Original Article
Mol Imaging Radionucl Ther 2022;31:1-6 DOI:10.4274/mirt.galenos.2021.63308

Relative Efficacy of ^{225}Ac-PSMA-617 and ^{177}Lu-PSMA-617 in Prostate Cancer Based on Subcellular Dosimetry

Prostat Kanserinde ^{225}Ac-PSMA-617 ve ^{177}Lu-PSMA-617'nin Subsellüler Dozimetriye Dayalı Göreceli Etkinliği

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Abstract

Objectives: Radionuclide therapy targeting prostate-specific membrane antigen (PSMA) with alpha-emitting ^{225}Ac-PSMA-617 has shown clinical efficacy even in cases of failed therapy with beta-emitting ^{177}Lu-PSMA-617. We investigated the efficacy of ^{225}Ac-PSMA-617 relative to ^{177}Lu-PSMA-617 using subcellular dosimetry.

Methods: A 3-dimensional model of prostate cancer was constructed. For each decay, the absorbed and equivalent radiation dose to the cell nuclei was calculated. The relative efficacy per administered activity was calculated by taking into account the differences in residence time and tumor uptake.

Results: As the tumor size increased, the absorbed dose from ^{225}Ac-PSMA-617 increased linearly (R^2: 0.99) and reached an asymptote near the maximum alpha range (85 µm), whereas the absorbed dose from ^{177}Lu-PSMA-617 continued to increase linearly (R^2: 0.99). The equivalent dose per decay was 2,320, 2,900, and 823-fold higher in favor of ^{225}Ac-PSMA-617 compared to ^{177}Lu-PSMA-617 in a single cell, 100 µm-radius micrometastasis, and macroscopic tumor, respectively. Per administered activity, the relative efficacy of ^{225}Ac-PSMA-617 compared to ^{177}Lu-PSMA-617 in respective tumor sizes was at least 3,480, 4,350, and 1,230-fold higher, and possibly 11,800, 14,900, and 4,200-fold higher considering differences in tumor uptake.

Conclusion: At commonly administered 1,000-fold lower activity of ^{225}Ac-PSMA-617 relative to ^{177}Lu-PSMA-617, the equivalent radiation dose deposited by ^{225}Ac-PSMA-617 is higher in measurable disease and much higher in microscopic disease compared to ^{177}Lu-PSMA-617.

Keywords: Prostate cancer, prostate-specific membrane antigen, radionuclide therapy, dosimetry, alpha particle, beta particle

Öz

Amaç: Alfa yayıcı ^{225}Ac-PSMA-617 ile prostata özgü membran antijenini (PSMA) hedefleyen radyonüklit tedavi, beta yayıcı ^{177}Lu-PSMA-617 ile tedavinin başarısız olduğu durumlarda bile klinik etkinlik göstermiştir. ^{177}Lu-PSMA-617'ye göre ^{225}Ac-PSMA-617'nin etkinliğini, subsellüler dozimetri kullanarak araştırdık.

Yöntem: Prostat kanserinin 3 boyutlu bir modeli oluşturuldu. Her bozunma için hücre çekirdeğine absorbe olan ve eşdeğer radyasyon dozu hesaplandı. Uygulanan aktivite başına göreceli etkinlik, kalış süresi ve tümör tutulumundaki farklılıklar dikkate alınarak hesaplandı.

Bulgular: Tümör boyutu arttıkça, ^{225}Ac-PSMA-617'den absorbe olan doz doğrusal olarak artıp (R^2: 0,99) maksimum alfa aralığına (85 µm) yakın bir asimptota ulaşırken, ^{177}Lu-PSMA-617'den absorbe olan doz doğrusal olarak artmaya devam etti (R^2: 0,99). Bozunma başına eşdeğer doz, tek bir hücrede, 100 µm yarıçaplı mikrometastazda ve makroskopik tümörde, ^{177}Lu-PSMA-617'ye kıyasla ^{225}Ac-PSMA-617 lehine sırasıyla 2.320, 2.900 ve 823 kat daha yüksekti. Uygulanan her aktivite için, ^{177}Lu-PSMA-617'ye kıyasla ^{225}Ac-PSMA-617'nin görece etkinliği ilgili tümör boyutlarında en az 3.480, 4.350 ve 1.230 kat ve tümör alımındaki farklılıklar dikkate alındığında muhtemelen 11.800, 14.900 ve 4.200 kat daha yüksekti.

