Original Article – Urological Oncology
Grand J Urol 2024;4(3):83-8
DOI: 10.5505/GJU.2024.54227

Predicting Response to Androgen Deprivation Therapy and Resistance to Castration in Metastatic Prostate Cancer

Metastatik Prostat Kanserinde Androjen Deprivasyon Tedavisine Yanıtın ve Kastrasyona Direncin Öngörülmesi

Abuzer Öztürk[1], İsmail Emre Ergin[2], Aydemir Asdemir[3], Hüseyin Saygın[3]

[1] Department of Urology, Sivas Numune Hospital, Sivas, Türkiye
[2] Department of Urology, Kızılcahamam State Hospital, Ankara, Türkiye
[3] Department of Urology, Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye

Cite as: Öztürk A, Ergin İE, Asdemir A, Saygın H. Predicting response to androgen deprivation therapy and resistance to castration in metastatic prostate cancer. Grand J Urol 2024;4(3):83-8

Submission date: 31 May 2024 **Acceptance date:** 28 August 2024 **Online first:** 02 September 2024 **Publication date:** 20 September 2024

Corresponding Author: Abuzer Öztürk / Sivas Numune Hospital, Department of Urology, Sivas, Türkiye / brusksidal@gmail.com / ORCID ID: 0000-0002-6090-6133

Abstract

Objective: We sought to identify predictive factors affecting time to castration resistance in metastatic prostate cancer patients receiving androgen deprivation therapy (ADT).

Materials and Methods: We retrospectively evaluated 47 patients who received ADT with the diagnosis of metastatic prostate cancer. The patients' age, International Society of Urological Pathology (ISUP) scores, baseline prostate specific antigen (PSA), alkaline phosphatase (ALP) value, prostate-specific membrane antigen (PSMA) tracer expression, represented by the maximum standardised uptake value (SUV max) at diagnosis, nadir PSA value, and time to resistance to ADT were recorded.

Results: All patients included in the study were resistant to treatment with ADT. The mean age of the patients was 70.81 ± 1.15 years. The mean time to develop resistance to treatment after castration was 31.51 ± 4.9 months. In the correlation analysis, a significant negative correlation was detected between PSA, nadir PSA values and time to treatment resistance. The relationship between the SUVmax value of the primary prostate lesion, ALP value at the time of diagnosis and time to response to ADT developed was not significant.

Conclusion: We found PSA values at diagnosis and nadir PSA values during follow-up to be predictive factors of treatment resistance in metastatic prostate cancer patients receiving ADT.

Keywords: prostate, cancer, castrate resistant, SUVmax, prostate specific antigen

Özet

Amaç: Androjen deprivasyon tedavisi (ADT) alan metastatik prostat kanseri hastalarında kastrasyon direncine kadar geçen süreyi etkileyen öngörücü faktörleri belirlemeye çalıştık.

Gereçler ve Yöntemler: Metastatik prostat kanseri tanısı ile ADT alan 47 hasta retrospektif olarak değerlendirildi. Hastaların yaşı, Uluslararası Ürolojik Patoloji Derneği (ISUP) skorları, başlangıçtaki prostat spesifik antijen (PSA), alkalin fosfataz (ALP) değeri, tanıdaki maksimum standardize edilmiş tutulum değeri (SUV max) ile temsil edilen prostat spesifik membran antijeni (PSMA) ekspresyonu, nadir PSA değeri ve ADT'ye direnç süresi kaydedildi.

Bulgular: Çalışmaya dahil edilen tüm hastalar ADT ile tedaviye dirençliydi. Hastaların yaş ortalaması 70,81 ± 1,15 yıldı. Kastrasyon sonrası tedaviye direnç gelişme süresi ortalama 31.51 ± 4.9 aydı. Korelasyon analizinde, PSA ve nadir PSA değerleri ile tedavi direncine kadar geçen süre arasında anlamlı negatif korelasyon saptandı. Primer prostat lezyonunun SUVmax değeri, tanı anındaki ALP değeri ve ADT'ye yanıt geliştirme süresi arasındaki ilişki anlamlı değildi.

Sonuç: ADT alan metastatik prostat kanseri hastalarında tanı anındaki PSA değerleri ve takip sırasındaki nadir PSA değerleri tedavi direncinin öngörücü faktörleri olarak bulunmuştur.

