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Case Report

Locally recurrent prostate cancer with RB1/TP53 alterations successfully treated by salvage focal brachytherapy: a case report

Takahiro Komori[1], Takeo Kosaka[1], Tomoki Tanaka[2], Keitaro Watanabe[1], Yota Yasumizu[1], Shuji Mikami[3], Mototsugu Oya[1]

[1]Department of Urology, Keio University School of Medicine, Tokyo, Japan; [2]Department of Radiology, Keio University School of Medicine, Tokyo, Japan; [3]Department of Pathology, National Hospital Organization Saitama Hospital, Tokyo, Japan

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Abstract: Retinoblastoma transcriptional corepressor 1 (RB1) and tumor protein p53 (TP53) are well-known tumor suppressor genes; their alterations are associated with poor prognosis in human malignancies and quite rare in locally recurrent cases. The patient was a 58-year-old man who was diagnosed with cT1cN0M0 prostate cancer with Gleason score of 3+3=6 and underwent brachytherapy as the initial treatment. Local recurrence was detected in the left lobe of the prostate 154 months later and whole-exome sequencing that was performed at the request of the patient revealed RB1 loss-of-heterozygosity and TP53 p.I162Rfs*27 mutations. He underwent salvage focal brachytherapy with ^{125}I seeds and serum prostate-specific antigen levels has been stabilized without any genitourinary or gastrointestinal toxicity.

Keywords: RB1, TP53, tumor suppressor gene, salvage focal brachytherapy, prostate cancer

Introduction

Prostate cancer is the most common cancer and second leading cause of cancer death among men in the United States, and its prevalence is increasing in Japan [1]. 5-year relative survival rate for men with local and regional disease is 100%. However, less than one-third of men diagnosed with metastatic disease survive 5 years. Androgen deprivation therapy (ADT) is the standard treatment for advanced prostate cancer, but they acquire resistance to ADT and progress to castrasion-resistant prostate cancer (CRPC) through a variety of mechanisms. Nowadays, various genetic abnormalities such as brest cancer 1/2 (BRCA 1/2), Retinoblastoma transcriptional corepressor 1 (RB1), tumor protein p53 (TP53), and Phosphatase and Tensine Homolog (PTEN) mutations have been reported and found to be related to drug resistance and treatment strategies have changed over time. New agents such as Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, have emerged as genetic analysis for prostate cancer have progressed and proved to be effective for metastatic CRPC with the DNA repair gene BRCA1/2 or ATM mutations in the Profound trial [2]. RB1 and TP53 are well-known tumor suppressor genes (TSGs); the loss of their function is associated with aggressive tumor progression. In prostate cancer, alterations in these genes are often found in advanced cases and rarely in localized cases [3]. Herein, we report a patient with a rare case of locally recurrent prostate cancer with RB1/TP53 alterations, for whom salvage focal brachytherapy was performed after first brachytherapy.

Case presentation

A 58-year-old man presented with a serum prostate-specific antigen (PSA) level of 7.4 ng/mL and prostate cancer was suspected. He underwent prostate needle biopsy, and adenocarcinoma with a Gleason score of 3+3=6 was detected in 1 of 12 cores. He was diagnosed with cT1cN0M0 prostate cancer; brachytherapy

