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Case Report

Two Patients with Rapidly Developing of Castration-Resistant Prostate Cancer: A Case Report and Update of Literature

Milan van Engelen[1], Charlotte Kweldam[2], Sjoerd OS Klaver[3], Ewout FW Courrech Staal[4] and Brigitte CM Haberkorn[5]*

[1]*Medical student, Erasmus MC, Rotterdam, The Netherlands*

[2]*Department of Pathology, Maasstad Hospital, Rotterdam, The Netherlands*

[3]*Department of Urology, Maasstad Hospital, Rotterdam, The Netherlands*

[4]*Department of Radiology, Maasstad Hospital, Rotterdam, The Netherlands*

[5]*Department of Oncology, Maasstad Hospital, Rotterdam, The Netherlands*

***Corresponding author**

Brigitte CM Haberkorn, Department of Oncology, Maasstad Hospital, Rotterdam, The Netherlands, 3079 DZ Rotterdam, The Netherlands, Tel: +31-102-911-911; E-mail: HaberkornB@maasstadziekenhuis.nl

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Abstract

Prostate Cancer (PCa) is one of the most common malignancies in men worldwide. Androgen Deprivation Therapy (ADT) is a cornerstone in the management of patients with metastatic hormone-sensitive prostate cancer. Recently, researchers found the presence of a subset of PCa cells with intrinsic properties of castration-resistance in hormone-naïve PCa. These pre-existing castration-resistant cells can rapidly expand during ADT and lead to the development of Castration-Resistant Prostate Cancer (CRPC).

We describe two patients with quickly development of CRPC, for whom further treatment was not beneficial. The histopathological and clinical presentation of PCa thus shows strong heterogeneity. To achieve precision medicine, further research should focus on the development and deployment of biomarker-selected targeted therapies. Patients with quickly developing of CRPC at diagnosis can then possibly be selected for alternative treatment strategies.

ABBREVIATIONS

AD: Tandrogen Deprivation Therapy; AR: Androgen Receptor; CRPC: Castration-Resistant Prostate Cancer; EGF: Epidermal Growth Factor Receptor; HSPC: Hormone-Sensitive Prostate Cancer; PCa: Prostate Cancer; PSA: Prostate Specific Antigen; PSMA: Prostate Specific Membrane Antigen

INTRODUCTION

Prostate Cancer (PCa) is one of the most common malignancies in men worldwide [1]. About 15% of cases present with de novo metastatic disease and a significant number of patients will develop metastasis despite prior therapy with curative intent [2]. Androgen Deprivation Therapy (ADT) is a cornerstone in the management of patients with metastatic Hormone- Sensitive Prostate Cancer (HSPC). While patients with PCa initially show disease reduction while on ADT, most will eventually develop castration-resistance and thereby disease recurrence [3].

We present two patients with suspected cases of primary Castration-Resistant Prostate Cancer (CRPC), for whom further treatment was not beneficial. On the basis of the literature, we will provide the latest insights into development of castration-resistant disease.

CASE REPORT

Case 1

In 2015, a 70-year-old male without positive family history for PCa presented to the general practitioner with mild lower urinary tract symptoms. Biochemical analysis showed an increased Prostate Specific Antigen (PSA) level of 8.3 µg/L, after which the patient was referred to a urologist. Digital rectal examination showed no abnormalities. Transrectal ultrasound showed a hypoechoic lesion in the right peripheral zone with an intact capsule and a prostate volume of 60 cc. Ten systematic biopsy specimens were obtained, five from either side, which showed acinar adenocarcinoma with a Gleason score of 4 + 5 = 9. The patient was referred to our hospital to discuss treatment options.

