

Bölüm 37

PROSTAT KANSERİNDE HEDEFE YÖNELİK RADYONÜKLİD TEDAVİLER

Duygu HAS ŞİMŞEK¹

GİRİŞ

Prostat kanseri (PK) dünyada erkeklerde görülen en sık tümör olup kansere bağlı ölümlerde ilk sıralarda yer almaktadır (1). Tarama yöntemlerinin yaygınlaşması ile hastaların çoğunda tanı anında lokalize hastalık izlenmekle birlikte takip eden dönemlerde hastaların %35'inde uzak metastaz görülebilmektedir (2). Metastatik hastalıkta androjen deprivasyon tedavisi altında progresyon gelişen hastalar metastatik kastrasyona dirençli prostat kanseri (mKDPK) tanısı almaktadırlar. Kastrasyona direnç gelişiminin sağkalım üzerinde belirgin negatif etkisi olup mKDPK tanılı hastalarda sağkalım 14 aya kadar düşmektedir (3). Bu aşamada taksan içerikli sistemik kemoterapiler öncelikli olarak kullanılmakla birlikte, sağkalım avantajı sınırlı süre devam etmekte ve nispeten yüksek yan etkileri nedeniyle yeni tedavi yöntemlerine ihtiyaç duyulmaktadır (4). Yeni geliştirilen ajanlardan abirateron ve enzalutamide, androjen sentezini bloke ederek sağkalım sürelerini 12.5 ile 18.4 aya kadar artırmaktadır (5, 6). Tedaviye yanıtı olmayan hastalarda alternatif tedavi seçeneği olarak immunoterapi ajanlarından T-Sipuleucel de kullanılmakta olup plasebo grubuna göre 4.1 aylık sağkalım avantajı gösterilmiştir (7). Ancak tüm bu tedavi seçeneklerine rağmen tedaviye yanıt vermeyen mKDPK hastalarının sayısı azımsanmayacak ölçüdedir. Bu aşamada hedefe yönelik radyonüklid tedaviler söz konusu olup, ülkemizde ve dünyada ¹⁷⁷Lu-PSMA, ²²⁵Ac-PSMA, ¹⁵³Sm-E-

DTMP, ¹⁸⁶Re-HEDP, ¹⁷⁷Lu-EDTMP ve ²²³Ra-diklorid tedavileri başarılı sonuçları ile giderek artan sayılarda uygulanmaktadır.

Hedefe yönelik radyonüklid tedavilerde beta veya alfa ışınlarından yararlanılmaktadır. Prostat kanserinde en sık uygulanan radyonüklid tedavi olan ¹⁷⁷Lu-PSMA tedavisinde ¹⁷⁷Lu izotopuna ait beta ışınları, daha az sayıda uygulanan ²²⁵Ac-PSMA tedavisinde ise ²²⁵Ac izotopuna ait alfa ışınları PSMA hedef molekülü ile birleştirilerek metastatik odaklara yüksek doz internal radyoterapi (RT) uygulanabilmektedir. PSMA bir transmembran glikoproteini olup normal prostat epitel hücreleri ile karşılaştırıldığında prostat kanseri metastazlarında 1000 kata varan artmış ekspresyonu saptanmış, vakaların %90'ında metastazların PSMA ekspresyonu gösterdiği bildirilmiştir (8, 9).

PSMA hedefli tedaviler tüm doku ve organ metastazlarını hedef almasına rağmen ¹⁵³Sm-EDTMP, ¹⁸⁶Re-HEDP, ¹⁷⁷Lu-EDTMP ve ²²³Ra-diklorid tedavileri yalnızca kemik metastazlarını kapsamaktadır. Prostat kanserinde sıklıkla osteoblastik kemik metastazları görüldüğünden kemik yapımına katılan kalsiyum ile kimyasal açıdan benzerlik gösteren ²²³Ra-diklorid ya da organik fosfatlar ile şelat oluşturan ¹⁵³Sm-EDTMP, ¹⁸⁶Re-HEDP, ¹⁷⁷Lu-EDTMP radyonüklidleri tedavide kullanılmaktadır. Bu radyonüklidler osteoblastik kemik metastazları içerisinde ve çevresinde oluşan yeni kemik dokuda osteoblastik aktivitenin yoğunluğu ile orantılı tutulmakta ve radyoterapötik etki göstermektedir.