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Received: 24.08.2021 **Accepted:** 16.10.2021

Sonuç: Genel kullanımda ^{177}Lu-PSMA-617'ye göre 1.000 kat daha düşük aktivitede uygulanan ^{225}Ac-PSMA-617'in oluşturduğu eşdeğer radyasyon dozu, ^{177}Lu-PSMA-617 ile karşılaştırıldığında ölçülebilir hastalıkta ve mikroskobik hastalıkta çok daha yüksektir.

Anahtar kelimeler: Prostat kanseri, prostata özgü membran antijeni, radyonüklid tedavi, dozimetri, alfa parçacığı, beta parçacığı

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) carries a poor prognosis despite multiple approved therapies with antiproliferative, immunologic, and endocrine effects (1). Targeted radionuclide therapy for mCRPC has gained much interest secondary to the development of small molecules and antibodies that target the prostate-specific membrane antigen (PSMA) (2). PSMA is a surface protein that is overexpressed in over 90% of prostate cancer cases, including mCRPC, and is a promising molecular target for radionuclide delivery based on the clinical success of PSMA-targeted imaging (3). PSMA-targeted radionuclide therapy was shown to successfully treat mCRPC with efficacy on both visceral and osseous metastases (4).

The most commonly used radionuclide in PSMA-targeted therapy is the beta emitter ^{177}Lu-PSMA-617 (4). With a half-life of 6.6 days, ^{177}Lu emits low-linear energy transfer (LET) beta particles with a maximum energy of 0.5 MeV and a soft tissue range of 1.7 mm (5). An alternative strategy in PSMA-targeted radionuclide therapy is the use of an alpha emitter such as ^{225}Ac-PSMA-617 (6). Alpha particles deposit MeV-scale energy within <100 μm range as a form of high-LET radiation, efficiently causing double-strand DNA breaks that lead to cytotoxicity (7). Specifically, ^{225}Ac decays with a half-life of 9.9 days to produce four alpha particles with 47-85 μm range (6). While there is relative paucity of pre-clinical and clinical literature on ^{225}Ac-PSMA-617 compared to ^{177}Lu-PSMA-617, the limited available literature on ^{225}Ac-PSMA-617 shows a higher biochemical response rate with survival benefit even among patients who previously failed ^{177}Lu-PSMA-617 therapy (8,9).

Clinical studies that involve ^{177}Lu-PSMA-617 generally have used 4-9 GBq of radioactivity compared to 4-8 MBq for ^{225}Ac-PSMA-617 therapy (6,10). The common use of a 1,000-fold lower dose for ^{225}Ac-PSMA-617 is based on empirical results and extrapolation of organ-level ^{177}Lu-PSMA-617 dosimetry (11,12). From a physics perspective, the required radioactivity of ^{225}Ac-PSMA-617 vs. ^{177}Lu-PSMA-617 to produce a comparable cytotoxic effect on the cellular level remains to be investigated.

The present study used subcellular dosimetry in a 3-dimensional prostate cancer model to calculate the relative efficacy of ^{225}Ac-PSMA-617 vs. ^{177}Lu-PSMA-617 for the delivery of absorbed and equivalent radiation doses to the cell nuclei of a single cell, micrometastasis, and macroscopic tumor. An estimation of the equivalent administered doses for the two radiopharmaceuticals was then performed.

Materials and Methods

Biophysical Modeling

Based on the existing literature, several assumptions were made for modeling the radiolabeled PSMA-617 therapy. Once bound to the PSMA protein on the cell surface, the radiolabeled PSMA-617 molecules were considered internalized (Figure 1A) (13). The activity was then considered uniformly distributed within the cytoplasm, based on the endosomal localization of the intracellular PSMA-radiotherapeutic complex (14).

Each prostate cancer cell was modeled as a sphere that contains a concentric, spherical nucleus (Figure 1B) (15). The cellular and nuclear diameters of 14 and 10 μm were used, respectively, based on the previously published cultured human prostate cancer cell measurements (16). For multicellular dosimetry, prostate cancer cells were considered densely packed in a 3-dimensional face-centered cubic structure with maximal packing efficiency, where each cell was in contact with 12 adjacent cells as previously illustrated (17). The distance between a given cell and each shell of neighboring cells was calculated up to the desired tumor size using a sub-lattice approach (18).

