

CASE REPORT

Stereotactic body radiation therapy for the treatment of oligoprogression on androgen receptor targeted therapy in castration-resistant prostate cancer

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Abstract

Castration-resistant prostate cancer is an incurable disease. To date, six agents-abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223 and sipuleucel-T- have shown clinical efficacy in phase III clinical trials, leading to their FDA approval. Patients are typically sequenced through most or all of these agents, and then eventually succumb to their disease. Development of new treatments remains an unmet need. We report a case of a patient who progressed on enzalutamide with a single enlarging metastatic lesion, was treated with ablative stereotactic body radiation therapy while maintaining the same systemic treatment, who then had durable complete remission. Our findings have important clinical implications and suggest novel clinical trials for this difficult to treat disease.

INTRODUCTION

Abiraterone and enzalutamide have been shown in phase III clinical trials to have efficacy in patients with castration-resistant prostate cancer (CRPC), leading to improved overall survival [1,2]. Abiraterone inhibits intratumoral production of androgens, thereby decreasing engagement of the androgen receptor (AR) for nuclear signaling. Enzalutamide inhibits AR

signaling by directly binding to AR. Acquired resistance to both abiraterone and enzalutamide inevitably develops due to AR mutations and other escape mechanisms [3]. Radiation has been shown to be effective after progression on AR targeted therapy, due to non-overlapping mechanism of resistance [4].

During cancer treatment, progression is due to the development of new mutations in the progressing lesions causing

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Received: June 22, 2017. Revised: September 8, 2017. Accepted: October 11, 2017

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treatment resistance, while responsive or stable lesions have not acquired those mutations [5]. For prostate cancer treatment, we hypothesize that ablative radiation of lesions progressing on AR targeted therapy would likely be effective as resistant lesions are ablated, while continuing AR targeting to keep responsive or stable lesions suppressed.

Stereotactic body radiation therapy (SBRT) is a highly conformal radiation technique that delivers high-dose radiation to a tumor while sparing much of the nearby normal organs [6]. Compared to conventional palliative radiation therapy, which is delivered over 10–15 days with the intent to control pain but not disease progression, SBRT is commonly delivered in 3–10 treatments with the intent of disease ablation. There is evidence that SBRT achieves local control rates in excess of 90% by sterilizing the treated area.

We report a case of a patient with metastatic prostate cancer who progressed with a growing solitary metastatic lymph node while on AR targeted therapy with enzalutamide, but went on to have durable complete remission after treatment with SBRT to the node while continuing enzalutamide.

CASE PRESENTATION

The patient is a 44-year-old male diagnosed with high-risk prostate cancer [clinical stage T1c, Gleason 4 + 4 = 8, prostate-specific antigen (PSA) 29.2 ng/ml]. He elected for primary treatment with robotic-assisted prostatectomy (final pathology revealed pT3b N1 M0, Gleason 5 + 4 = 9, with seminal vesicle invasion and involvement of bilateral obturator lymph nodes). His PSA post-prostatectomy was undetectable. Adjuvant radiation was not offered due to residual urinary incontinence. He was offered adjuvant androgen deprivation therapy (ADT) in the form of leuproreotide which maintained his PSA at undetectable levels for ~3 years when it increased to 1.9 ng/ml (Fig. 1). At that time, he received salvage external beam radiation therapy (64.8 Gy) to the

pelvic region including the obturator bed and prostatic resection bed. ADT was continued throughout radiation therapy.

One year later, he developed biochemical recurrence with his PSA going up from 0.05 ng/ml to 1.19 ng/ml for which bicalutamide was added to ADT. His PSA continued to rise to 2.05 ng/ml along with enlarging external iliac lymph nodes (Fig. 1). Bicalutamide was discontinued and the patient was started on abiraterone and prednisone with excellent response, with undetectable PSA and complete response of his lymph nodes for the next 2 years. However, his PSA gradually increased to 0.06 ng/ml and he was switched to enzalutamide, which led to stable PSA for another 6 months until it increased to 0.4 ng/ml when imaging was done to evaluate for metastatic disease. CT scan showed an enlarging para-aortic lymph node (Fig. 2A). Thereafter, the patient was evaluated for SBRT to the lymph node, which was however, not considered feasible at the time due to its small size. A follow-up CT scan 4 months later showed an increase in the size of the lymph node to 1.5 cm with PSA rising to 2.74 ng/ml (Figs 1 and 2B). The patient then received SBRT 50 Gy in 10 fractions to the para-aortic lymph node (Fig. 3). During this entire time, enzalutamide was continued. Six months post treatment, CT scan showed marked decrease in the size of the para-aortic lymph node and decline in PSA (Figs 1 and 2C). At the latest follow-up 6 months thereafter, the patient had been doing well on enzalutamide and his PSA remained low.