Anahtar kelimeler: prostat, kanser, kastrasyona dirençli, SUVmax, prostat spesifik antijen

ORCID ID: **İ.E. Ergin** 0000-0002-3115-0533 **A. Asdemir** 0000-0002-9141-6727 **H. Saygın** 0000-0002-6875-0882

© Copyright 2024 by Grand Journal of Urology. This is an Open Access article distributed under the terms of the Creative Commons Attribution NonCommercial License 4.0 (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Prostate cancer is the most frequently diagnosed cancer among men in 105 countries and is the second leading cause of cancer-related deaths [1]. In patients with advanced prostate cancer (PCa), androgen deprivation therapy (ADT) is the standard treatment and currently the most frequently used drugs in ADT are gonadotropin-releasing hormone agonists (GnRHs) [2]. After a median time of 18-24 months of ADT treatment, castration- resistant prostate cancer (CRPC) will develop in most patients [3,4]. In patients with metastatic CRPC (mCRPC), median survival time is 16 months [5]. In most studies, various prognostic factors have been identified indicating progression to castration therapy, such as Gleason score (GS), the presence of bone and visceral metastases, and performance status [6,7].

The prostate-specific antigen (PSA) is a useful tool in diagnosing prostate cancer. Additionally, PSA levels are evaluated periodically after completion of ADT for advanced prostate cancer and used to estimate life expectancy based on its serum levels. However, there is disagreement about the prognostic significance of various PSA indices after hormone therapy. Additionally, there are few studies on whether these PSA indices accurately predict progression towards hormone-resistant prostate cancer. ALP is one of the oldest known tumor markers whose main sources are liver and bone. ALP is a prognostic marker for overall survival (OS). In castration-resistant metastatic prostate cancer patients, and its increased levels correlate with the spread of metastatic bone disease. Although there is not enough correlation between PSA and ALP values in the evaluation of treatment responses, it is stated that the evaluation of the treatment response with ALP is more meaningful [8]. ALP is often used as a prognostic marker of bone metastases. Although not certain, ALP is associated with increased bone turnover, osteoblastic activity and osteoid formation in the presence of bone metastasis. According to a meta-analysis, high serum ALP levels in patients with hormone-sensitive prostate cancer were associated with increased overall mortality and disease progression, but not with cancer-specific mortality rates [9].

Positron emission tomography/computed tomography (PET/CT) is a hybrid imaging method that demonstrates molecular processes of tissues as well as morphological imaging, providing superior diagnostic performance. Prostate-specific membrane antigen (PSMA) is a transmembrane protein primarily present in all prostatic tissues and PSMA expression increases in prostate cancer patients [10]. In recent years 68Ga PSMA PET/CT has been the standard assessment method for prostate cancer staging, evaluation of biochemical recurrence and treatment response [11].

In patients receiving ADT for advanced prostate cancer, PSA levels increase 6 to 12 months before emengence of any clinical indicators of disease progression [12,13]. The time to disease progression is important for planning treatment. Indeed, when the tumor burden is at a minimum level, the general health status of the patients can tolerate alternative treatments. Therefore, it is important to determine a suitable factor that can predict progression to hormone-refractory prostate cancer (HRPC) before the serum PSA value rises again. In this way, alternative treatments can be applied at appropriate times. In this study, we investigated the relationship between PSA levels measured before GnRH treatment in metastatic prostate cancer patients, ALP levels, SUVmax values obtained by Ga-68 PSMA PET/CT, and nadir PSA levels during follow-up and the time to the development of castration- resistant PCa.

Materials and Methods

Ethical approval for this study was obtained from Cumhuriyet University Medical Faculty Ethics Committee (Approval Number: 2023-12/21, date: 12.21.2023). We retrospectively evaluated 47 patients who received ADT for metastatic prostate cancer. Prostatic SUVmax values measured by 68Ga-PSMA PET/CT imaging method, ISUP grade, PSA, ALP, nadir PSA values were recorded for all patients at the time of diagnosis. None of the patients in the study received local treatment for prostate cancer. Patients receiving medical or surgical treatment for prostate cancer and patients with existing liver or bone disease were excluded from the study. Patients whose prostatic SUVmax values and ALP levels were not measured at the time of diagnosis and before ADT were not included in the study. Histopathological and treatment data of the patients were obtained from the hospital information management system and patient records.

According to the European Association of Urology (EAU) guidelines patients were considered to have CRPC as soon as biochemical (three consecutive rises in PSA values at least one week apart resulting in two 50% increases over the nadir, and a PSA>2 ng/mL) or radiological progression [(emergence of two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (response evaluation criteria in solid tumours)] was observed when serum testosterone was <50 ng/dL or 1.7 nmol/L [14]. The time from the start of ADT until castration therapy was recorded.