At time of diagnosis, preoperative MRI prostate was not routinely performed and staging was based on clinical findings. Since investigations were not suspicious for extracapsular

extension, surgery seemed to be feasible. Patient underwent a robot assisted, non-nerve- sparing radical prostatectomy. Due to physical features and obesity, a pelvic lymph node dissection was abandoned. Perioperatively, tumour extension towards the rectum was noted. Histopathological examination showed presence of Gleason 4 + 5 = 9 acinar adenocarcinoma (Figure 1A) with presence of extra prostatic extension and seminal vesicle invasion. Surgical margins were extensively positive with a total linear extent of approximately 10 centimetres. Thus, the pathological stage was pT3bNxR1.

The patient showed biochemical and clinical response with a PSA level of < 0.1 µg/L at one month post-prostatectomy (Figure 2A). During follow-up however, patient developed biochemical recurrence. Based on clinical findings disease was considered unfavorable and therefore salvage EBRT was. Over the following years, the patient intermittently received one-month courses of bicalutamide 50mg once daily in the referring hospital.

Biochemical response to this treatment was observed only three times, none of which persisted for longer than the following examination. PSA levels rose to 227.7 µg/L by early 2022 and ADT with goserelin (10.8 mg implant) was added to the bicalutamide regimen (Figure 2B).

However, biochemical analysis showed no signs of stagnation, and the patient was once again referred to our hospital. The patient had developed acute on chronic kidney disease, a normocytic anaemia, high alkaline phosphatase levels, and nocturnal pain in the right femoral region. Abdominal CT-scan showed bilateral hydroureteronephrosis (Figure 3A) and

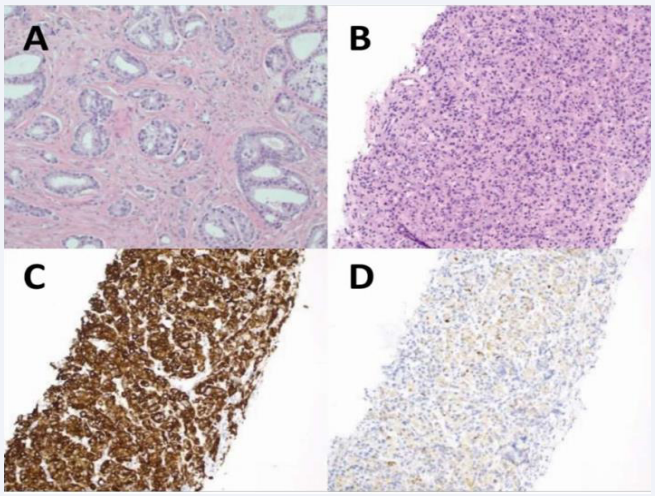

Figure 1 Histopathological analysis of the radical prostatectomy specimen and parailiac lymph node biopsy in Case 1.
Histopathological analysis of the prostate and parailiac lymph node biopsy in Case 1.
Panel A shows a haematoxylin and eosin stain of the radical prostatectomy specimen, showing acinar adenocarcinoma, 20X objective.
Panel B shows a haematoxylin and eosin stain of the parailiac lymph node biopsy, showing poorly differentiated carcinoma, 20X objective.
Panel C shows a AE1/AE3 immunohistochemical stain of the parailiac lymph node biopsy, 20X objective.
Panel D shows a PSA immunohistochemical stain of the parailiac lymph node biopsy, 20X objective.

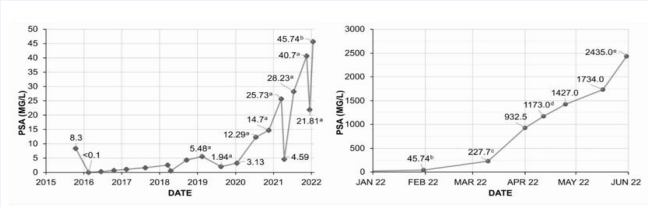

Figure 2 Development of PSA levels in Case 1.
Development of serum PSA levels in Case 1 before (A) and after (B) initiation of goserelin therapy in March 2022.
[a]Followed by one-month course of bicalutamide 50 mg daily.
[b]Followed by 15-day course of nilutamide 150 mg daily.
[c]Goserelin treatment initiation (10.8 mg implant).
[d]Followed by addition of abiraterone 1000 mg daily.
[e]Discontinuation of treatment.