Subcellular Dosimetry

The physical decay data of the ^{225}Ac and ^{177}Lu were obtained from the MIRD Radionuclide Data and Decay Schemes (19). MIRDcell v2.1 (Newark, NJ) was used to obtain the self and cross-dose S values for the decay of ^{225}Ac and ^{177}Lu, including the daughter isotopes of ^{225}Ac (15). The contribution from every cell in the tumor model was considered for cross-dose calculation. The radiation dose to the cell nucleus at the center of the tumor was used to estimate the cytotoxic efficacy for one decay event in each tumor cell. The conversion from absorbed dose to equivalent dose was made using the value of 5 for the relative biological effectiveness (RBE) of alpha particles (11,20).

The equivalent dose per decay was first scaled by the physical half-lives of the radionuclides to account for the

difference in residence time to compare the equivalent dose per administered activity. The difference in the tumor cell uptake per administered activity was estimated by the relative tumor uptake level between ^{225}Ac-PSMA-617 and ^{177}Lu-PSMA-617. The tumor uptake levels were based on the recently published *ex vivo* biodistribution work in the RM-1 mouse model of prostate cancer with 100% PSMA expression (21).

Subcellular dosimetry was first performed in a single cell to compare the relative efficacy of ^{225}Ac-PSMA-617 and ^{177}Lu-PSMA-617 in circulating tumor cells. Then, micrometastatic disease was modeled up to 100 μm diameter. Finally, in a macroscopic tumor (>2 mm radius), the results of subcellular dosimetry were compared against conventional macroscopic dosimetry based on uniform distribution of activity within a spherical volume (Figure 1B).

The study did not involve any statistical analysis.

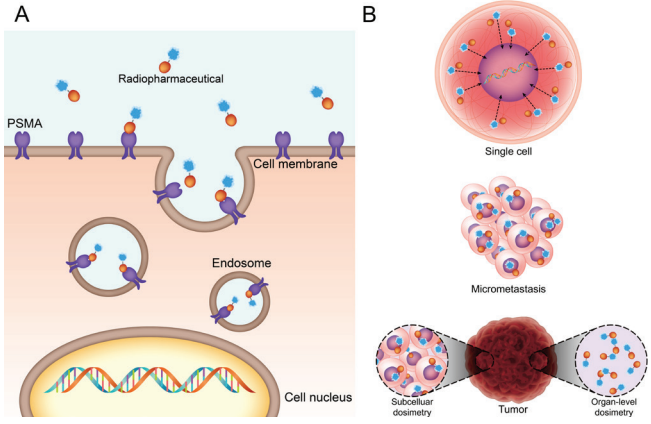

Figure 1. A) A diagram illustrating the uptake of PSMA-targeting radiopharmaceuticals into the cytoplasmic endosomes. B) A densely packed 3-dimensional model of prostate cancer for subcellular dosimetry of PSMA-targeted radionuclide therapy in a single cell, micrometastasis, and macroscopic tumor, with comparison to the conventional organ-level dosimetry in the macroscopic tumor

PSMA: Prostate-specific membrane antigen

Results

Single-cell Dosimetry

For each decay event, ^{225}Ac-PSMA-617 deposited 0.129 Gy in the nucleus resulting in a 464-fold higher absorbed dose compared to ^{177}Lu-PSMA-617, which deposited 2.78×10^{-4} Gy. The equivalent dose per decay was 2,320-fold higher in favor of ^{225}Ac-PSMA-617 taking into account the RBE of 5.

Micrometastasis

As the size of the micrometastasis increased, the absorbed dose from ^{225}Ac-PSMA-617 initially linearly increased up to approximately 50 μm in radius (R^2: 0.99), and then reached an asymptote at approximately 85 μm to reach 2.06 Gy per decay in each tumor cell (Figure 2A). In comparison, the absorbed dose from ^{177}Lu-PSMA-617 continued to increase linearly (R^2: 0.99) with the tumor size and reached 3.55×10^{-3} Gy per decay at 100 μm radius (Figure 2B). In relative scale, the equivalent dose per decay was over 4,000-fold higher for ^{225}Ac-PSMA-617 compared to ^{177}Lu-PSMA-617 up to 60 μm radius (Figure 2C). As the tumor size increased, the relative dose difference between the