tır (66). 2 kür ^{186}Re -HEDP alan hastalarda ağrı palyasyonun 1 kür alan gruptan daha iyi olduğu, her iki grupta hematolojik toksisitenin benzer olduğu bildirilmiştir. Ayrıca 2 kür tedavi alan hastaların %39'unda %50'den fazla PSA yanıtı izlenirken bu oran 1. Kür alan hastalarda %7 olarak raporlanmıştır. Progresyonsuz sağkalım ve genel sağkalım 2 kür ^{186}Re -HEDP alan grupta 7 ay ve 12.7 ay iken 1.kür ^{186}Re -HEDP alan grupta 2.3 ay ve 7 ay olarak belirtilmiştir. ^{186}Re -HEDP, ^{153}Sm -EDTMP ile benzer tedavi etkinliği ve toksisite profiline sahip olmakla birlikte iyi tasarlanmış faz-3 çalışması bulunmaması nedeniyle FDA onayı alınamamış olup sıklıkla Avrupa'da uygulanmaktadır.

Son yıllarda lojistik ve ekonomik avantajı nedeniyle ^{177}Lu -EDTMP tedavisinin klinik kullanımı ve yayınlanan çalışma sayısı hızla artış göstermektedir. Ağrı palyasyonun vizüel, analjezik ve Karnofsky performans skorlaması ile değerlendirildiği faz-2 çalışmasında ^{177}Lu -EDTMP tedavisi alan metastatik prostat kanseri tanılı hastalar tedavi sonrası 16 hafta takip edilerek tedavi yanıtları raporlanmıştır (30). Prostat kanseri tanılı hastalarda genel tedavi yanıtı %84 iken, visüel ağrı ve analjezik skorunun belirgin azaldığı, Karnofsky skorlarının ise artış gösterdiği bildirilmiştir. ^{153}Sm -EDTMP ve ^{177}Lu -EDTMP tedavisinin karşılaştırıldığı bir başka çalışmada, hastaların yarısı ^{153}Sm -EDTMP ile diğer yarısı ^{177}Lu -EDTMP ile tedavi edilmiş ve tedavi sonrası vizüel, analjezik ve Karnofsky performans skorları karşılaştırılmıştır (67). ^{177}Lu -EDTMP tedavisi alan hastaların %80'inde ağrı yanıtı izlenirken, ^{153}Sm -EDTMP tedavisi alan hastaların %75'inde ağrı yanıtı görülmüştür. Her iki tedavi grubunda da yaşam kalitesinin düzeldiği, Karnofsky skorlarının anlamlı olarak arttığı gösterilmiştir. Kemik proliferasyon göstergeleri iki grupta da belirgin azalırken, benzer şekilde sınırlı hematolojik toksisite bildirilmiştir.

SONUÇ

Prostat kanserinde hedefe yönelik radyonüklid tedaviler düşük yan etki profili ve yüksek tedavi etkinliği ile multiple sistemik tedavi öyküsü olan hastalarda bile güvenle kullanılabilir. Yapılan çalışma sonuçları kombine tedaviler ile uygulandığında radyonüklid tedavilerin başarısının arttığını göstermektedir. Metastatik hastalığın bi-

yolojisi, tümörlerin dağılımı ve hasta profili göz önüne alınarak hedefe yönelik radyonüklid tedavi seçimi ile kişiye özel tedavi rejimleri uygulanmalıdır.