Statistical Analysis

SPSS 23.0 program was used for statistical analysis. For the data that did not comply with normal distribution, a non-parametric test was used. Mann-Whitney U test was used to compare two independent groups. Correlation analysis was performed to understand the co-movement between variables. Since parametric variables were not available, Spearman correlation analysis was used. In our study, G-power analysis was performed with a moderate effect (d=0.5) according to Cohen's standards for various effect sizes, with α:0.05 (95% confidence) error level β:0.80 power. According to the results of the analysis, taking 47 samples would be sufficient to obtain statistically significant study results. All tests were performed at a 95% confidence.

Results

Forty-seven patients were included in the study. All of the patients were resistant to treatment after ADT. The mean age of the patients was 70.81 ± 1.15 years. According to the pathology results, the patients were ISUP Grade 2 (n:2), 3 (n:8), 4 (n;15), and 5 (n:22). Based on the transrectal prostate biopsy results of the patients, perineural invasion was detected in 34 out of 47

Table 1. Patient characteristics

Variables	N: 47
Age	70.81 ± 1.15 years
ISUP Grade	
ISUP 1	0
ISUP 2	2
ISUP 3	8
ISUP 4	15
ISUP 5	22
PNI	
Yes	34
No	13
SVI	
Yes	21
No	26
Pre-ADT PSA	214.2 ± 92.6 ng/mL
nPSA	1.94 ± 9.6 ng/mL
Pre-ADT ALP	219.6 ± 29.2 IU/L
Pre-ADT SUVmax	17.6 ± 1.8
Time to castration resistance	31.51 ± 4.9 months

Table 2. Spearman correlation analysis of variables

		Time to castration resistance
Age	Correlation coefficient (r) Sig. (2-tailed) (p)	0.108 0.478
ISUP	Correlation coefficient Sig. (2-tailed)	-0.233 0.427
Pre-ADT PSA	Correlation coefficient Sig. (2-tailed)	-0.646 0.002*
nPSA	Correlation coefficient Sig. (2-tailed)	-0.517 0.042*
Pre-ADT ALP	Correlation coefficient Sig. (2-tailed)	-0.369 0.284
Pre-ADT SUVmax	Correlation coefficient Sig. (2-tailed)	-0.142 0.373

* significant correlation

patients. Dynamic magnetic resonance imaging (MRI) studies revealed the presence of seminal vesicle invasion only in 21 patients.

The average pre-treatment PSA (214.2 ± 92.6 ng/mL), ALP (219.6 ± 29.2 IU/L) and prostatic SUVmax (17.6 ± 1.8) values were as indicated. The mean nadir PSA level of the patients during their follow-up was calculated as 1.94 ± 9.6 ng/mL. The average time to develop resistance to treatment after castration was 31.51 ± 4.9 months. The distribution of these data of the patients is summarized in **Table 1.**

In the correlation analysis, there was no significant correlation between age at diagnosis and time to relapse (p=0.478 r=0.108), and between time to relapse and ISUP scores (p=0.427 r=-0.233). A moderately significant negative correlation existed between PSA levels and time to recurrence (p=0.002, r=-0.646). Still, a significant negative correlation was detected between nadir PSA values and time to recurrence (p=0.042, r=-0.517). No correlation was found between the SUVmax value of the primary prostatic lesion and time to recurrence (p=0.373, r=-0.142). The relationship between ALP value at diagnosis and time to recurrence was also not significant (p=0.284 r=-0.369). Correlation relationships are summarized in **Table 2.**

Discussion

ADT has been the primary treatment standard in metastatic prostate cancer for more than 50 years [15]. Although prostate cancer is considered an androgen-dependent tumor, the response to ADT depends primarily on patient and disease characteristics (presence and location of metastasis, performance status, pain score, pre-treatment PSA, GS, etc.).

Median survival for newly diagnosed metastatic prostate cancer patients has been reported to be approximately 42 months with ADT alone. However, since the characteristics of the metastatic lesions are not the same, time to metastatic spread varies greatly [16]. Various prognostic factors for survival have been proposed, including the number and location of bone metastases, the presence of visceral metastases, ISUP grade, PS (performance score) status, and baseline PSA and alkaline phosphatase levels, but only a few of them have been validated [17–20]. In this study, we aim to evaluate factors that may predict treatment resistance in patients receiving ADT.