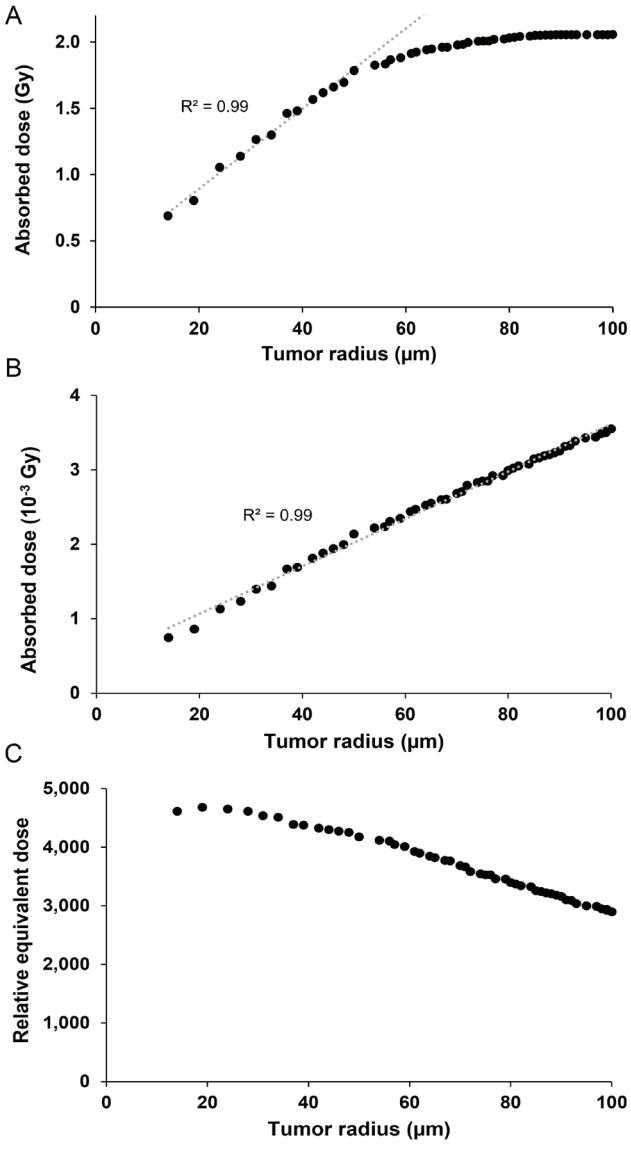

Figure 2. Radiation dose deposition per decay/cell in micrometastases of various sizes by ^{225}Ac-PSMA-617 (A) and ^{177}Lu-PSMA-617 (B), with relative equivalent dose comparison (^{225}Ac: ^{177}Lu) (C)

PSMA: Prostate-specific membrane antigen

two radiopharmaceuticals gradually decreased, reaching a 2,900-fold difference at 100 μm tumor radius.

Macroscopic Tumor

The absorbed dose per decay in each tumor cell was 165-fold higher for ^{225}Ac-PSMA-617 (2.06 Gy) compared to ^{177}Lu-PSMA-617 (1.25×10^{-2} Gy), which translated to an 823-fold difference in equivalent dose with RBE of 5, based on subcellular dosimetry. Using the conventional dosimetry, ^{225}Ac-PSMA-617 and ^{177}Lu-PSMA-617 deposited 2.25 Gy and 1.26×10^{-2} Gy per decay, resulting in a 178-fold and 892-fold difference in the absorbed and equivalent doses, respectively.

Relative Equivalent Dose Per Administered Activity

The longer physical half-life of ^{225}Ac conferred 50% longer residence time to ^{225}Ac-PSMA-617 compared to ^{177}Lu-PSMA-617. After scaling using this factor, the relative differences in equivalent dose per administered activity (^{225}Ac-PSMA-617 vs. ^{177}Lu-PSMA-617) were 3,480-fold, 4,350-fold, and 1,230-fold for a single cell, 100 μm-radius micrometastasis, and macroscopic tumor, respectively. Then, using 3.4 times higher uptake per administered activity for ^{225}Ac-PSMA-617 (4.66% injected dose/g of tumor) compared to ^{177}Lu-PSMA-617 (1.36% injected dose/g of tumor) (21), the relative differences in equivalent dose per administered activity (^{225}Ac-PSMA-617 vs. ^{177}Lu-PSMA-617) were 11,800-fold, 14,900-fold, and 4,200-fold for a single cell, 100 μm-radius micrometastasis, and macroscopic tumor, respectively.

