Case report

Apalutamide as a therapeutic option in case of local failure in the nmCRPC patient with an 18-year course of the disease

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ABSTRACT

Apalutamide is a non-steroidal selective androgen receptor inhibitor approved for the treatment of high-risk non-metastatic castration-resistant prostate cancer and metastatic hormone-sensitive prostate cancer. The paper describes a case of a patient diagnosed with prostate cancer with a long-term course of the disease. The patient was diagnosed with a non-metastatic castration-resistant stage 18 years after primary treatment. Systemic treatment with apalutamide was recommended. Initially, the treatment was carried out as part of the expanded access to apalutamide program and from March 2022 as part of the B.56 drug program. The study presents the effectiveness and safety of the therapy in a 12-month follow-up period and discusses controversial aspects of the patient's previous treatments.

Key words: prostate cancer, castration resistance, apalutamide

INTRODUCTION

Prostate cancer is the most common cancer in Polish men (incidence rate: 20.6%). It is the second leading cause of cancer death, after lung cancer (mortality rate: 10.3%). It has the highest rate of increase in morbidity. Mortality remained constant at the beginning of the 21st century, but since 2004 it has shown an upward trend [1]. The effectiveness of prostate cancer treatment is relatively high. Nevertheless, it remains one of the major causes of premature mortality in adult men.

Prostate cancer treatment methods depend on the disease stage at the time of diagnosis. In the early stages, treatment options include surgery, various radiotherapy techniques (including stereotactic radiotherapy and brachytherapy) and hormone therapy (HT) based on gonadotropin-releasing hormone (GnRH) analogues or antagonists. In the case of metastatic or castrate-resistant prostate cancer (CRPC), in addition to aforementioned radiation therapy and hormone therapy, chemotherapy based on docetaxel or cabazitaxel, hormone therapy using modern antiandrogens and ^{223}Ra are also used. The European Association of Urology (EAU) recommends that patients diagnosed with M0 CRPC and PSA doubling time (PSADT) < 10 months should be offered treatment based on apalutamide, darolutamide or enzalutamide [2].

The population diagnosed with prostate cancer is elderly, often with numerous comorbidities. The safety profile is an essential factor in treatment decision-making. Hormone therapy based on second-generation antiandrogens effectively extends progression-free and overall survival, and is very well tolerated.