Anahtar Kelimeler: Radyonüklid, tedavi, prostat,

KAYNAKÇA

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA: a cancer journal for clinicians. 2017;67(1):7-30.
2. Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Human pathology. 2000;31(5):578-83.
3. Kirby M, Hirst C, Crawford E. Characterising the castration-resistant prostate cancer population: a systematic review. International journal of clinical practice. 2011;65(11):1180-92.
4. Sartor AO, Oudard S, Sengelov L, Daugaard G, Saad F, Hansen S, et al. Cabazitaxel vs docetaxel in chemotherapy-naïve (CN) patients with metastatic castration-resistant prostate cancer (mCRPC): A three-arm phase III study (FIRSTANA). American Society of Clinical Oncology; 2016.
5. De Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. New England Journal of Medicine. 2011;364(21):1995-2005.
6. Beer TM, Armstrong AJ, Rathkopf D, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. European urology. 2017;71(2):151-4.
7. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. New England Journal of Medicine. 2010;363(5):411-22.
8. Slovin SF. Targeting novel antigens for prostate cancer treatment: focus on prostate-specific membrane antigen. Expert opinion on therapeutic targets. 2005;9(3):561-70.
9. Wright Jr GL, Haley C, Beckett ML, Schellhammer PF, editors. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urologic Oncology: Seminars and Original Investigations; 1995: Elsevier.
10. Ritter MA, Cleaver JE, TOBIAS CA. High-LET radiations induce a large proportion of non-rejoining DNA breaks. Nature. 1977;266(5603):653.
11. Kratochwil C, Fendler WP, Eiber M, Baum R, Bozkurt MF, Czernin J, et al. EANM procedure guidelines for radionuclide therapy with (177)Lu-labelled PSMA-ligands ((177)Lu-PSMA-RLT). Eur J Nucl Med Mol Imaging. 2019 Aug 22. PubMed PMID: 31440799. Epub 2019/08/24. eng.
12. Kratochwil C, Bruchertseifer F, Giesel FL, Weis M, Verburg FA, Mottaghy F, et al. 225Ac-PSMA-617 for PSMA-targeted α -radiation therapy of metastatic castration-resistant prostate cancer. Journal of Nuclear Medicine. 2016;57(12):1941-4.