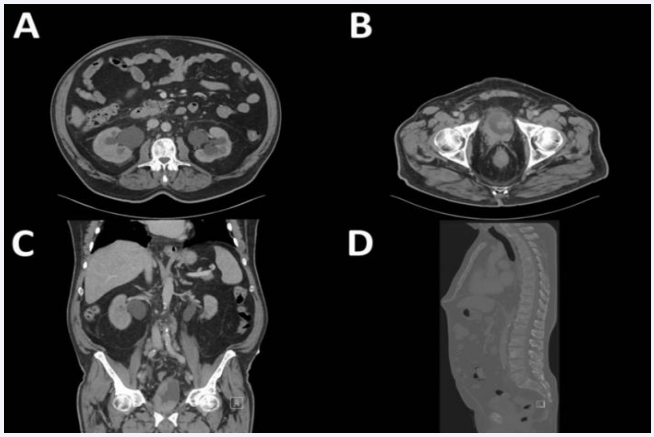

Figure 3 CT-scan imaging in Case 1 showing disease progression.
CT-scan imaging in Case 1 showing disease progression while undergoing ADT.
Panel A shows an axial view depicting bilateral hydronephrosis.
Panel B shows an axial view depicting thickening of the urinary bladder wall inferiorly and near the ureteral ostia
Panel C shows a coronal view depicting thickening of the urinary bladder wall inferiorly and near the ureteral.
Panel D shows a sagittal view depicting multiple osseous lesions suspicious for bone metastases.

thickening of the urinary bladder wall inferiorly and near the ureteral ostia (Figure 3B-C), initially suspicious for bladder cancer. Lymphadenopathy was identified in the inner pelvic, hilar and paraesophageal areas. Multiple skeletal lesions were identified, suspicious for bone metastases (Figure 3D). Urine cytology showed strongly atypical PSA-negative epithelial cells. Although no certain distinction could be made between urothelial carcinoma and prostate carcinoma, multidisciplinary consultation regarded the latter more likely. The patient received bilateral nephrostomy catheters. Histopathological examination of a parailiac lymph node biopsy revealed a poorly differentiated carcinoma (Figure 1B), resembling a Gleason score of 5 + 5 = 10. Immunohistochemistry showed weak positivity for PSA (Figure 1D) and strong positivity for alpha-methylacyl-CoA racemase staining. Additional neuroendocrine markers, synaptophysin and chromogranin, were negative.

Three weeks of treatment with ADT showed no biochemical

effect. A tertiary cancer institute was consulted, after which abiraterone 1000 mg once daily initiated. During the following weeks, the patient suffered from multiple nephrostomy catheter complications and developed acute on chronic kidney disease in response to the initiated ciprofloxacin treatment, due to tubulo-interstitial nephritis. Initially the kidney function recovered, though after a few days catheter failure recurred and the catheters were replaced, after which the patient developed urosepsis. Despite adequate antibiotic treatment and fluid administration due to hypotension, the patient was now in a very poor condition.

By now, PSA levels had risen to 2435.0 µg/L. It was concluded that there were no further treatment options regarding the PCa; the patient's condition was too poor to initiate docetaxel or lutetium-177 treatment. Antibiotic treatment was discontinued and comfort care was initiated. In accordance with the wishes of the patient and the patient's family, the patient was discharged with palliative terminal home care. The patient died six weeks after discharge.

Case 2

A 76-year-old male without positive family history for PCa was referred to our urologist for acute urinary retention in August 2021. Decatheterisation was unsuccessful and further research was initiated. Digital rectal examination was suspicious of a clinical stage T3.