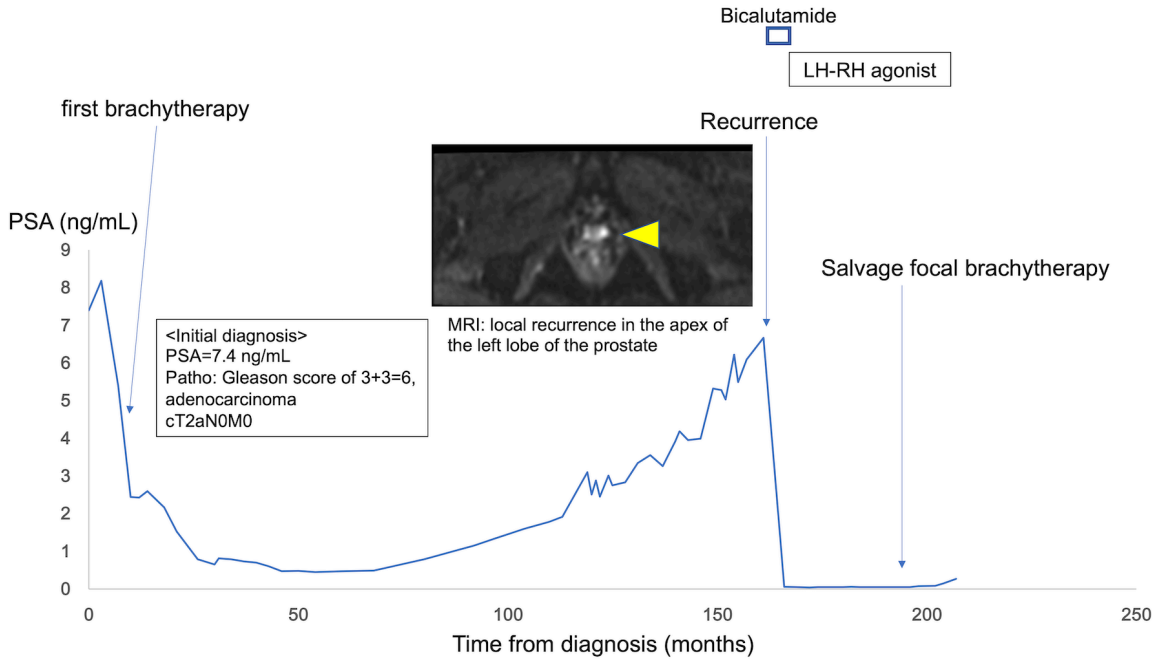

Figure 1. Serum PSA levels and treatment course.

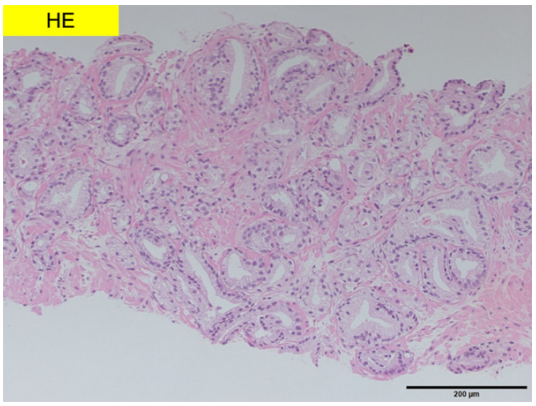

Figure 2. Representative images of hematoxylin and eosin-stained prostate tissue sections (100×). Scale bar =0.2 mm.

was administered. Initially, he showed a good response to the therapy, but 154 months after brachytherapy, the serum PSA level gradually rose to 6.7 ng/mL (**Figure 1**). Magnetic resonance imaging (MRI) showed low signal intensity on diffusion-weighted imaging (DWI) at the apex of the left lobe of the prostate, and local recurrence was suspected. No metastasis was detected in the whole-body computed tomography (CT) analysis. Transperineal prostate saturation needle biopsy revealed adenocarcinoma without neuroendocrine differentiation in the left lobe (**Figure 2**). He was administered salvage androgen deprivation therapy (ADT), which decreased the serum PSA level to the nadir of 0.048 ng/mL; the serum PSA level was maintained at around 0.05 ng/mL for about two years. Despite the stable serum PSA level, whole-exome sequencing was performed using specimens acquired in the saturation biopsy before ADT at the request of the patient; this led to the identification of the RB1 loss-of-heterozygosity and TP53 p.I162Rfs*27 mutations (**Table 1**). These findings suggested the possibility of aggressive tumor progression. Whole-body CT and pelvic MRI were performed again, and recurrence was still detected only in the left lobe of the prostate; therefore, curative local therapy was considered to prevent tumor progression. Because salvage focal brachytherapy has been reported to be successful in treating locally recurrent castration-resistant prostate cancer (CRPC) after radiation therapy in one of our previous studies [4], focal brachytherapy with ^{125}I seeds was administered in this case. While salvage prostatectomy and continuation of ADT were also considered, urinary incontinence and muscle weakness were a concern because he was an enthusiastic tennis player. A prescribed radiation dose of 140 Gy was administered to the patient. The clinical target volume (CTV) was determined using the MRI and biopsy results. The postimplant dosim-

Table 1. Results of FoundationOne® companion diagnostic (CDx) assay

Biomarker findings		Genomic findings	
MSI	stable (0.36%)	RB1	Loss of heterozygosity
TMB	3 Muts/Mb	TP53	p.I162Rfs*27

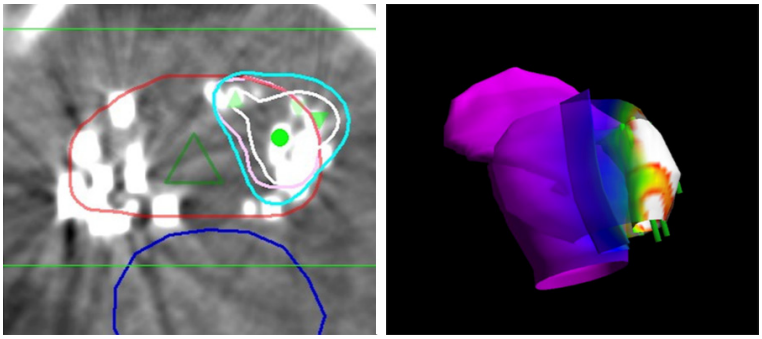

Figure 3. The distribution of radiation doses during the post-planning stage of the salvage implantation. Isodose lines: 140 Gy (100%), cyan; 280 Gy (150%), white. Contours: prostate, red line; CTV, pink line; urethra, green line; rectum, blue line.