13. Kratochwil C, Bruchertseifer F, Rathke H, Hohenfellner M, Giesel FL, Haberkorn U, et al. Targeted α -therapy of metastatic castration-resistant prostate cancer with ^{225}Ac -PSMA-617: swimmer-plot analysis suggests efficacy regarding duration of tumor control. *Journal of Nuclear Medicine*. 2018;59(5):795-802.
14. Network NCC. NCCN Clinical practice guidelines in oncology: prostate cancer. Version 4.2018. 2018.
15. Poeppel TD, Handkiewicz-Junak D, Andreeff M, Beccherer A, Bockisch A, Fricke E, et al. EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer. *European journal of nuclear medicine and molecular imaging*. 2018;45(5):824-45.
16. Smith M, Parker C, Saad F, Miller K, Tombal B, Ng QS, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2019;20(3):408-19.
17. Bodei L, Lam M, Chiesa C, Flux G, Brans B, Chiti A, et al. EANM procedure guideline for treatment of refractory metastatic bone pain. *European journal of nuclear medicine and molecular imaging*. 2008;35(10):1934.
18. Ahmadzadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with ^{177}Lu -PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget*. 2016;7(11):12477.
19. Yordanova A, Becker A, Eppard E, Kürpig S, Fisang C, Feldmann G, et al. The impact of repeated cycles of radioligand therapy using [^{177}Lu] Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. *European journal of nuclear medicine and molecular imaging*. 2017;44(9):1473-9.
20. Hohberg M, Eschner W, Schmidt M, Dietlein M, Kobe C, Fischer T, et al. Lacrimal glands may represent organs at risk for radionuclide therapy of prostate cancer with [^{177}Lu] DKFZ-PSMA-617. *Molecular Imaging and Biology*. 2016;18(3):437-45.
21. Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, et al. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *The Lancet Oncology*. 2018;19(6):825-33.
22. Weineisen M, Schottelius M, Simecek J, Baum RP, Yildiz A, Beykan S, et al. ^{68}Ga - and ^{177}Lu -Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2015 Aug;56(8):1169-76. PubMed PMID: 26089548. Epub 2015/06/20. eng.
23. Yordanova A, Becker A, Eppard E, Kürpig S, Fisang C, Feldmann G, et al. The impact of repeated cycles of radioligand therapy using [(177)Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. *European journal of nuclear medicine and molecular imaging*. 2017 Aug;44(9):1473-9. PubMed PMID: 28337529. Epub 2017/03/25. eng.
24. Fendler WP, Reinhardt S, Ilhan H, Delker A, Boning G, Gildehaus FJ, et al. Preliminary experience with dosimetry, response and patient reported outcome after ^{177}Lu -PSMA-617 therapy for metastatic castration-resistant prostate cancer. *Oncotarget*. 2017 Jan 10;8(2):3581-90. PubMed PMID: 27683041. Pubmed Central PMCID: PMC5356905. Epub 2016/09/30. eng.
25. Baum RP, Kulkarni HR, Schuchardt C, Singh A, Wirtz M, Wiessalla S, et al. ^{177}Lu -Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2016 Jul;57(7):1006-13. PubMed PMID: 26795286. Epub 2016/01/23. eng.
26. Violet JA, Jackson P, Ferdinandus J, Sandhu S, Akhurst T, Iravani A, et al. Dosimetry of Lu-177 PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pre-therapeutic imaging and "whole body" tumor dosimetry with treatment outcomes. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2018 Oct 5. PubMed PMID: 30291192. Epub 2018/10/07. eng.
27. Rahbar K, Ahmadzadehfar H, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German multicenter study investigating ^{177}Lu -PSMA-617 radioligand therapy in advanced prostate cancer patients. *Journal of Nuclear Medicine*. 2017;58(1):85-90.
28. Kratochwil C, Giesel FL, Stefanova M, Benesova M, Bronzel M, Afshar-Oromieh A, et al. PSMA-Targeted Radionuclide Therapy of Metastatic Castration-Resistant Prostate Cancer with ^{177}Lu -Labeled PSMA-617. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2016 Aug;57(8):1170-6. PubMed PMID: 26985056. Epub 2016/03/18. eng.
29. Afshar-Oromieh A, Holland-Letz T, Giesel FL, Kratochwil C, Mier W, Haufe S, et al. Diagnostic performance of ^{68}Ga -PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *European journal of nuclear medicine and molecular imaging*. 2017;44(8):1258-68.
30. Agarwal KK, Singla S, Arora G, Bal C. ^{177}Lu -EDTMP for palliation of pain from bone metastases in patients with prostate and breast cancer: a phase II study. *European journal of nuclear medicine and molecular imaging*. 2015;42(1):79-88.
31. Yuan J, Liu C, Liu X, Wang Y, Kuai D, Zhang G, et al. Efficacy and safety of ^{177}Lu -EDTMP in bone metastatic pain palliation in breast cancer and hormone refractory prostate cancer: a phase II study. *Clinical nuclear medicine*. 2013;38(2):88-92.
32. Taïeb D, Foletti J-M, Bardies M, Rocchi P, Hicks RJ, Haberkorn U. PSMA-targeted radionuclide therapy and salivary gland toxicity: why does it matter? : *Soc Nuclear Med*; 2018.
33. Ahmadzadehfar H, Wegen S, Yordanova A, Fimmers R, Kürpig S, Eppard E, et al. Overall survival and response pattern of castration-resistant metastatic prostate cancer to multiple cycles of radioligand therapy using [(177)Lu]Lu-PSMA-617. *Eur J Nucl Med Mol Imaging*. 2017 Aug;44(9):1448-54. PubMed PMID: 28488028. Epub 2017/05/11. eng.
34. Emmett L, Willowson K, Violet J, Shin J, Blanksby A, Lee J. Lutetium (^{177}Lu) PSMA radionuclide therapy for