CASE STUDY

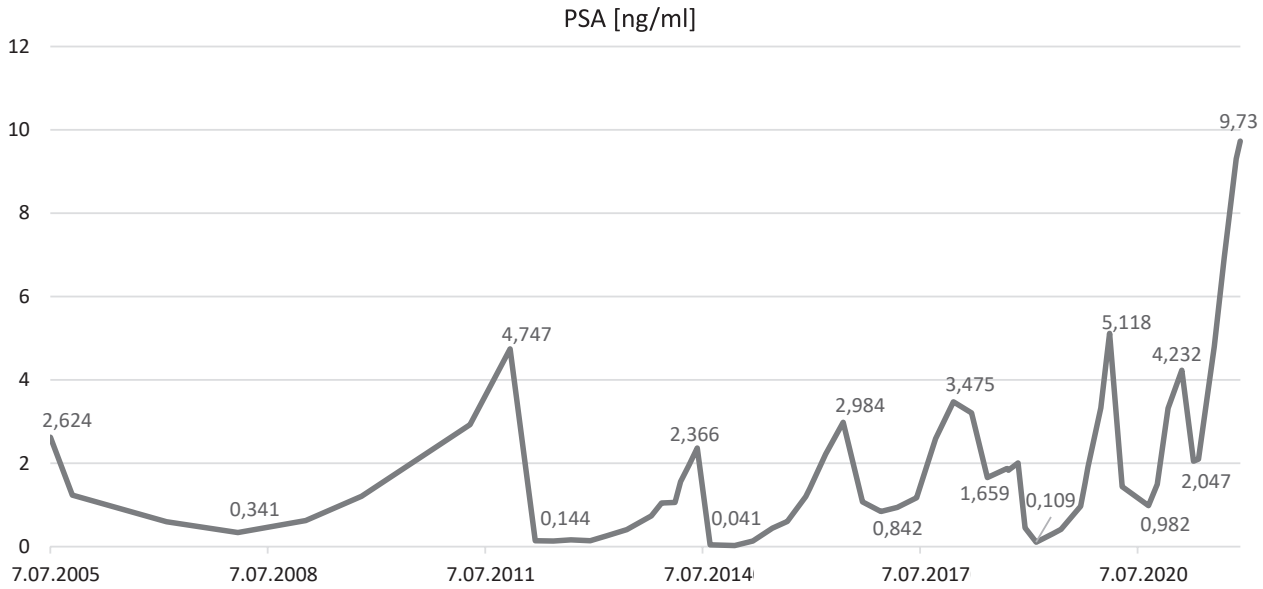
A 60-year-old patient underwent prostate cancer diagnostics in July 2004 due to an elevated PSA (prostate-specific antigen) level of 8.3 ng/mL. A core needle biopsy confirmed the histopathological diagnosis of adenocarcinoma Gleason 3+3. The biopsy caused several complications: acute prostatitis and cystitis, and a temporary urinary catheterisation was required. Imaging tests did not reveal any regional lymph nodes or distant metastases. Based on the digital rectal examination, the local stage was assessed as cT2b. The patient was in the intermediate-risk group for biochemical recurrence [2] and was planned for radiation treatment according to the scheme used in our centre at the time. As the first phase of treatment, on November 20, 2004, a high-dose-rate brachytherapy (HDR-BT) boost using an iridium ^{192}Ir source was administered – a total dose of 10 Gy in a single fraction. Subsequently, between December 6, 2004, and January 12, 2005, external beam radiotherapy (EBRT) was delivered with a fraction dose of 2 Gy to a total dose of 44 Gy to the regional lymph nodes area and a total dose of 54 Gy to the prostate. No hormonal treatment was applied at the time.

After radiotherapy completion, the patient was followed-up with regular PSA level measurements every 3–6 months. Due to the PSA concentration increase, meeting the Phoenix criteria for biochemical recurrence (PSA nadir + 2 ng/mL) [3], in November 2011, magnetic resonance imaging (MRI) was performed. It confirmed the local recurrence within the right lateral lobe of the prostate. Systemic treatment based on goserelin was initiated in December 2011. From May 2013, a slow increase in PSA level was observed despite hormone therapy (fig. 1). Due to the ineffectiveness of the pharmacotherapy, local treatment was recommended – salvage radiotherapy or radical prostatectomy. The patient did not consent to surgical treatment. Therefore, salvage treatment with stereotactic body radiation therapy (SBRT) was advised.

Between June 10 and June 20, 2014, the patient underwent CyberKnife® SBRT with 6 MV photons to the recurrence area in the right lobe of the prostate with a margin. A total dose of 30 Gy in 5 fractions of 6 Gy was delivered. A year after salvage radiotherapy, despite continuous GnRH analogue therapy, the PSA concentration increased again, reaching in June 2016 a value that met the Phoenix criteria for biochemical recurrence. Due to the lack of other therapeutic options, additional treatment with bicalutamide was started. However, an increase in PSA level was observed after 12 months of maximal androgen blockade (MAB). On November 30, 2017, a prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) was performed to search for lesions suspected of local recurrence or dissemination. The PET scan revealed a relapse in the right side of the prostate without the metabolic features of distant metastases. Due to the unavailability of other treatment methods, the current hormone therapy was continued. The PSA level decreased, possibly because of the initiation of dutasteride therapy.

After the next biochemical progression, an MRI of the prostate was performed (September 27, 2018), revealing the disease progression – the neoplastic lesion was located in the central and the peripheral zone of the right lobe of the prostate, infiltrating the bladder wall on the right side and the right seminal vesicle. On October 15, 2018, a prostate biopsy was performed, which confirmed a recurrence within the right lobe of the prostate and the right seminal vesicle. Gleason score was assessed as 4 + 5.

Figure 1. PSA kinetics in the years 2005–2021.



