereas 47/95 (49%) centers treated mCRPC and hormone-sensitive prostate cancer (HSPC) patients. 2/95 (2%) centers only treated HSPC.

Initiation of PSMA RLT
Of the participating centers, the first PSMA RLT was performed using I-131-MIP-1095 in 2011. 10/95 (11%) centers started PSMA RLT before 2015, 64/95 (67%) between 2015 and 2020, and 21/95 (22%) between 2021 and 2022. Overall, 50% of centers were already treating patients before 2018. See Figure 3 for increments of PSMA RLT sites per continent.

Figure 3



Pre-treatment imaging and PSMA PET eligibility criteria

Pre-treatment PSMA imaging
PSMA PET and/or PSMA SPECT were performed at all participating centers to assess patient eligibility for Lu-PSMA RLT (Figure 4). 68Ga-PSMA-11 was the most frequently used PET radiotracer (73/95; 77%), followed by 18F-PSMA-1007 (39/95; 41%), 68Ga-PSMA-I&T (21/95; 22%), and 18F-DCFPyL (18/95; 19%). In 12/95 (13%) centers, 99mTc-labeled PSMA for SPECT imaging was sufficient to assess Lu-PSMA RLT eligibility and these were located predominantly in Germany (5/12), Iran (2/12) and Mexico (2/12).

Additional pre-treatment imaging
FDG-PET/CT was performed in 49% centers when Lu-PSMA therapy was provided as SOC, CCA, or LARP not sponsored by industry, and in 26% of centers when patients were enrolled in industry sponsored clinical trials (Figure 4).
Additional pre-therapy imaging included computed tomography (SOC+CCA+LARP 32%, industry sponsored trials 60%), bone scintigraphy (SOC+CCA+LARP 15%, industry sponsored trials 67%), renal scintigraphy (SOC+CCA+LARP 30%, industry sponsored trials 21%), and others (Figure 4). Geographical differences were evident mainly for pre-therapy renal scintigraphy, as for instance part of the eligibility process in 15 of 21 centers in Germany, and Choline-PET, performed in 9 of 11 (82%) centers in France.

PSMA PET eligibility criteria
The most frequently applied PSMA PET eligibility criteria for Lu-PSMA RLT was a subjective visual whole-body tumor PSMA positivity evaluation (33%), followed by assessment of tumor PSMA uptake in comparison to liver defined as majority (>50%) of tumor lesions with uptake > liver (26%), VISION criteria (23%), and TheraP criteria (13%) (Figure 5). No significant differences were observed for applied eligibility criteria between continents.