Discussion

Dosimetry using imaging-based measurements of ^{225}Ac-PSMA-617 uptake is challenging due to the low administered activity and unfavorable physical decay characteristics of ^{225}Ac with low gamma emission probability and the competing Bremsstrahlung radiation (11). Therefore, previous dosimetry on ^{225}Ac-PSMA-617 and ^{225}Ac-PSMA-I&T extrapolated the uptake of respective ^{177}Lu-labeled analogs on imaging (11,12,22). Alternatively, extrapolation of ^{68}Ga-PSMA-617 uptake on positron emission tomography was previously used for dosimetry of ^{213}Bi-PSMA-617 (20). However, recent studies have shown that the degree of radiolabeled PSMA-617 uptake differs based on the radionuclide (23,24), which suggests that independent characterization of ^{225}Ac-PSMA-617 uptake will improve its dosimetry. At present, the only study that examined the tumor uptake of ^{225}Ac-PSMA-617 and ^{177}Lu-PSMA-617 is the pre-clinical study by Current et al. (21), where *ex vivo* activity measurements were used for accurate uptake estimation. The study was based on a mouse model without human validations, thus we considered the 3.4-fold higher ^{225}Ac-PSMA-617 uptake only as a possibility and interpreted the unscaled results as the lower bound of the relative efficacy of ^{225}Ac-PSMA-617.

Conventional organ-level dosimetry fails to take into consideration the subcellular distribution of the radiopharmaceutical even if accurate tumor uptake measurements could be obtained. It leads to radiation dose overestimation for an alpha emitter with cytoplasmic localization, such as ^{225}Ac-PSMA-617, and underestimation for an alpha emitter with nuclear localization. In addition, organ-level dosimetry cannot be applied to microscopic tumor deposits that are smaller than the range of alpha or beta particles. In contrast, the dosimetry model used in the present study incorporates the subcellular location of a radiopharmaceutical for accurate estimation of alpha and beta radiation dose at all tumor sizes of interest.

Two observations of interest were made in a macroscopic tumor. First, ^{225}Ac-PSMA-617 delivered at least 1,230-fold higher and possibly 4,200-fold higher equivalent dose per administered activity compared to ^{177}Lu-PSMA-617, which may explain the better efficacy of ^{225}Ac-PSMA-617 when 1,000-fold lower activity was administered in the clinical setting and even with subsequent de-escalation to 4 MBq doses (8,25). Second, conventional macroscopic dosimetry calculation resulted in no difference for ^{177}Lu-PSMA-617 and overestimation by 9% for ^{225}Ac-PSMA-617 compared to the subcellular dosimetry estimates of the radiation dose to the cell nuclei. The cross-fire effect of beta particles resulted in normalization of radiation dose within the tumor regardless of the subcellular source location for ^{177}Lu-PSMA-617, whereas the subcellular dose estimation for ^{225}Ac-PSMA-617 was slightly lower due to the absence of alpha emission from the cell nucleus. For both ^{225}Ac-PSMA-617 and ^{177}Lu-PSMA-617 therapy, conventional organ-level dosimetry yields acceptable dose estimates in measurable tumors.

In micrometastatic disease and circulating tumor cells, the alpha particles from ^{225}Ac-PSMA-617 were far more potent than beta particles from ^{177}Lu-PSMA-617, resulting in at least 3,000-4,000 times and possibly 10^4 times higher efficacy per administered activity. The findings are in keeping with the recognized advantage of alpha radiation in killing single cells and micrometastatic clusters (7). Therefore, at currently used doses, ^{225}Ac-PSMA-617 likely exerts a stronger cytotoxic effect on radiologically occult metastases, which will otherwise survive ^{177}Lu-PSMA-617 treatment due to insufficient cross-fire effect. While the therapeutic effect on micrometastatic disease may not produce a large decline in PSA, it potentially contributes

to the overall survival and progression-free survival benefits that are seen in ^{225}Ac-PSMA-617 therapy (8,9).

The calculated relative efficacy values can be applied to estimate the dose contribution from each radionuclide in the setting of tandem therapy with ^{225}Ac-PSMA-617/^{177}Lu-PSMA-617. For example, in a previously used treatment regimen that involves the median activities of 5.3 MBq ^{225}Ac-PSMA-617 and 6.9 GBq ^{177}Lu-PSMA-617, the dose contribution of ^{225}Ac-PSMA-617 relative to ^{177}Lu-PSMA-617 would be at least 94% for a macroscopic tumor. The contribution would increase to at least 270% and 330% for a single cell and micrometastatic cluster, respectively. The present study focused on radiolabeled PSMA-617 due to the larger body of available literature, but the results can be applied to dosimetry of PSMA-targeted radionuclide therapy using other molecules such as ^{225}Ac/^{177}Lu-PSMA-I&T.