PSA values and baseline Gleason scores have been reported as the most important predictors of the time to transition to castrate resistant state in metastatic prostate cancer [21]. Kwak et al. confirmed this information by showing that pre-treatment PSA, PSA 6 months after treatment and the number of bone metastases were significantly associated with progression to castration-resistant prostate cancer [22]. According to the study conducted by Divrik et al., approximately a quarter of the patients responded appropriately to ADT without failure for a long time, while the remaining patients became resistant to treatment after an average of 12-18 months. According to the results of this study, it has been shown that the initial response to ADT can be predicted by the pre-treatment PSA level, and that the duration of response to treatment is affected by factors such as PSA levels and Gleason scores (GS). The unresponsiveness to ADT increased 4-fold in patients with a GS of 8-10, compared to patients with a GS of 6 [23]. Kafka et al. showed that total PSA level at diagnosis was not an indicator of clinical outcome. However, in the same study, they showed a strong correlation between nPSA levels and OS, progression-free survival (PFS) and time to progression. In this study, lower PSA levels were associated with statistically significantly prolonged PFS and time to progression [24]. In their study, Bonde et al., did not find a relationship between pre-treatment PSA levels and the risk of resistance to castration therapy. In the same study, the nadir

PSA level reached after castration was shown to be a strong indicator of the development of resistance to castration therapy, regardless of pre-treatment PSA levels. With these results, they emphasized the importance of PSA monitoring immediately after starting ADT to determine whether additional treatment is needed [25]. In our study, we examined factors that could predict the time to development of resistance to treatment in metastatic prostate cancer patients receiving only ADT. The time to develop resistance to treatment was found to be 31.51 ± 4.9 months. There was no significant correlation between the time to treatment resistance and the ISUP scores (p=0.427 r=-0.233). However, a moderately statistically significant negative correlation was found between the time to treatment resistance and PSA levels (p=0.002, r=-0.646). In addition, a significant negative correlation was detected between nadir PSA and recurrence time (p=0.042, r=-0.517). Pre-ADT PSA and nadir PSA are strong factors in predicting treatment resistance in metastatic prostate cancer. This emphasizes the importance of rapid PSA monitoring from the start of ADT and measuring the PSA level at the time of diagnosis to detect the need for additional treatment.

Previous studies have shown that increased serum ALP, and lactate dehydrogenase (LDH) levels, and the presence of visceral metastases are associated with poor survival [26,27]. Fizazi et al. associated increased ALP levels with decreased PFS and OS in a large cohort of patients receiving chemotherapy for mCRPC [28]. In our study, no significant relationship was found between the ALP levels at the time of diagnosis and the time to recurrence which we think is related to the inhomogeneity of the metastatic burden in our patient group. We think that ALP values can predict resistance to ADT in patient groups where metastatic foci are homogeneous in location and size.

Jadvar et al. reported the prognostic value of SUVmax values defined based on FDG-PET results in 87 mCRPC patients. In the same study, it was reported that the survival rate of patients with high SUVmax values decreased [29]. However, in a study evaluating the response of 34 patients with mCRPCa to enzalutamide treatment, age, ISUP grade, SUVmax, and pre-treatment PSA values, and the presence of local recurrence or metastasis in any region were not found to be significant in predicting response to treatment [30]. Another study using SPECT/CT found no significant correlation between changes in SUV values and PFS or OS [31]. In our study, age at diagnosis, ISUP scores, and SUVmax values of the primary prostatic lesions on PSMA-PET imaging could not predict resistance to ADT.

Our study has several limitations. The first of these is that our patient group is not homogeneous in terms of metastatic burden and diversity of metastases. Secondly, the number of patients included in our study is relatively small. For these reasons, our findings should be interpreted as exploratory rather than definitive results. However, we think that our study conveys importance in that we examined many valuable prognostic parameters such as age, ISUP scores, pre-ADT PSA, nPSA, Pre-ADT ALP and pre-ADT SUVmax. We think that future analyzes with a larger and more homogeneous sample size will support our results.

Conclusion

We found that PSA and nadir PSA values at the time of diagnosis were significant in predicting the duration of resistance to ADT in metastatic prostate cancer patients receiving ADT. These results show the importance of PSA values measured at the time of diagnosis and PSA monitoring during follow-up.