Local treatment with the use of brachytherapy was recommended. On November 20, 2018, HDR ^{192}Ir brachytherapy under spinal anaesthesia was performed. A total dose of 19 Gy in one fraction was delivered to the recurrence area in the right prostate lobe and the right seminal vesicle. The rapid decrease in PSA concentration after irradiation resulted in the discontinuation of hormone therapy, which had already been used for seven years (fig. 1, 2).

Another biochemical progression occurred after eight months, with a PSA level of 5.118 ng/mL in February 2020. The MRI scan performed on October 22, 2019, showed a partial regression of infiltrative lesions in the right part of the prostate. The infiltration of the posterior wall on the right side of the bladder was stable compared to the previous examination. However, there was an ambiguous area in the base of the prostate on the left side and a pathological area suspected of inflammatory or neoplastic infiltration in the left side of the superior bladder wall, which had not been visible before. The PET PSMA examination of February 26, 2020, showed a local recurrence of cancer in both prostate lobes without metabolic features of dissemination. In March 2020, treatment with MAB (leuprorelin + flutamide) was started, leading to a rapid response in the form of PSA concentration decrease to 0.982 ng/mL within 5 months. With subsequent biochemical progression and exclusion of dissemination, considering the treatment performed so far and the use of maximum androgen blockade, in the absence of other options, it was decided to switch from flutamide to bicalutamide. A short-term stabilisation of the PSA level was achieved, followed by another rapid biochemical progression (fig. 1, 2). In September 2021, PET PSMA revealed a single localisation of cancer in the prostate and the posterior wall of the bladder, with features of partial metabolic regression compared to the February 26, 2020 examination. The prior treatment proved ineffective. Repeated pelvis irradiation precluded another local treatment, using either radiotherapy or surgery. The lack of dissemination in imaging studies prevented using other systemic therapies than the already used MAB. In December 2021, the PSA concentration reached 9.73 ng/mL, with a testosterone concentration of 0.2 ng/mL, the PSADT was 8.3 months. The neck, chest, abdomen and pelvis computed tomography and bone scintigraphy revealed no distant or nodal metastases. The diagnosis was non-metastatic castration-resistant prostate cancer (nmCRPC or M0 CRPC).

According to EAU recommendations, patients diagnosed with M0 CRPC and PSADT < 10 months should be offered treatment based on apalutamide, darolutamide or enzalutamide [2]. By dint of the expanded drug access program, on December 14, 2021, the patient started treatment with apalutamide. Whereas, from March 2022, after the update of the B.56 drug program, the treatment was continued within this program.

After the initiation of apalutamide treatment, a rapid decrease in PSA concentration was achieved, which in mid-January 2022 was 0.323 ng/mL (fig. 3). In March 2022, the undetectable concentration was reached (< 0.004 ng/mL), which maintained until November 2022. After nearly 2 weeks of treatment, the patient reported an itchy skin rash, which resolved within a few days af-

ter administering antihistamines. The CT performed on February 28, 2022, confirmed a local recurrence with the right posterolateral bladder wall infiltration of a similar extent to the previous examination, according to RECIST 1.1 – stagnation. No bone metastases were observed in the bone scintigraphy of June 8, 2022.

In May 2022, urinary retention occurred. In the urology outpatient clinic, after repeated dilatation of the urethra with plastic dilators, urinary catheterisation was performed, followed by urethral bleeding. From June 2022, the patient reported worsening symptoms: diarrhoea, pain in the lower abdomen and perineum. At the end of June, a suprapubic cystostomy was recommended due to post-inflammatory exacerbation of chronic pain and the inability to maintain urethral patency without a catheter as a consequence of the prior treatment. At the beginning of August, the body temperature increased, and pelvic pain intensified, radiating to the groin, hip joints and lower limbs, causing difficulty moving. Therefore, apalutamide was discontinued. In the urology clinic, antibiotic therapy was started, and laboratory and imaging tests were planned. On August 18, 2022, an MRI revealed areas of pathological enhancement with restricted diffusion around the bladder neck and urethra. Similar lesions were observed in the muscles and pubic symphysis, more pronounced on the left side. The diagnostic imaging and clinical data suggested massive inflammatory infiltration with abscesses in the above locations. *Pseudomonas aeruginosa* CP(-) (>1,000,000 CFU/mL) and *Enterococcus faecalis* HLAR(-) (>1,000,000 CFU/mL) were cultured in the urine.