Transrectal ultrasound showed a strongly deviated prostate with hyper- and hypoechogenic areas and a prostate volume of 118 cc. Cystoscopy showed tumour extension around the left ostium. Biochemical analysis revealed an increased PSA level of 263 µg/L (Figure 4).

During transurethral resection of the bladder, ten systematic biopsy specimens were taken, five from either side, which all showed acinar adenocarcinoma with a Gleason score of 4 + 5 = 9 (Figure 5). Biopsy from the bladder neck also showed localisation of prostate cancer. Staging with Prostate Specific Membrane Antigen (PSMA) PET-scan showed irregular intense accumulation throughout the prostate and lymph node metastasis (Figure 6A), local depositions ventral of the bladder and dorsal of the seminiferous vesicles (Figure 6B), and skeletal metastasis.

In conclusion, this case involved a lymphogenic and limited osseous metastatic prostate carcinoma, so called "low volume" metastatic disease. The patient was discussed in a multidisciplinary consultation and lifelong treatment with ADT was initiated in combination with external beam radiotherapy to the prostate. Treatment with ADT was started in November 2021. Radiotherapy treatment was postponed pending response to ADT due to large prostate volume and still in situ catheter. In March 2022, bicalutamide was added to the regimen due to minimal PSA response. After three more months PSA levels still showed no response, despite adequately suppressed testosterone. The patient was referred to the oncologist to discuss treatment options.

Imaging showed disease progression with an increase in tumour depositions in the small pelvis (Figure 6C) and an increase in osseous metastases (Figure 6D). Imaging also showed new onset hydronephrosis on the left side with decline

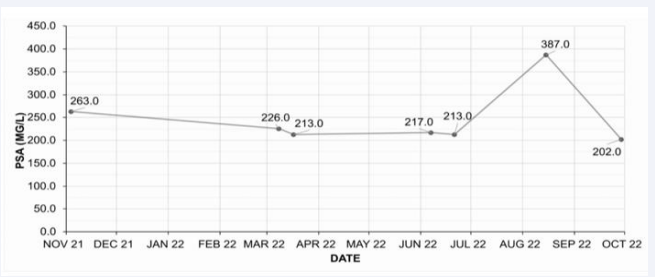

Figure 4 Development of serum PSA levels in Case 2.
Development of serum PSA levels in Case 2 while undergoing ADT.

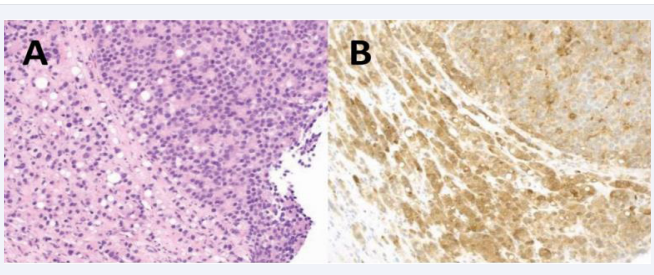

Figure 5 Histopathological analysis of the prostate needle biopsy in Case 2 at diagnosis.
Histopathological analysis of the prostate in Case 2 at diagnosis.
Panel A shows a haematoxylin and eosin stain of the prostate needle biopsy at diagnosis, showing acinar adenocarcinoma, 20X objective.
Panel B shows a PSA immunohistochemical stain of the prostate needle biopsy at diagnosis, 20X objective.