The present study used physical dose estimates for comparison of theoretical efficacy, but its translation to clinical efficacy would be affected by differences in the radiobiological effects of alpha and beta particles. For example, untargeted effects, such as bystander or abscopal effect, may modify the dose-efficacy relationship by different degrees for alpha and beta particles (26). Direct DNA damage due to high-LET alpha particles does not require the presence of oxygen, whereas hypoxia has a high impact on low-LET radiation, which relies on reactive oxygen species formation for cytotoxicity (27,28). In addition, cytotoxicity due to high-LET radiation was previously shown to be independent of dose rate, likely due to the difficulty in repairing complex double-strand DNA breaks (29). Proliferating cells are more susceptible to ionizing radiation in general, but the cell cycle status of target cells affects the efficacy of low- and high-LET radiation to different extents (30). Beyond radiobiological considerations, increased tumor cell death may not necessarily produce a meaningfully better disease response or survival benefit on a patient level. Therefore, much remains to be known about the downstream consequences beyond radiation dose deposition in radionuclide therapy of prostate cancer.

Study Limitations

In addition to the difficulty in tumor ^{225}Ac-PSMA-617 uptake estimation, our study has several limitations. Mainly, the assumptions made in the simplified dosimetry model may be challenged. Intra-tumor heterogeneity in PSMA expression has been reported (31), and variable non-spherical shapes of prostate cancer cells were previously described (16). When ^{225}Ac decays before the internalization into endosomes, the daughter isotopes are no longer linked to PSMA-617 due to the recoil energy of alpha decay, which results in reduced dose deposition to the target cell (32). Radiation dose deposition outside the cell nucleus can also result in cytotoxicity by indirect effects (33). The RBE of 5 for alpha radiation is commonly employed (11,20) and is an oversimplification as discussed above, lacking validation in the setting of ^{225}Ac-based therapy in prostate cancer. Finally, the study does not address the toxicity that is associated with PSMA-targeted radionuclide therapy, which is not necessarily PSMA-mediated (34).

Conclusion

The equivalent radiation dose deposited by alpha-emitting ^{225}Ac-PSMA-617 is higher in measurable disease and especially higher in microscopic disease compared to beta-emitting ^{177}Lu-PSMA-617 at commonly administered doses based on subcellular dosimetry. Possible differences in tumor uptake based on the labeled radionuclide can lead to further amplification of the relative efficacy of ^{225}Ac-PSMA-617. Additional research is needed for tumor ^{225}Ac-PSMA-617 uptake characterization on both macroscopic and microscopic levels, as well as for an improved understanding of the biological effectiveness of alpha radiation in prostate cancer.

Ethics

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Peer-review: Externally and internally peer-reviewed.

Financial Disclosure: The author declared that this study has received no financial support.

References

1. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Hurwitz M, Ippolito JE, Kane CJ, Kuettel MR, Lang JM, McKenney J, Netto G, Penson DF, Plimack ER, Pow-Sang JM, Pugh TJ, Richey S, Roach M, Rosenfeld S, Schaeffer E, Shabsigh A, Small EJ, Spratt DE, Srinivas S, Tward J, Shead DA, Freedman-Cass DA. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17:479-505.
2. Sadaghiani MS, Sheikhbahaei S, Werner RA, Pienta KJ, Pomper MG, Solnes LB, Gorin MA, Wang NY, Rowe SP. A systematic review and meta-analysis of the effectiveness and toxicities of lutetium-177-labeled Prostate-specific membrane antigen-targeted radioligand therapy in metastatic castration-resistant prostate cancer. Eur Urol 2021;80:82-94.
3. Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-specific membrane antigen PET: clinical utility in prostate cancer, normal patterns, pearls, and pitfalls. Radiographics 2018;38:200-217.
4. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G, Park CH, Beer TM, Armour A, Pérez-Contreras WJ, DeSilvio M, Kpamegan E, Gericke G, Messmann

RA, Morris MJ, Krause BJ. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2021;385:1091-1103.