Targeted antibiotic therapy was introduced according to the results of urine culture with an antibiogram (fig. 4). Significant improvement was achieved, pain, fever and gastrointestinal complaints subsided. Symptoms occurring since June were most likely related to the exacerbation of radiation-induced inflammatory changes in the pelvis due to urological interventions.

DISCUSSION

There is much controversy in the presented disease history. The discussion should begin with the first radiotherapy regimen used at the turn of 2004 and 2005. EBRT treatment with a fraction dose of 2 Gy to a total dose of 44 Gy to the pelvic lymph nodes and 54 Gy to the prostate with HDR-BT boost with a total dose of 10 Gy in 1 fraction is characterised by insufficient effectiveness and has not been used for many years. Assuming the value of $\alpha/\beta = 3$ Gy for prostate cancer, the biologically effective dose (BED) in the presented treatment was equal to 133.3 Gy. Our centre's retrospective analysis of prostate cancer treatment results showed that a BED higher than 135 Gy is associated with a significantly lower risk of biochemical recurrence [4]. The presented case confirms this irradiation regimen's ineffectiveness in biochemical and local control.

Further doubts may arise from the use of salvage SBRT. Such therapy was chosen mainly due to the patient's lack of consent for surgical treatment. Available studies suggest high effectiveness and low toxicity of salvage SBRT [5–8]. However, the number of patients treated this way is relatively small, and the follow-up

Figure 2. Scheme of applied therapies on the PSA concentration diagram in the years 2005–2021.

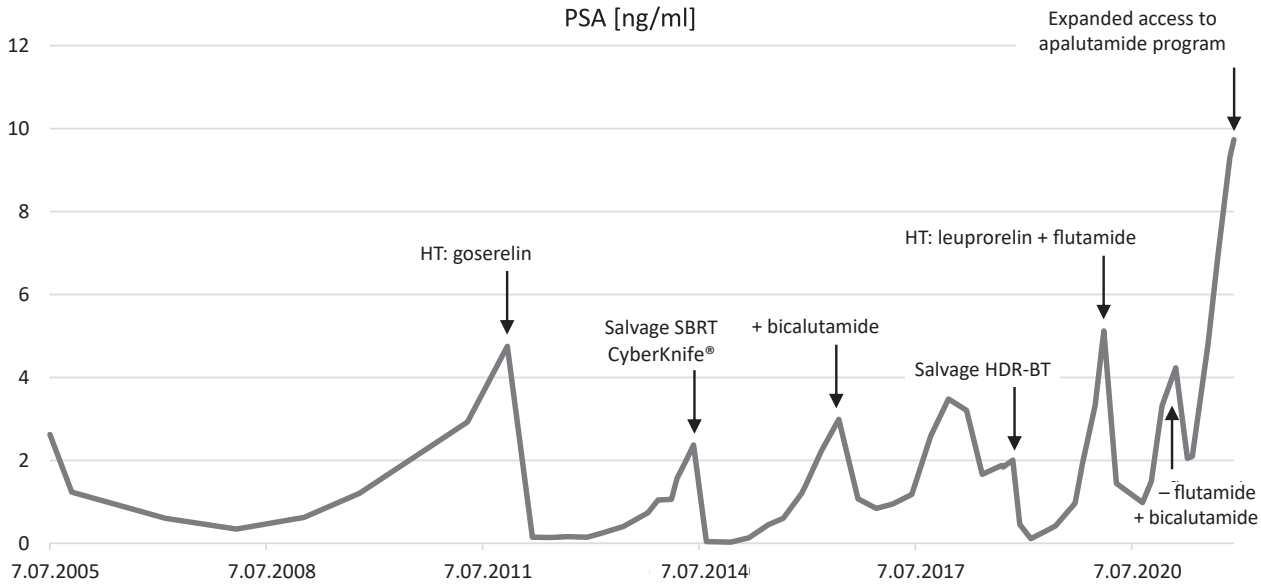


Figure 3. PSA kinetics during the treatment with apalutamide.