- men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci.* 2017 Mar;64(1):52-60. PubMed PMID: 28303694. Pubmed Central PMCID: PMC5355374. Epub 2017/03/18. eng.
35. Demir M, Abuqbeith M, Uslu-Beşli L, Yıldırım Ö, Yeyin N, Çavdar İ, et al. Evaluation of radiation safety in ¹⁷⁷Lu-PSMA therapy and development of outpatient treatment protocol. *Journal of Radiological Protection.* 2016;36(2):269.
 36. Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *The lancet oncology.* 2005;6(6):392-400.
 37. Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for ¹⁷⁷Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *European journal of nuclear medicine and molecular imaging.* 2016;43(1):42-51.
 38. Okamoto S, Thieme A, Allmann J, D'Alessandria C, Maurer T, Retz M, et al. Radiation dosimetry for ¹⁷⁷Lu-PSMA I&T in metastatic castration-resistant prostate cancer: absorbed dose in normal organs and tumor lesions. *Journal of Nuclear Medicine.* 2017;58(3):445-50.
 39. Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. Post-therapeutic dosimetry of ¹⁷⁷Lu-DKFZ-PSMA-617 in the treatment of patients with metastatic castration-resistant prostate cancer. *Nuclear medicine communications.* 2017;38(1):91-8.
 40. Emami B, Lyman J, Brown A, Cola L, Goitein M, Munzenrider J, et al. Tolerance of normal tissue to therapeutic irradiation. *International Journal of Radiation Oncology* Biology* Physics.* 1991;21(1):109-22.
 41. Hey J, Setz J, Gerlach R, Janich M, Hildebrandt G, Vordermark D, et al. Parotid gland-recovery after radiotherapy in the head and neck region-36 months follow-up of a prospective clinical study. *Radiation oncology.* 2011;6(1):125.
 42. Bhandare N, Moiseenko V, Song WY, Morris CG, Bhatti MT, Mendenhall WM. Severe dry eye syndrome after radiotherapy for head-and-neck tumors. *International Journal of Radiation Oncology* Biology* Physics.* 2012;82(4):1501-8.
 43. Bergsma H, Konijnenberg MW, van der Zwan WA, Kam BL, Teunissen JJ, Kooij PP, et al. Nephrotoxicity after PRRT with ¹⁷⁷Lu-DOTA-octreotate. *European journal of nuclear medicine and molecular imaging.* 2016;43(10):1802-11.
 44. Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, et al. Repeated (¹⁷⁷Lu)-Labeled PSMA-617 Radioligand Therapy Using Treatment Activities of Up to 9.3 GBq. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine.* 2018 Mar;59(3):459-65. PubMed PMID: 28798031. Epub 2017/08/12. eng.
 45. Chittenden SJ, Hindorf C, Parker CC, Lewington VJ, Pratt BE, Johnson B, et al. A phase 1, open-label study of the biodistribution, pharmacokinetics, and dosimetry of ²²³Ra-dichloride in patients with hormone-refractory prostate cancer and skeletal metastases. *Journal of Nuclear Medicine.* 2015;56(9):1304-9.
 46. Eary JF, Collins C, Stabin M, Vernon C, Petersdorf S, Baker M, et al. Samarium-153-EDTMP biodistribution and dosimetry estimation. *Journal of nuclear medicine: official publication, Society of Nuclear Medicine.* 1993;34(7):1031-6.
 47. Graham MC, Scher HI, Liu G-B, Yeh SD, Curley T, Daghighian F, et al. Rhenium-186-labeled hydroxyethylidene diphosphonate dosimetry and dosing guidelines for the palliation of skeletal metastases from androgen-independent prostate cancer. *Clinical cancer research.* 1999;5(6):1307-18.
 48. Bal C, Arora G, Kumar P, Damle N, Das T, Chakraborty S, et al. Pharmacokinetic, Dosimetry and Toxicity Study of ¹⁷⁷Lu-EDTMP in Patients: Phase 0/I study. *Current radiopharmaceuticals.* 2016;9(1):71-84.
 49. Parker C, Nilsson S, Heinrich D, Helle SI, O'sullivan J, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *New England Journal of Medicine.* 2013;369(3):213-23.
 50. Kratochwil C, Giesel F, Bruchertseifer F, Rius-Montraveta M, Apostolidis C, Haberkorn U, et al. Ac-225-PSMA617-a single center experience of 40 patients receiving PSMA-targeted Alpha therapy. *Journal of Nuclear Medicine.* 2016;57(supplement 2):1431-.
 51. Sathekge M, Bruchertseifer F, Vorster M, Lawal IO, Knoesen O, Mahapane J, et al. Predictors of Overall and Disease-Free Survival in Metastatic Castration-Resistant Prostate Cancer Patients Receiving ²²⁵Ac-PSMA-617 Radioligand Therapy. *Journal of Nuclear Medicine.* 2020;61(1):62-9.
 52. Kim YJ, Kim YI. Therapeutic Responses and Survival Effects of ¹⁷⁷Lu-PSMA-617 Radioligand Therapy in Metastatic Castrate-Resistant Prostate Cancer: A Meta-analysis. *Clinical nuclear medicine.* 2018 Oct;43(10):728-34. PubMed PMID: 30059428. Epub 2018/07/31. eng.
 53. von Eyben FE, Roviello G, Kiljunen T, Uprimny C, Virgolini I, Kairemo K, et al. Third-line treatment and (¹⁷⁷)Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review. *Eur J Nucl Med Mol Imaging.* 2018 Mar;45(3):496-508. PubMed PMID: 29247284. Pubmed Central PMCID: PMC5787223. Epub 2017/12/17. eng.
 54. Barber TW, Singh A, Kulkarni HR, Niepsch K, Billah B, Baum RP. Clinical outcomes of (¹⁷⁷)Lu-PSMA radioligand therapy in taxane chemotherapy pretreated and taxane chemotherapy naive patients with metastatic castration resistant prostate cancer. *J Nucl Med.* 2019 Jan 25. PubMed PMID: 30683770. Epub 2019/01/27. eng.
 55. Ahmadzadehfar H, Schlöglaut S, Fimmers R, Yordanova A, Hirzebruch S, Schlenkhoff C, et al. Predictors of overall survival in metastatic castration-resistant prostate cancer patients receiving [(¹⁷⁷)Lu]Lu-PSMA-617 radioligand therapy. *Oncotarget.* 2017 Nov 28;8(61):103108-16. PubMed PMID: 29262549. Pubmed Central PMCID: PMC5732715. Epub 2017/12/22. eng.
 56. Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. *Journal of nuclear medicine : official publication, Society of Nuclear Me-*