5. Hosono M, Ikebuchi H, Nakamura Y, Nakamura N, Yamada T, Yanagida S, Kitaoka A, Kojima K, Sugano H, Kinuya S, Inoue T, Hatazawa J. Manual on the proper use of lutetium-177-labeled somatostatin analogue (Lu-177-DOTA-TATE) injectable in radionuclide therapy (2nd ed.). Ann Nucl Med 2018;32:217-235.
6. Juzeniene A, Stenberg VY, Bruland ØS, Larsen RH. Preclinical and clinical status of PSMA-targeted alpha therapy for metastatic castration-resistant prostate cancer. Cancers (Basel) 2021;13:779.
7. Makvandi M, Lee H, Puentes LN, Reilly SW, Rathi KS, Weng CC, Chan HS, Hou C, Raman P, Martinez D, Xu K, Carlin SD, Greenberg RA, Pawel BR, Mach RH, Maris JM, Pryma DA. Targeting PARP-1 with alpha-particles is potently cytotoxic to human neuroblastoma in preclinical models. Mol Cancer Ther 2019;18:1195-1204.
8. Sathekge M, Bruchertseifer F, Vorster M, Lawal IO, Knoesen O, Mahapane J, Davis C, Reyneke F, Maes A, Kratochwil C, Lengana T, Giesel FL, Van de Wiele C, Morgenstern A. Predictors of overall and disease-free survival in metastatic castration-resistant prostate cancer patients receiving 225Ac-PSMA-617 radioligand therapy. J Nucl Med 2020;61:62-69.
9. Feuerecker B, Tauber R, Knorr K, Heck M, Beheshti A, Seidl C, Bruchertseifer F, Pickhard A, Gafita A, Kratochwil C, Retz M, Gschwend JE, Weber WA, D'Alessandria C, Morgenstern A, Eiber M. Activity and adverse events of actinium-225-PSMA-617 in advanced metastatic castration-resistant prostate cancer after failure of lutetium-177-PSMA. Eur Urol 2021;79:343-350.
10. von Eyben FE, Roviello G, Kiljunen T, Uprimny C, Virgolini I, Kairemo K, Joensuu T. Third-line treatment and 177Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review. Eur J Nucl Med Mol Imaging 2018;45:496-508.
11. Kratochwil C, Bruchertseifer F, Rathke H, Bronzel M, Apostolidis C, Weichert W, Haberkorn U, Giesel FL, Morgenstern A. Targeted α-therapy of metastatic castration-resistant prostate cancer with 225Ac-PSMA-617: dosimetry estimate and empiric dose finding. J Nucl Med 2017;58:1624-1631.
12. Belli ML, Sarnelli A, Mezzenga E, Cesarini F, Caroli P, Di Iorio V, Strigari L, Cremonesi M, Romeo A, Nicolini S, Matteucci F, Severi S, Paganelli G. Targeted alpha therapy in mCRPC (metastatic castration-resistant prostate cancer) patients: predictive dosimetry and toxicity modeling of 225Ac-PSMA (prostate-specific membrane antigen). Front Oncol 2020;10:531660.
13. Kratochwil C, Bruchertseifer F, Giesel FL, Weis M, Verburg FA, Mottaghy F, Kopka K, Apostolidis C, Haberkorn U, Morgenstern A. 225Ac-PSMA-617 for PSMA-targeted α-radiation therapy of metastatic castration-resistant prostate cancer. J Nucl Med 2016;57:1941-1944.
14. Bavelaar BM, Lee BQ, Gill MR, Falzone N, Vallis KA. Subcellular targeting of theranostic radionuclides. Front Pharmacol 2018;9:996.
15. Vaziri B, Wu H, Dhawan AP, Du P, Howell RW; SNMMI MIRD Committee. MIRD pamphlet No. 25: MIRDcell V2.0 software tool for dosimetric analysis of biologic response of multicellular populations. J Nucl Med 2014;55:1557-1564.
16. Park S, Ang RR, Duffy SP, Bazov J, Chi KN, Black PC, Ma H. Morphological differences between circulating tumor cells from prostate cancer patients and cultured prostate cancer cells. PLoS One 2014;9:e85264.
17. Lee H, Riad A, Martorano P, Mansfield A, Samanta M, Batra V, Mach RH, Maris JM, Pryma DA, Makvandi M. PARP-1-targeted auger emitters display high-LET cytotoxic properties in vitro but show limited therapeutic utility in solid tumor models of human neuroblastoma. J Nucl Med 2020;61:850-856.
18. Wiley JD, Seman JA. The enumeration of neighbors on cubic and hexagonal-based lattices. Bell Syst Tech J 1970;49:355-378.
19. Eckerman K, Endo A. MIRD: radionuclide data and decay schemes 2nd edn (Reston, VA: Society for Nuclear Medicine). Published online 2008.