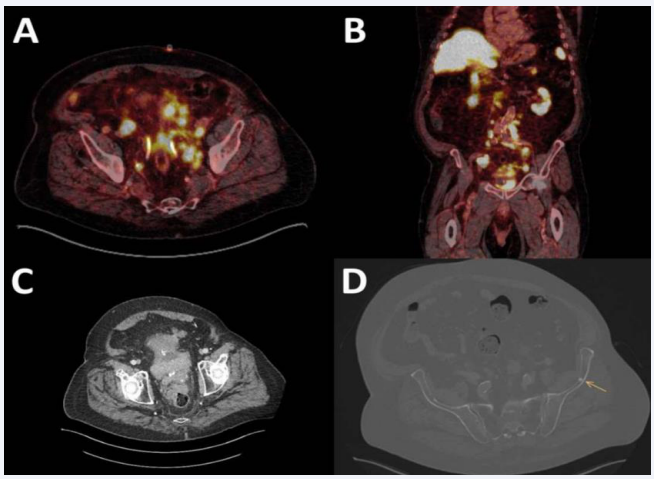

Figure 6 PSMA-PET-scan and CT-scan imaging in Case 2.
PSMA-PET-scan imaging at initial staging (A-B) and CT-scan imaging showing disease progression after biochemical nonresponse to ADT (C-D) in Case 2.
Panel A shows an axial view depicting irregular intense accumulation in a lymph node metastasis and local depositions ventral of the bladder.
Panel B shows a coronal view depicting the irregular intense accumulation in the lymph node metastasis.
Panel C shows an axial view depicting an increase in tumor depositions in the small pelvis.
Panel D shows an axial view depicting a new sclerotic lesion in the left ilium suspicious for osseous metastasis.

in renal function, for which a nephrostomy catheter was placed. Treatment with docetaxel chemotherapy was started in July 2022. After the second course of chemotherapy, the patient was admitted with urosepsis for which he was treated with antibiotics and replacement of the nephrostomy catheter. The course was complicated by renal impairment, most consistent with acute tubular necrosis after hypotension in sepsis or tubulointerstitial nephritis after antibiotic treatment. The clinical condition of the patient deteriorated progressively which made further treatment impossible, in spite of the recovering renal function. In October 2022, the patient was readmitted due to dysfunction of nephrostomy catheter. After catheter replacement, the patient again developed urosepsis. The patient died despite fluid administration and antibiotic treatment in October 2022.

DISCUSSION

Prostate cancer is one of the most common malignancies in men worldwide [1]. In 2021, the Netherlands Comprehensive Cancer Organisation reported approximately 13600 new cases of prostate cancer in the Netherlands resulting in about 3000 deaths annually [2]. The clinical presentation of PCa can range from localised indolent to a rapidly progressing lethal metastatic disease [4-6]. Although the majority of men are diagnosed with organ-confined disease, long-term oncological outcomes can vary greatly [7-9].

Furthermore, histomorphological and molecular tumour characteristics show substantial diversity between different patients and within a given tumour. The vast majority of primary PCa occur multifocally [10]. This means that a diseased prostate gland harbours multiple topographically separate tumour foci. A large body of literature demonstrates that these distinct tumour foci show unique non-overlapping mutation profiles, suggesting that these tumours arise independently and follow separate evolutionary trajectories. Therefore, a given patient can harbour more than one genomically and phenotypically distinct prostate cancer. This poses diagnostic challenges and has major implications for clinical management [10-12]. This also illustrates that focal treatment carries inherent risk of an insufficient treatment option and a “whole gland approach” is preferred as the safest strategy.

Cheng et al. recently found that a subset of PCa cells with intrinsic properties of castration- resistance is present in hormone-naïve PCa before the initiation of ADT [13]. Progression toward castration resistance was initiated from subtype-specific lineage plasticity and clonal expansion of pre-existing neuroendocrine and CRPC-like cells in early PCa. These pre-existing castration-resistant cells can rapidly expand during ADT and lead to the development of CRPC.