Figure 5

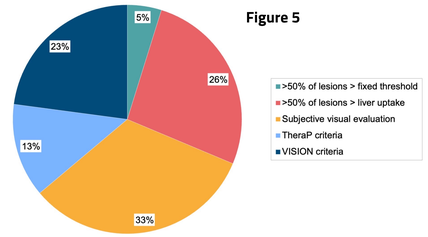


Figure 2

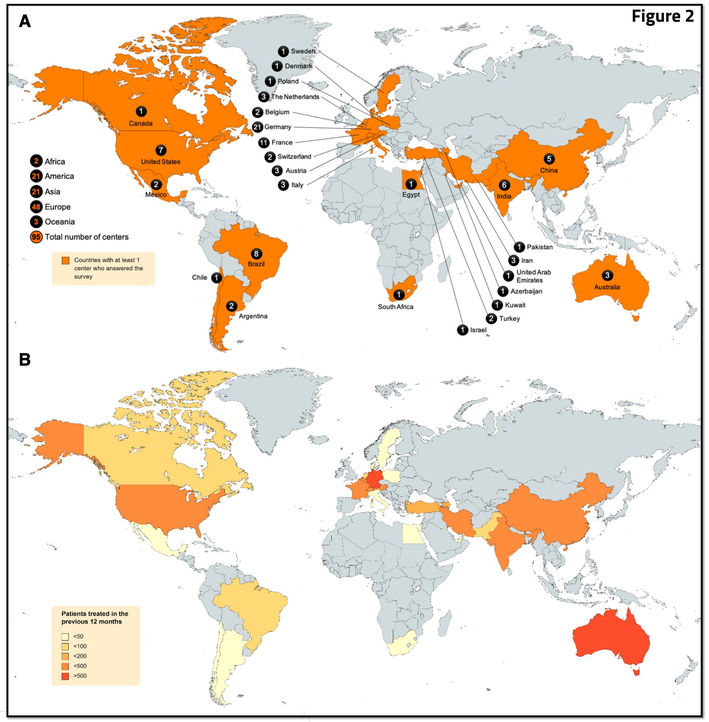


Figure 4

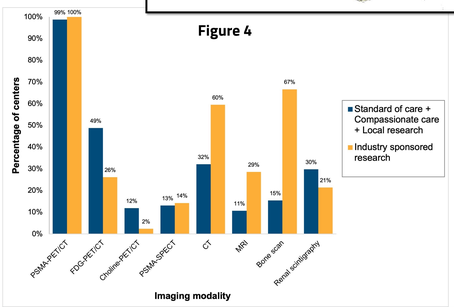
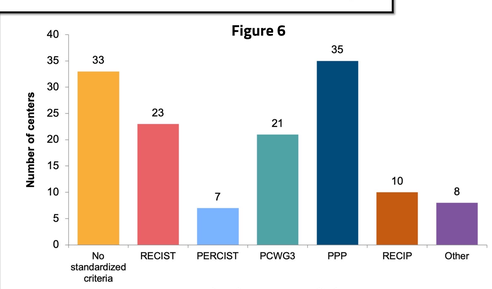


Figure 6



Treatment
Administered radiopharmaceuticals
For RLT agents, 48/95 (51%) centers stated to use 177Lu PSMA-617 only, 21/95 (22%) 177Lu PSMA-I&T only, and 26/95 (27%) both 177Lu PSMA-617 and 177Lu PSMA-I&T. Additionally, 7/95% (7%) were using also other labeled PSMA-targeting agents such as 225Ac-PSMA. Therapy dose and time interval between treatment cycles. Mean standard injected radioactivity per cycle for Lu-PSMA RLT was 7.3 GBq (range 5.5-11.1 GBq). Continent-based subanalysis showed an average injected radioactivity per cycle of 7.5±0.1, 7.3±0.4, 7.5±1.1, 7.1±0.7, and 8.2±0.3 for Africa, America, Asia, Europe and Oceania, respectively. Dose de-escalation was performed in 10/95 (11%) centers. Injected activity was adapted based on bone marrow, salivary gland, renal, or liver function in 50/95 (53%) sites, on the patients' PSMA positive tumor volume in 12/95 (13%), on patient weight in 9/95 (9%), and based on dosimetry measurements in 6/95 (6%) centers.
Most frequent time intervals between Lu-PSMA RLT cycles was 6 weeks in 57/95 (60%), and 8 weeks in 26/95 (27%) centers. 6/95 (7%) centers adapted the time intervals between cycles based on PSA levels and clinical parameters.

Response assessment
Imaging response criteria
The PSMA PET Progression Criteria (PPP) were most frequently applied (35/95; 37%), followed by the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST) (23/95; 24%), the Prostate Cancer Working Group Criteria (PCWG3) (21/95; 22%), the Response Evaluation Criteria in Prostate Cancer 1.0 (RECIP) (10/95; 11%) and the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) (7/95; 7%) (Figure 6). Multiple answers were allowed for this question. 33/95 (35%) centers did not apply standardized radiographic criteria for response assessment.

Lu-PSMA gamma imaging
Post-treatment Lu-PSMA gamma imaging was acquired in 90/95 (95%) of centers. Regarding each treatment cycle, 94% of centers performed Lu-PSMA gamma imaging after the 1st cycle, 87% after the 2nd, 85% after the 3rd and 4th cycle. Whole body planar acquisition was most frequently used (77%), followed by semi-quantitative SPECT with 2 or more beds (37%). Time of Lu-PSMA gamma image acquisition was 4h, 24h, 48h, 72h after injection in 18%, 62%, 32% and 12% of centers, respectively. 10/95 (11%) stated to acquire always at least two different timepoints.

Lu-PSMA RLT reimbursement
Lu-PSMA RLT was completely covered by the healthcare system in 51/95 (54%) centers, while 19/95 (20%) centers reported only partial coverage. No insurance coverage was reported in 25/95 (26%) centers.
Lu-PSMA RLT was performed as an outpatient procedure in 46/95 (48%) centers, and as a 1-, 2-, and 3-day inpatient procedure in 19/95 (20%), 16/95 (17%), and 14/95 (15%) of sites, respectively.

Conclusion

Results from this international survey revealed significant inter-institutional differences regarding multiple aspects of Lu-PSMA RLT, e.g. assessment of eligibility, administered activity and response assessment strategy. In part, this reflects differences in accepted practice standards supported by evolving clinical practice guidelines. Some responses, however, raise concern and highlight the need for theranostic centers, the need for specific training and also the need to improve evidence base as theranostics is widely adopted.

Acknowledgements

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