20. Kratochwil C, Schmidt K, Afshar-Oromieh A, Bruchertseifer F, Rathke H, Morgenstern A, Haberkorn U, Giesel FL. Targeted alpha therapy of mCRPC: dosimetry estimate of (213)Bismuth-PSMA-617. Eur J Nucl Med Mol Imaging 2018;45:31-37.
21. Current K, Meyer C, Magyar CE, Mona CE, Almajano J, Slavik R, Stuparu AD, Cheng C, Dawson DW, Radu CG, Czernin J, Lueckerath K. Investigating PSMA-targeted radioligand therapy efficacy as a function of cellular PSMA levels and intratumoral PSMA heterogeneity. Clin Cancer Res 2020;26:2946-2955.
22. Gosewisch A, Schleske M, Gildehaus FJ, Berg I, Kaiser L, Brosch J, Bartenstein P, Todica A, Ilhan H, Böning G. Image-based dosimetry for (225)Ac-PSMA-I&T therapy using quantitative SPECT. Eur J Nucl Med Mol Imaging 2021;48:1260-1261.
23. Sinnes JP, Bauder-Wüst U, Schäfer M, Moon ES, Kopka K, Rösch F. (68)Ga, (44)Sc and (177)Lu-labeled AAZTA(5)-PSMA-617: synthesis, radiolabeling, stability and cell binding compared to DOTA-PSMA-617 analogues. EJNMMI Radiopharm Chem 2020;5:28.
24. Umbricht CA, Benešová M, Schmid RM, Türler A, Schibli R, van der Meulen NP, Müller C. (44)Sc-PSMA-617 for radiotheragnostics in tandem with (177)Lu-PSMA-617-preclinical investigations in comparison with (68)Ga-PSMA-11 and (68)Ga-PSMA-617. EJNMMI Res 2017;7:9.
25. Sathekge M, Bruchertseifer F, Knoesen O, Reyneke F, Lawal I, Lengana T, Davis C, Mahapane J, Corbett C, Vorster M, Morgenstern A. (225)Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study. Eur J Nucl Med Mol Imaging 2019;46:129-138.
26. Boyd M, Ross SC, Dorrens J, Fullerton NE, Tan KW, Zalutsky MR, Mairs RJ. Radiation-induced biologic bystander effect elicited in vitro by targeted radiopharmaceuticals labeled with alpha-, beta-, and auger electron-emitting radionuclides. J Nucl Med 2006;47:1007-1015.
27. Barendsen GW, Koot CJ, Van Kersen GR, Bewley DK, Field SB, Parnell CJ. The effect of oxygen on impairment of the proliferative capacity of human cells in culture by ionizing radiations of different LET. Int J Radiat Biol Relat Stud Phys Chem Med 1966;10:317-327.
28. Wenzl T, Wilkens JJ. Theoretical analysis of the dose dependence of the oxygen enhancement ratio and its relevance for clinical applications. Radiat Oncol 2011;6:171.
29. Wozny AS, Alphonse G, Battiston-Montagne P, Simonet S, Poncet D, Testa E, Guy JB, Rancoule C, Magné N, Beuve M, Rodriguez-Lafrasse C. Influence of dose rate on the cellular response to low- and High-LET radiations. Front Oncol 2016;6:58.
30. Lyckesvärd MN, Delle U, Kahu H, Lindegren S, Jensen H, Bäck T, Swanpalmer J, Elmroth K. Alpha particle induced DNA damage and repair in normal cultured thyrocytes of different proliferation status. Mutat Res 2014;765:48-56.
31. Brady L, Kriner M, Coleman I, Morrissey C, Roudier M, True LD, Gulati R, Plymate SR, Zhou Z, Birditt B, Meredith R, Geiss G, Hoang M, Beechem J, Nelson PS. Inter- and intra-tumor heterogeneity of metastatic prostate cancer determined by digital spatial gene expression profiling. Nat Commun 2021;12:1426.
32. Kruijff RM, Raavé R, Kip A, Molkenboer-Kuenen J, Morgenstern A, Bruchertseifer F, Heskamp S, Denkova AG. The in vivo fate of (225)Ac daughter nuclides using polymersomes as a model carrier. Sci Rep 2019;9:11671.
33. Ku A, Facca VJ, Cai Z, Reilly RM. Auger electrons for cancer therapy - a review. EJNMMI Radiopharm Chem 2019;4:27.
34. Rupp NJ, Umbricht CA, Pizzuto DA, Lenggenhager D, Töpfer A, Müller J, Muehlematter UJ, Ferraro DA, Messerli M, Morand GB, Huber GF, Eberli D, Schibli R, Müller C, Burger IA. First clinicopathologic evidence of a non-PSMA-related uptake mechanism for (68)Ga-PSMA-11 in salivary Glands. J Nucl Med 2019;60:1270-1276.