Acknowledgments: We would like to thank to Nuclear Medicine Specialist who is Zekiye Hasbek for her helps during PSMA-PET processing.
Ethics Committee Approval: Ethical approval for this study was obtained from Cumhuriyet University Medical Faculty Ethics Committee (Approval Number: 2023-12/21, date: 12.21.2023).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – A.Ö., İ.E.E., A.A., H.S.; Design – A.Ö., A.A., H.S.; Supervision – A.Ö., İ.E.E., H.S.; Resources – A.Ö., İ.E.E., A.A.; Materials – A.Ö., A.A., H.S.; Data Collection and/or Processing – A.Ö., İ.E.E.; Analysis and/or Interpretation – A.Ö., İ.E.E., H.S.; Literature Search – A.Ö., İ.E.E., A.A.; Writing Manuscript – A.Ö., İ.E.E.; Critical Review –A.Ö., A.A., H.S.
Conflict of Interest: The authors declare that they have no conflicts of interest.
Financial Disclosure: The authors declare that this study received no financial support.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Es timates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 May;71(3):209-49. https://doi.org/10.3322/caac.21660

[2] Schröder F, Crawford ED, Axcrona K, Payne H, Keane TE. Androgen deprivation therapy: past, present and future. BJU Int. 2012;109(s6): 1-12. https://doi.org/10.1111/j.1464-410X.2012.11215.x

[3] Hamberg P, Verhagen PC, de Wit R. When to start cytotoxic ther apy in asymptomatic patients with hormone refractory prostate cancer? Eur J Cancer. 2008;44(9):1193-7. https://doi.org/10.1016/j.ejca.2008.04.005

[4] Sternberg CN. Systemic chemotherapy and new experimental approaches in the treatment of metastatic prostate cancer. Ann Oncol. 2008;19(Suppl 7):vii91-5. https://doi.org/10.1093/annonc/mdn473

[5] Petrylak DP, Tangen CM, Hussain MH, Lara PN Jr, Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351(15):1513-20. https://doi.org/10.1056/NEJMoa041318

[6] Hussain M, Tangen CM, Higano C, Schelhammer PF, Faulkner J, Crawford ED, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from southwest oncology group trial 9346 (INT-0162). J Clin Oncol. 2006;24(24):3984-90. https://doi.org/10.1200/JCO.2006.06.4246

[7] Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, et al. Abiraterone acetate plus pred nisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU AA-302): final overall survival analysis of a randomised, double blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152-60. https://doi.org/10.1016/S1470-2045(14)71205-7

[8] Heinrich D, Bruland Ø, Guise TA, Suzuki H, Sartor O. Alkaline phosphatase in metastatic castration-resistant prostate can cer: reassessment of an older biomarker. Future Oncol. 2018 Oct;14(24):2543-56. https://doi.org/10.2217/fon-2018-0087

[9] Mori K, Janisch F, Parizi MK, Mostafaei H, Lysenko I, Enikeev DV, et al. Prognostic value of alkaline phosphatase in hormone-sensitive prostate cancer: a systematic review and meta-analysis. Int J Clin Oncol. 2020;25(2):247-57. https://doi.org/10.1007/s10147-019-01578-9.

[10] Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, et al. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017;44(6):1014-24. https://doi.org/10.1007/s00259-017-3670-z

[11] Grubmüller B, Senn D, Kramer G, Baltzer P, D'Andrea D, Grubmüller KH, et al. Response Assessment Using 68 Ga-PSMA Ligand PET in Patients Undergoing 177 Lu-PSMA Radioli gand Therapy for Metastatic Castration-Resistant Prostate Cancer. Eur J Nucl Med Mol Imaging. 2019;46(5):1063-72. https://doi.org/10.1007/s00259-018-4236-4

[12] Denis LJ, Carnelro de Moura JL, Bono A, Sylvester R, Whelan P, Newling D, et al: Goserelin acetate and flutamide versus bilateral orchiectomy: a phase III EORTC trial (30853). EORTC GU Group and EORTC Data Center. Urology. 1993;42(2):119-29. https://doi.org/10.1016/0090-4295(93)90634-m

[13] Mulders PF, Fernandez del Moral P, Theeuwes AG, Oosterhof GO, van Berkel HT, Debruyne FM. Value of biochemical markers in the management of disseminated prostatic cancer. Eur Urol. 1992;21(1)21:2-5. https://doi.org/10.1159/000474790

[14] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. https://doi.org/10.1016/j.ejca.2008.10.026

[15] Viani GA, Arruda CV, Assis Pellizzon AC, De Fendi LI. HDR brachytherapy as monotherapy for prostate cancer: A systematic review with meta-analysis. Brachytherapy. 2021;20(2):307-14. https://doi.org/10.1016/j.brachy.2020.10.009

[16] No authors listed. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. Br J Urol. 1997;79(2):235-46. https://doi.org/10.1046/j.1464-410x.1997.d01-6840.x