etry was performed a month after seed implantation; the CTV was found to be 2.3 cc, the CTV V_{100} (volume receiving 100% of the prescribed dose) was 98.5%, the CTV D_{90} (the minimal dose received by 90% of the volume) was 178.9 Gy, the rectum V_{100} was 0 cc, and the urethral V_{150} (volume receiving 150% of the prescribed dose) was 0 cc. The biologically effective dose considering the CTV is 190 Gy [5] (**Figure 3**). There is no consensus on how long ADT should be continued, so ADT was stopped after focal brachytherapy, and the PSA level was found to be stable for 15 months with no genitourinary or gastrointestinal adverse events (**Figure 1**).

Discussion

Aggressive nature

Alterations in well-known TSGs, such as RB1, TP53, and Phosphatase and Tensine Homolog (PTEN), can be detected by next-generation sequencing; alterations in these genes are common in prostate cancer [6, 7]. The loss of function of these TSGs is associated with aggressive tumor progression [8-10]. These alterations are common in advanced tumor stages but are rarely found in cases of localized tumor recurrence and are associated with neuroendocrine differentiation and androgen receptor (AR) resistance [3].

A recent study indicated that recurrent prostate cancer tumors observed after radiation therapy are often enriched in specific genomic alterations in TSGs, such as defects in TP53, breast cancer 2 (BRCA2), and partner and localizer of breast cancer 2 (PALB2) and loss of PTEN [11]. Another study evaluated the clinical outcomes of single or compound TSG alterations across a broad spectrum of prostate cancers; localized prostate cancer cases with TSG alterations showed shorter event-free survival and a shorter time to CRPC than those without TSG alterations. Furthermore, cumulative gene hits have been found to increase the risk of relapse [12]. In another study, whole-exome sequence data from 410 samples obtained via metastatic biopsy were evaluated, and prostate cancers with combined RB1 and TP53 loss were found to exhibit stem cell-like features and loss of AR activity [13].

Focal brachytherapy

In this case of localized prostate cancer with RB1/TP53 alterations, early tumor progression was anticipated and focal brachytherapy was administered; salvage prostatectomy and continuation of ADT were also considered.

Despite insufficient evidence regarding the use of focal brachytherapy for treating the local recurrence of prostate cancer after first brachytherapy, it is aimed at reducing the risk of gastrointestinal or genitourinary toxicity while maintaining antineoplastic effects. The results obtained after the treatment of 12 patients with focal brachytherapy were reviewed in a retrospective study; the 4-year biochemical disease-free survival rate was 78%, and no patient had grade 3 genitourinary/gastrointestinal toxicity [14]; furthermore, other studies have also reported its effectiveness [15-17]. Furthermore, a recent study showed that significantly lower urinary toxicity was found at six months in patients who underwent focal brachytherapy at the apex than in those who underwent focal

brachytherapy at the base of the prostate [18]; hence, focal brachytherapy is suitable for patients with local recurrence at the apex of the prostate.

The present report describes a patient with locally recurrent prostate cancer (at the apex of the left lobe of the prostate) after brachytherapy harboring RB1/TP53 alterations. In most cases, ADT is administered for local recurrence after brachytherapy, and actually it was applied in this case. However, whole-exome sequencing suggested the possibility of aggressive tumor progression. The strategies of local control for such cases have not been established and these are the unmet medical needs, so salvage focal brachytherapy was administered. ADT was stopped after the salvage focal brachytherapy, and the PSA level have been stable for 15 months without any adverse events. Thus, focal brachytherapy may represent an effective therapeutic modality for the treatment of locally recurrent prostate cancer. However, long-term follow-up is needed to ensure the consistency of our findings.

Conclusion

To our knowledge, this is the first case of locally recurrent prostate cancer after first brachytherapy harboring RB1/TP53 alterations controlled successfully by salvage focal brachytherapy. It may serve as an effective treatment option for locally recurrent prostate cancer with such malignant genetic features. This case provides insights into genetic analysis-based treatment strategies for such rare malignancies.

Disclosure of conflict of interest

None.

Abbreviations

RB1, Retinoblastoma transcriptional corepressor 1; TP53, tumor protein p53; TSG, tumor suppressor gene; PSA, prostate-specific androgen; MRI, magnetic resonance imaging; CT, computed tomography; ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; CTV, clinical target volume; PTEN, Phosphatase and Tensine Homolog; AR, androgen receptor.

Address correspondence to: Dr. Takeo Kosaka, Department of Urology, Keio University School of Medicine, Japan 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Tel: +81-3-5363-3825; ORCID: 0000-0002-4371-4594; Fax: +81-3-3225-1985; E-mail: takemduro@gmail.com

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