DISCUSSION

CRPC is defined as progressive prostate cancer while on ADT with serum testosterone <50 mg/dl. Median overall survival is limited, ranging from 9 to 30 months [7]. At present, six agents have shown overall survival benefit in phase III clinical trials and are approved for use in patients with CRPC. They include docetaxel, abiraterone, enzalutamide, cabazitaxel, sipuleucel-T and radium-223 [7]. Although, the sequencing of these agents has not been clearly defined, certain clinical situations favor the use of one agent over another. Sipuleucel-T seems to require at least 6 months duration after treatment to have beneficial effect. Therefore, it is indicated primarily in minimally symptomatic or asymptomatic patients with at least 6 months life expectancy. Docetaxel is the preferred initial agent in symptomatic patients with extensive disease burden or with visceral metastases. For asymptomatic patients with less disease burden or non-visceral metastases, the AR targeting agents, abiraterone or enzalutamide, are preferable over docetaxel, as they are better tolerated. For patients with progression or relapse post-docetaxel not previously on AR targeted therapy, abiraterone or enzalutamide are usually the preferred next drugs given their better tolerability profile, followed by cabazitaxel. For patients with multi-focal painful bony metastases, radium-223, an α -emitter, can be used and has been shown to improve survival.

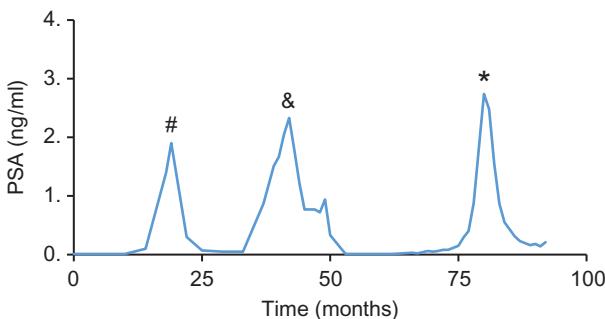


Figure 1: Trend of PSA over time. # marks salvage radiation to prostate bed and pelvis; & marks starting AR targeted therapy with abiraterone; *marks SBRT treatment to metastatic para-aortic lymph node.



Figure 2: Computed Tomography (CT) scans showing enlarging metastatic para-aortic lymphadenopathy (A) 4 months prior to SBRT, (B) at SBRT; and then responding to treatment and (C) 4 months after SBRT.

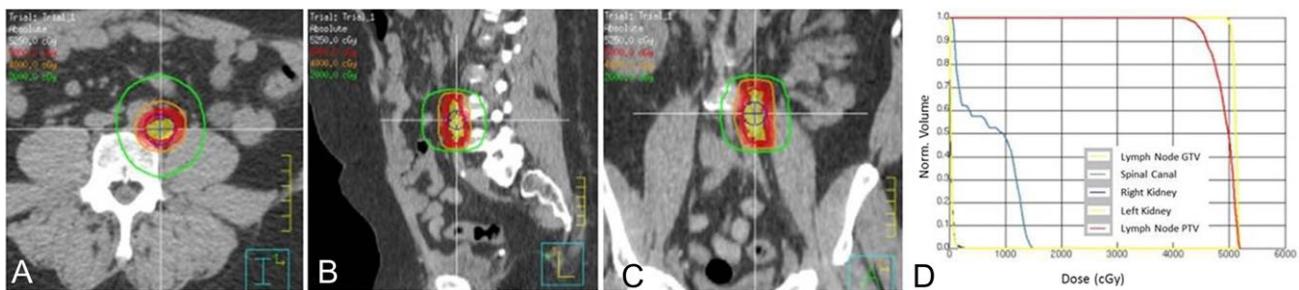


Figure 3: SBRT for a LEFT iliac lymph node. The prescribed dose was 50 Gy in 5 Gy fractions. Isodose lines are shown in (A, axial; B, sagittal and C, coronal). The dose volume histogram is shown in D.

Although these treatments are effective, unfortunately patients eventually run out of treatments and succumb to their disease.

The use of SBRT has been applied to the treatment of castration-sensitive prostate cancer (CSPC) with oligometastatic disease, defined as five or fewer metastatic lesions. To date, two retrospective studies have been completed showing a strong trend towards improved long-term disease control and outcomes. Schick et al. published a series of 50 patients with CSPC with a total of 79 metastatic lesions including lymph nodes, bones and lungs [8]. Their cohort showed a 3-year biochemical recurrence free survival of 55%, clinical recurrence free survival of 59% and 3-year overall survival of 92%. None of their patients showed Grade 3 or worse adverse events. Similarly, Muacevic et al. completed a series of 40 patients with CSPC with a total of 64 bony lesions [9]. Their 2-year local control was 95.5%.

Our case report is the first to show that SBRT can be effectively added to control oligoprogression while on AR targeted therapy for CRPC, with improved disease control. We have previously shown such treatment approach using SBRT can be applied to gastrointestinal cancer patients with oligoprogression on chemotherapy [10]. Our data suggests that larger studies using SBRT for oligoprogression should be proposed to assess survival outcomes for the treatment of CRPC. Incorporating more sensitive imaging techniques for prostate cancer like ¹¹C-Choline or Axumin PET-CT scans, oligoprogression may be detected earlier in the disease course and treatment with SBRT may even be more effective.

CONCLUSION

This case report emphasize use of SBRT as an additional tool in long-term control of oligoprogression of CRPC while preserving the mainline therapy.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

FUNDING

No funding was required for this report.

DECLARATIONS

Ethics approval and consent to participate: We followed University of Florida (UF) Institutional Review Board (IRB) guidelines for this case study. UF IRB grants waiver or does not require prior IRB approval for this study. <http://irb.ufl.edu/wp-content/uploads/op-casereports.pdf>

CONSENT FOR PUBLICATION

Consent to publish has been obtained from patient.

AVAILABILITY OF DATA AND MATERIAL

Any applicable data can be provided upon request.

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