[17] Walsh P.C. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. J Uro.l 1997;158(4):1623-4. https://pubmed.ncbi.nlm.nih.gov/9302187/

[18] No authors listed. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet. 2000; 355(9214):1491-8. https://pubmed.ncbi.nlm.nih.gov/10801170/

[19] Schmitt B, Bennett C, Seidenfeld J, Samson D, Wilt T. Maximal androgen blockade for advanced prostate cancer. Cochrane Database Syst Rev. 2000;1999(2):CD001526. https://doi.org/10.1002/14651858.CD001526

[20] Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med. 2019;381(2):121-31. https://doi.org/10.1056/NEJMoa1903835

[21] Benaim EA, Pace CM, Lam PM, Roehrborn CG. Nadir prostate-specific antigen as a predictor of progression to androgen-independent prostate cancer. Urology. 2002;59(1):73-8. https://doi.org/10.1016/s0090-4295(01)01440-6

[22] Kwak C, Jeong SJ, Park MS, Lee E, Lee SE: Prognostic significance of the nadir prostate specific antigen level after hormonal therapy for prostate cancer. J Urol 2002;168(3):995-1000. https://doi.org/10.1016/S0022-5347(05)64559-4

[23] Divrik RT, Türkeri L, Şahin AF, Akdoğan B, Ateş F, Çal Ç, et al. Prediction of response to androgen deprivation therapy and castration resistance in primary metastatic prostate cancer. Urol Int. 2012;88(1);25-33. https://doi.org/10.1159/000334539

[24] Kafka M, Burtscher T, Fritz J, Schmitz M, Bektic J, Ladurner M, et al. Real-world comparison of Docetaxel versus new hormonal agents in combination with androgen-deprivation therapy in metastatic hormone-sensitive prostate cancer descrying PSA Nadir≤0.05 ng/ml as marker for treatment response. World J Urol. 2023;41(8):2043-50. https://doi.org/10.1007/s00345-022-04189-8

[25] Bonde TM, Westerberg M, Aly M, Eklund M, Adolfsson J, Bill-Axelson A, et al. Time to castration-resistant prostate cancer and prostate cancer death according to PSA response in men with non-metastatic prostate cancer treated with gonadotropin releasing hormone agonists. Scand J Urol. 2022;56(3):169-75. https://doi.org/10.1080/21681805.2022.2070275

[26] Heck MM, Tauber R, Schwaiger S, Retz M, D'Alessandria C, Maurer T, et al. Treatment outcome, toxicity, and predictive factors for radioligand therapy with (177)Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. Eur Urol. 2019;75(6):920-6. https://doi.org/10.1016/j.eururo.2018.11.016

[27] Kessel K, Seifert R, Schafers M, Weckesser M, Schlack K, Boegemann M, et al. Second line chemotherapy and visceral metastases are associated with poor survival in patients with mCRPC receiving (177)Lu-PSMA-617. Theranostics. 2019;9(17):4841-8. https://doi.org/10.7150/thno.35759

[28] Fizazi K, Massard C, Smith M, Rader M, BrownJ, Milecki P, et al. Bone-related parameters are the main prognostic factors for overall survival in men with bonemetastases from castration-resistant pros tate cancer. Eur Urol. 2015;68(1):42–50. https://doi.org/10.1016/j.eururo.2014.10.001

[29] Jadvar H, Desai B, Ji L, Conti PS, Dorff TB, Groshen SG, et al. Baseline 18F-FDG PET/CT parameters as imaging biomarkers of overall survival in castrate-resistant metastatic prostate cancer. J Nucl Med. 2013;54(8):1195–201. https://doi.org/10.2967/jnumed.112.114116

[30] Karyağar S, Güven O, Karyağar SS, Arici S, Selvi O, Geredeli Ç, et al. Can 68Ga-PSMA PET/CT-derived prostate-specific membrane antigen expression parameters predict prostate-specific antigen response to enzalutamide treatment? Nucl Med Commun. 2021;42(9):1011-6. https://doi.org/10.1097/MNM.0000000000001431

[31] Pathmanandavel S, Crumbaker M, Ho B, Yam AO, Wilson P, Niman R, et al. Evaluation of (177)Lu-PSMA-617 SPECT/CT quantitation as a response biomarker within a prospective (177) Lu-PSMA-617 and NOX66 combination trial (LuPIN). J Nucl Med. 2023;64(2):221-6. https://doi.org/10.2967/jnumed.122.264398