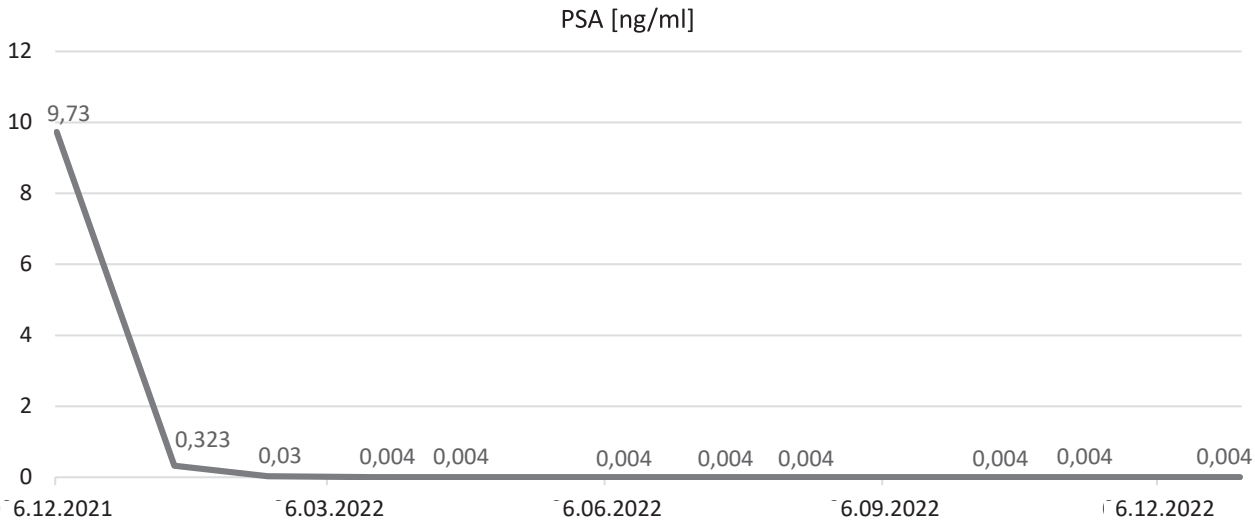


Figure 4. Urine culture test result of August 25, 2022.

	Antibiogram			
	1		2	
Antibiotic – name	**Result**	**MIC**	**Result**	**MIC**
Nitrofurantoin			S	32
Amikacin	WZE	16		
Ampicillin			S	2
Ceftazidime	WZE	8		
Ciprofloxacin	WZE	0,5	S	1
Cefepime	WZE	8		
Gentamicin	R			
Gent. Synergy			S	500
Levofloxacin	WZE	2	S	1
Pip/Tazo	WZE	16		
Strep. Synergy			S	1000

S – sensitive, WZL – sensitive, increased exposure, R – resistant, MIC (mg/L) zone (mm). Interpretation of drug sensitivity according to EUCAST guidelines.

times are too short to consider this procedure the standard of care. In the described case, focal irradiation of the recurrence area with a margin was performed – this treatment aimed to limit the toxicity of subsequent pelvic radiotherapy. The data on this type of therapy are scarce; small groups of patients with short follow-ups have been described. It is suggested that such treatment is well tolerated and has satisfactory efficacy. However, no clear criteria exist for selecting patients for this therapy [9, 10].

Treating with radiotherapy for the third time seems to be the most controversial. In retrospect, salvage surgery would probably be more effective but also associated with a high risk of complications. In 2018, after two rounds of pelvic radiotherapy, the patient was not eligible for surgical treatment. The lack of other therapeutic options and the risk of uncontrolled local progression contributed to that bold treatment attempt. There are no data on the efficacy and safety of repeated salvage treatment with ionizing radiation. HDR-BT with a total dose of 19 Gy in a single fraction was considered safe and effective in salvage and primary treatment. Researchers also suggested the effectiveness of such dosage in focal therapy [11–13]. However, after a longer follow-up, it was significantly less efficient than multi-fraction regimens, and its current use is not justified [14, 15].

According to the EAU guidelines, in the case of biochemical recurrence after radiation treatment in patients fit for curative salvage treatment, a PSMA PET-CT, choline PET-CT, or fluciclovine PET-CT should be performed. According to these recommendations, salvage local treatment should be offered to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.