- dicine. 2016 Oct;57(Suppl 3):97s-104s. PubMed PMID: 27694180. Epub 2016/10/04. eng.
57. Fendler WP, Rahbar K, Herrmann K, Kratochwil C, Eiber M. (177)Lu-PSMA Radioligand Therapy for Prostate Cancer. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2017 Aug;58(8):1196-200. PubMed PMID: 28663195. Epub 2017/07/01. eng.
58. Sathekge M, Knoesen O, Bruchertseifer F, Reyneke F, Kratochwil C, Lengana T, et al. Initial experience with 225Ac-PSMA-617 in patients with advanced-stage prostate cancer. *Journal of Nuclear Medicine*. 2018;59(supplement 1):528-.
59. Bal C, Yadav M, Ballal S, Tripathi M, Sahoo R. Clinical Experience on 225Ac-PSMA-617 Targeted Alpha Therapy in Metastatic Castration Resistant Prostate Cancer Patients: Safety and Efficacy Results. *Journal of Nuclear Medicine*. 2019;60(supplement 1):462-.
60. Hoskin P, Sartor O, O'Sullivan JM, Johannessen DC, Helle SI, Logue J, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *The Lancet Oncology*. 2014;15(12):1397-406.
61. Sartor O, Hoskin P, Coleman RE, Nilsson S, Vogelzang NJ, Petrenciuc O, et al. Chemotherapy following radium-223 dichloride treatment in ALSYMPCA. *The Prostate*. 2016;76(10):905-16.
62. Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Ell PJ, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *Journal of Clinical Oncology*. 1998;16(4):1574-81.
63. Morris MJ, Pandit-Taskar N, Carrasquillo J, Divgi CR, Slovin S, Kelly WK, et al. Phase I study of samarium-153 lexidronam with docetaxel in castration-resistant metastatic prostate cancer. *Journal of Clinical Oncology*. 2009;27(15):2436.
64. Fizazi K, Beuzeboc P, Lumbroso J, Haddad V, Massard C, Gross-Goupil M, et al. Phase II trial of consolidation docetaxel and samarium-153 in patients with bone metastases from castration-resistant prostate cancer. *Journal of Clinical Oncology*. 2009;27(15):2429-35.
65. Han SH, de Klerk JM, Tan S, van het Schip AD, Derksen BH, van Dijk A, et al. The placorhen study: a double-blind, placebo-controlled, randomized radionuclide study with 186Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. *Journal of nuclear medicine*. 2002;43(9):1150-6.
66. Palmedo H, Manka-Waluch A, Albers P, Schmidt-Wolf IG, Reinhardt M, Ezziddin S, et al. Repeated bone-targeted therapy for hormone-refractory prostate carcinoma: randomized phase II trial with the new, high-energy radiopharmaceutical rhenium-188 hydroxyethylidenediphosphonate. *Journal of clinical oncology*. 2003;21(15):2869-75.
67. Thapa P, Nikam D, Das T, Sonawane G, Agarwal JP, Basu S. Clinical efficacy and safety comparison of 177Lu-EDTMP with 153Sm-EDTMP on an equidose basis in patients with painful skeletal metastases. *Journal of Nuclear Medicine*. 2015;56(10):1513-9.