Several mechanisms have been proposed that may be responsible for the development of CRPC. Firstly, the Androgen Receptor (AR) gene appears amplified in tissue samples taken from CRPC. Thereby, even in low androgen environments such as during ADT, AR can still be activated to stimulate growth [14]. Additionally, cells expressing excess AR showed agonist activity when exposed to AR antagonists such as bicalutamide and atypical ligands such as oestrogen [15]. Secondly, constitutively active, ligand-independent AR splice variants have been identified in CRPC, suggesting that activity of these splice variants is not affected by anti-androgen drugs, thereby promoting growth in an androgen-depleted environment [16]. Thirdly, intraprostatic testosterone levels have been shown to decline less than serum testosterone levels following ADT [17]. Increased intraprostatic testosterone levels have been associated with progression to CRPC [17]. Gene expression studies indicate an increased intratumoural synthesis as a possible cause, both by increased conversion of weak adrenal androgens into testosterone and de novo synthesis from cholesterol [17]. Thereby, intratumoural androgen levels are sufficient to stimulate AR despite adequate systemic suppression [18]. Lastly, alternate signalling pathways may be upregulated in metastatic PCa. For example, increased expression of Epidermal Growth Factor (EGF) receptor has been detected in patient with metastatic PCa, stimulating cell division [19]. This was associated with poorer disease-free survival [19]. Alternate pathways are logically not directly suppressed by treatment with AR inhibitors.

These potential mechanisms, among others, may be responsible for progression from HSPC to CRPC. Our patients, however, showed very poor response to ADT directly after treatment initiation, suggesting possible primary CRPC. This inherently poor response to ADT underlines that castration-resistance not only develops through deprivation of androgens, but may also present in hormone-naïve PCa.

In the two patients described above, we wanted to use whole-genome sequencing to test the hypothesis of primary castration-resistance. This was, however, not possible due to the need of fresh frozen tissue, high costs of the analysis and fast clinical deterioration of our patients.

This substantial intratumoural heterogeneity poses diagnostic challenges and has major implications for clinical management. At present patients with CRPC are treated as if they have the same disease, while the complex molecular heterogeneity of prostate cancer asks for a more individual approach. To achieve precision medicine, further research should focus on the development and deployment of biomarker-selected targeted therapies. Patients with rapidly development of castration-resistant prostate cancer at diagnosis can then possibly be selected for alternative treatment strategies.

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Conflicts of Interest and Source of Funding

The authors declare no conflicts of interest. This study did not receive funding.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics

According to institutional regulations, ethical approval is not required for case reports based on retrospective analysis. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. In case 1, informed consent could not be obtained due to death of the patient and subsequent unavailability of family for their approval. In case 2 informed consent could be obtained from the surviving relatives. In both cases there is no information that can be traced back to the patients.

REFERENCES

1. Ziegler A, Koch A, Krockenberger K, Grosshennig A. Personalized medicine using DNA biomarkers: a review. Hum Genet. 2012; 131(10): 1627-1638. doi: 10.1007/s00439-012-1188-9. Epub 2012 Jul 1. PMID: 22752797; PMCID: PMC3432208.

2. Integraal Kankercentrum Nederland. Incidentie prostaatkanker. 2022.

3. Galletti G, Leach BI, Lam L, Tagawa ST. Mechanisms of resistance to systemic therapy in metastatic castration-resistant prostate cancer. Cancer Treat Rev. 2017; 57: 16-27. doi: 10.1016/j.ctrv.2017.04.008. Epub 2017 May 8. PMID: 28527407.

4. Attard G, Parker C, Eeles RA, Schröder F, Tomlins SA, Tannock I, et al. Prostate cancer. Lancet. 2016; 387(10013): 70-82. doi: 10.1016/S0140-6736(14)61947-4. Epub 2015 Jun 11. PMID: 26074382.

5. Sartor O, de Bono JS. Metastatic Prostate Cancer. N Engl J Med. 2018; 378(7): 645-657. doi: 10.1056/NEJMra1701695. Epub 2018 Feb 7. PMID: 29412780.

6. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med. 2003; 349(4): 366-381. doi: 10.1056/NEJMra021562. PMID: 12878745.

7. von Eschenbach AC. The biologic dilemma of early carcinoma of the prostate. Cancer. 1996; 78(2): 326-329. doi: 10.1002/(SICI)1097-0142(19960715)78:2<326::AID-CNCR21>3.0.CO;2-X. PMID: 8674011.

8. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA. 1999; 281(17): 1591-1597. doi: 10.1001/jama.281.17.1591. PMID: 10235151.

9. Litwin MS, Tan HJ. The Diagnosis and Treatment of Prostate Cancer: A Review. JAMA. 2017; 317(24): 2532-2542. doi: 10.1001/jama.2017.7248. PMID: 28655021.

10. Mitchell T, Neal DE. The genomic evolution of human prostate cancer. Br J Cancer. 2015; 113(2): 193-198. doi: 10.1038/bjc.2015.234. Epub 2015 Jun 30. PMID: 26125442; PMCID: PMC4506396.

11. Andreoiu M, Cheng L. Multifocal prostate cancer: biologic, prognostic, and therapeutic implications. Hum Pathol. 2010; 41(6): 781-793. doi: 10.1016/j.humpath.2010.02.011. PMID: 20466122.

12. Cyll K, Ersvær E, Vlatkovic L, Pradhan M, Kildal W, Avranden Kjær M, et al. Tumour heterogeneity poses a significant challenge to cancer biomarker research. Br J Cancer. 2017; 117(3): 367-375. doi: 10.1038/bjc.2017.171. Epub 2017 Jun 15. PMID: 28618431; PMCID: PMC5537489.

13. Cheng Q, Butler W, Zhou Y, Zhang H, Tang L, Perkinson K, et al. Pre-existing Castration-resistant Prostate Cancer-like Cells in Primary Prostate Cancer Promote Resistance to Hormonal Therapy. Eur Urol. 2022; 81(5): 446-455. doi: 10.1016/j.eururo.2021.12.039. Epub 2022 Jan 17. Erratum in: Eur Urol. 2023 Jun;83(6):e170-e171. PMID: 35058087; PMCID: PMC9018600.

14. Wang G, Zhao D, Spring DJ, DePinho RA. Genetics and biology of prostate cancer. Genes Dev. 2018; 32(17-18): 1105-1140. doi: 10.1101/gad.315739.118. PMID: 30181359; PMCID: PMC6120714.

15. Chen CD, Welsbie DS, Tran C, Baek SH, Chen R, Vessella R, Rosenfeld MG, Sawyers CL, et al. Molecular determinants of resistance to antiandrogen therapy. Nat Med. 2004; 10(1):33-39. doi: 10.1038/nm972. Epub 2003 Dec 21. PMID: 14702632.

16. Guo Z, Yang X, Sun F, Jiang R, Linn DE, Chen H, et al. A novel androgen receptor splice variant is up-regulated during prostate cancer progression and promotes androgen depletion-resistant growth. Cancer Res. 2009; 69(6): 2305-2313. doi: 10.1158/0008-5472.CAN-08-3795. Epub 2009 Feb 24. PMID: 19244107; PMCID: PMC2672822.

17. Cai C, Balk SP. Intratumoral androgen biosynthesis in prostate cancer pathogenesis and response to therapy. Endocr Relat Cancer. 2011; 18(5): R175-R182. doi: 10.1530/ERC-10-0339. PMID: 21712345; PMCID: PMC3815562.

18. Bluemn EG, Coleman IM, Lucas JM, Coleman RT, Hernandez-Lopez S, Tharakan R, et al. Androgen Receptor Pathway-Independent Prostate Cancer Is Sustained through FGF Signaling. Cancer Cell. 2017; 32(4): 474-489.e6. doi: 10.1016/j.ccell.2017.09.003. PMID: 29017058; PMCID: PMC5750052.

19. Mandel A, Larsson P, Sarwar M, Semenas J, Syed Khaja AS, Persson JL. The interplay between AR, EGF receptor and MMP-9 signaling pathways in invasive prostate cancer. Mol Med. 2018; 24(1): 34. doi: 10.1186/s10020-018-0035-4. PMID: 30134822; PMCID: PMC6020326.