The toxicity of the treatment was relatively low for many years, especially considering three hypofractionated irradiations of the prostate area. Even before primary treatment, the patient had a positive history of post-void residual urine requiring bladder catheterisation. After radiotherapy, the symptoms subsided. Urinary symptoms worsened in February 2018 – haematuria, bladder obstruction and recurrent urinary tract infections accompanied by dysuria and urinary frequency appeared. Empiric antibiotic therapy was applied with good effect. In June 2018, it was necessary to perform a bilateral bladder neck incision. After the procedure, mild urinary incontinence and nocturia

(4–5 times a night) were observed. The use of dutasteride and mirabegron lead to symptom improvement. One year after salvage brachytherapy, weak urine stream, nocturia (4 times a night), intermittent burning sensation of the urethra at the end of micturition and urinary urgency were observed. In October 2019, bladder catheterisation was necessary in order to maintain the patency of the urethra. Moreover, pelvic pain and haematuria occurred. Recurrent urinary tract infections responded well to targeted antimicrobial therapy based on the urine culture and antibiogram results. In October 2020, the catheter was removed. Due to the observed recurring prostatic urethral stricture, urethra dilation was performed, and the outflow of clean urine was obtained. Because of urinary incontinence, a permanent external catheter was placed. The most severe symptoms appeared in mid-2022 (discussed in the "Case study" section).

Due to the diagnosis of the nmCRPC stage, thanks to the program of expanded drug access, the patient was treated according to international recommendations [2, 16]. The effectiveness of apalutamide in the treatment of M0 CRPC patients was proven in the SPARTAN study. The use of apalutamide in combination with androgen deprivation therapy (ADT) in nmCRPC patients was associated with improved distant metastasis-free survival and time to symptomatic progression. This treatment was very well tolerated [17]. Further analyses also confirmed the prolongation of the time to the second progression. Moreover, apalutamide improved overall survival and reduced the hazard of death by 25% [18, 19].

The described case of the patient with a long-term course of prostate cancer confirms the efficacy and safety of apalutamide in treating the M0 CRPC stage during a short, 12-month follow-up. This treatment is effective and well-tolerated. It allows for the control of prostate cancer. The patient experienced only one side effect that could be related to the use of apalutamide. It was a skin rash that quickly resolved after symptomatic treatment.

CONCLUSION

In recent years, there has been a breakthrough in the treatment of castration-resistant prostate cancer, not only in the metastatic stage but also in patients without distant metastases. Nevertheless, this disease remains incurable. The results of prospective clinical trials indicate the effectiveness of several drugs, which statistically significantly improve overall survival and progression-free survival, with an acceptable toxicity profile, in patients with M0 castration-resistant prostate cancer [17, 20, 21]. Changes in the regulations of the B.56 drug program introduced in March 2022 allowed for the treatment of patients in the nmCRPC stage using medications approved for this indication. Although the number of effective therapeutic options in patients diagnosed with CRPC has increased, direct comparisons of the effectiveness and safety of these treatment methods are lacking. Treatment decisions should be individualised. It seems that in asymptomatic patients in good general condition diagnosed with M0 CRPC, modern antiandrogens are a valuable therapeutic method that should be considered as first-line treatment.

References

1. Didkowska J, Wojciechowska U, Olasek P et al. Nowotwory złośliwe w Polsce w 2019 roku. Cent. Onkol. Inst. im M Skłodowskiej-Curie, Warszawa 2021.
2. Mottet N, Cornford P, van den Bergh RCN et al. EAU-EANM-ESTRO-ESUR-ISUP -SIOG Guidelines on Prostate Cancer 2022. Eur Urol. In: EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022; EAU Guidelines Office, Arnhem, the Netherlands. Online: http://uroweb.org/guidelines/compilations-of-all-guidelines/.
3. Cox J, Grignon D, Kaplan R et al. Consensus statement: guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys. 1997; 37: 1035--41.
4. Miszczyk M, Jabłońska I, Krzysztofiak T et al. Does Brachytherapy Boost Improve Biochemical Control in Intermediate and High-Risk Prostate Cancer Patients Compared to External Beam Radiotherapy Alone? Int J Radiat Oncol. 2021; 111(3): e286-7.
5. Jereczek-Fossa BA, Beltramo G, Fariselli L et al. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. Int J Radiat Oncol Biol Phys. 2012; 82(2): 889-97.
6. Vavassori A, Jereczek-Fossa BA, Beltramo G et al. Image-guided robotic radiosurgery as salvage therapy for locally recurrent prostate cancer after external beam irradiation: Retrospective feasibility study on six cases. Tumori. 2010; 96(1): 71-5.
7. Arcangeli S, Agolli L, Donato V. Retreatment for prostate cancer with stereotactic body radiation therapy (SBRT): Feasible or foolhardy? Reports Pract Oncol Radiother. 2015; 20(6): 425-9. http://dx.doi.org/10.1016/j.rpor.2014.08.001.
8. Jereczek-Fossa BA, Marvaso G, Zaffaroni M et al. Salvage stereotactic body radiotherapy (SBRT) for intraprostatic relapse after prostate cancer radiotherapy: An ESTRO ACROP Delphi consensus. Cancer Treat Rev. 2021; 98: 102206.
9. Scher N, Bauduceau O, Bollet M et al. Stereotactic prostate focal reirradiation therapy for local recurrence: preliminary results of Hartmann Oncology Radiotherapy Group. BJR Open. 2019; 1(1): 20180027.
10. Mbeutcha A, Chauveinc L, Bondiau PY et al. Salvage prostate re-irradiation using high-dose-rate brachytherapy or focal stereotactic body radiotherapy for local recurrence after definitive radiation therapy. Radiat Oncol. 2017; 12(1): 1-10.
11. Chitmanee P, Tsang Y, Tharmalingam H et al. Single-Dose Focal Salvage High Dose Rate Brachytherapy for Locally Recurrent Prostate Cancer. Clin Oncol. 2020; 32(4): 259-65. http://doi.org/10.1016/j.clon.2019.10.008.
12. Maenhout M, Peters M, van Vulpen M et al. Focal MRI-Guided Salvage High-Dose-Rate Brachytherapy in Patients With Radiorecurrent Prostate Cancer. Technol Cancer Res Treat. 2017; 16(6): 1194-201.
13. Tharmalingam H, Tsang Y, Ostler P et al. Single dose high-dose rate (HDR) brachytherapy (BT) as monotherapy for localised prostate cancer: Early results of a UK national cohort study. Radiother Oncol. 2020; 143: 95-100. http://doi.org/10.1016/j.radonc.2019.12.017.
14. Siddiqui ZA, Gustafson GS, Ye H et al. Five-Year Outcomes of a Single-Institution Prospective Trial of 19-Gy Single-Fraction High-Dose-Rate Brachytherapy for Low- and Intermediate-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys. 2019; 104(5): 1038-44. http://doi.org/10.1016/j.ijrobp.2019.02.010.
15. Salari K, Ye H, Sebastian E et al. 21 Gy Single Fraction Prostate HDR Brachytherapy: Mature Results of a Single Institution Prospective Study. Brachytherapy. 2022; 21(6): S22.
16. Schaeffer EM, Srinivas S, Adra N et al. NCCN Guidelines® Insights: Prostate Cancer, Version 1.2023. J Natl Compr Canc Netw. 2022; 20(12): 1288-98.
17. Smith MR, Saad F, Chowdhury S et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018; 378(15): 1408-18.
18. Smith MR, Saad F, Chowdhury S et al. Apalutamide and Overall Survival in Prostate Cancer. Eur Urol. 2021; 79(1): 150-8.
19. Small EJ, Saad F, Chowdhury S et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. Ann Oncol. 2019; 30(11): 1813-20. http://doi.org/10.1093/annonc/mdz397.
20. Sternberg CN, Fizazi K, Saad F et al. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2020; 382(23): 2197-206.
21. Fizazi K, Shore N, Tammela TL et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2019; 380(13): 1235-46.

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The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed with the content of the manuscript as written. The paper complies with the Helsinki Declaration, EU Directives and harmonized requirements for biomedical journals.