Case - Long-term management of oligo-progressive metastatic castrate sensitive prostate cancer with recurrence-directed radiotherapy

Shan Grewal[1,2], Hsin-Pei Hu[1,3], Andre Gouveia[1,3], Theodoros Tsakiridis[1,2,3]

[1]Department of Radiation Oncology, Juravinski Cancer Center, Hamilton Health Sciences, Hamilton, ON, Canada; [2]Center for Discovery in Cancer Research, McMaster University, Hamilton, ON, Canada; [3]Department of Oncology, Juravinski Cancer Center, Hamilton Health Sciences, Hamilton, ON, Canada

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INTRODUCTION

Although localized prostate cancer (PCa) has a favorable prognosis, with a five-year progression-free survival (PFS) rate of 65–85%, many patients develop distant metastatic disease, which carries a reported five-year survival rate of 41% in Canada in 2023.[1] The survival rate for patients with metastatic castrate-sensitive PCa (mCSPC) has further improved through the use of androgen deprivation therapy (ADT), androgen pathway inhibitors (ARPIs), docetaxel chemotherapy, and metastasis- or recurrence-directed therapy (RDT). ADT remains a cornerstone in the management of recurrent and metastatic PCa, but studies have reported its impact on patient-reported quality of life (QoL),[2] increased cardiovascular morbidity and mortality,[3] and osteoporotic skeletal fracture risks.[4] This side effect profile demonstrates a need to explore pathways to limit and/or postpone its use.

RDT includes stereotactic body radiation therapy (SBRT) to precisely deliver high-dose radiation to metastatic sites with or without concomitant systemic therapy, elective nodal irradiation, and surgery. SBRT has shown promising efficacy in managing oligometastatic disease in various cancer types.

This case report details a patient with CSPC who presented with episodes of oligo-progression, resisted treatment with standard-of-care ADT over a period of nine years, and was managed with nine courses of RDT with limited ADT. This case highlights the potential of RDT in addressing some therapeutic challenges posed by progressing metastatic PCa.

CASE REPORT

A 61-year-old male presented with an elevated prostate-specific antigen (PSA) of 5.53 ng/mL in 2012. Medical history was significant for hypertension, sleep apnea, knee arthroplasty, and burn trauma surgery. He underwent laparoscopic radical prostatectomy, revealing pT3a, N0, International Society of Urological Pathology (ISUP) grade group 3 (Gleason score of 7 [4+3]) prostatic adenocarcinoma. Post-surgery PSA was 0.066 ng/mL, and it increased to 0.22 ng/mL in April 2014, with a doubling time of six months. He then participated in the RTOG-0534 trial and was randomized to prostatic bed radiotherapy alone, 6480 cGy in 36 daily fractions, for salvage treatment (Figure 1A).

After radiotherapy, his PSA reached a nadir of 0.09 ng/mL in October 2014, but it progressed to 2.4 ng/mL over the next four years, with a 10-month doubling time (Figure 2A). The patient denied physical symptoms, but bone scan and computed tomography (CT) scans in June 2018 revealed metastatic foci in the chest wall (L-3rd rib) and spine (T7) (Figures 1B, 1D). He refused standard of care ADT and requested local therapy alone. Both metastatic sites were treated with low-dose radiotherapy of 2000 cGy in five consecutive daily fractions using 3D-conformal techniques without complications (Figures 1C, 1E).

His PSA decreased significantly to 0.48 ng/mL by November 2018 but rose again to 1.0 ng/mL after 10 months (Figure 2A). Prostate-specific membrane antigen-positron emission tomography PSMA-PET/CT (^{18}F-DCFPyL) scan showed no activity in previously detected sites but identified new metastatic foci in the right scapula, right ilium, sacrum, and two iliac nodes (Figure 1F). The patient once again declined ADT, opting for further courses of RDT (Figures 1G–L). All newly identified sites were treated with SBRT in March 2020 using a moderate dose (3000cGy in five fractions delivered every other day). He had no observable toxicity and showed rapid biochemical response (Figure 2A).

KEY MESSAGES

- While ADT is a cornerstone in the management of recurrent and metastatic prostate cancer, it can significantly impact patient-reported QoL and increase cardiovascular and skeletal morbidity and mortality.
- Metastasis- or recurrence-directed therapy (RDT) with the use of stereotactic body radiotherapy (SBRT) has shown promising efficacy in managing oligometastatic disease in various cancer types.
- Future studies may further define the role of RDT in the long-term management of metastatic prostate cancer to delay systemic therapy in certain clinical scenarios.

Our patient's PSA steadily rose to 3.3 ng/mL in the subsequent two years. A PSMA-PET/CT scan in July 2022 identified disease recurrence at the previously treated T7 vertebra and two novel sites in a perirectal and left external iliac lymph node (Figure 1M). At this point, the patient agreed to ADT, alongside SBRT (3000cGy in five fractions delivered every other day) to the new metastatic sites (Figures 1N–S). The patient had no observable gastrointestinal or neurologic toxicity from the treatments.

Undetectable PSA levels were obtained in September 2022 and in January 2023. At that point, ADT was discontinued at the patient's request. The patient has remained in biochemical remission (undetectable PSA) as testosterone began to rise to eugonadal testosterone levels (T=5.2 nmol/L) in October 2023. At the time of the preparation of this report, the patient enjoyed 18 months of eugonadal complete biochemical remission (Figure 2A).

DISCUSSION

We report a patient with oligo-progressive CSPC who underwent well-tolerated RDT, guided by high-sensitivity modern PSMA-PET imaging, to achieve biochemical disease control over a period of five years while deferring ADT for a significant amount of time (Figure 2B). This treatment approach is unconventional and diverges from clinical guidelines, driven by the patient's refusal of systemic therapy. Although unconventional, this case and surmounting research underscore the promise of RDT

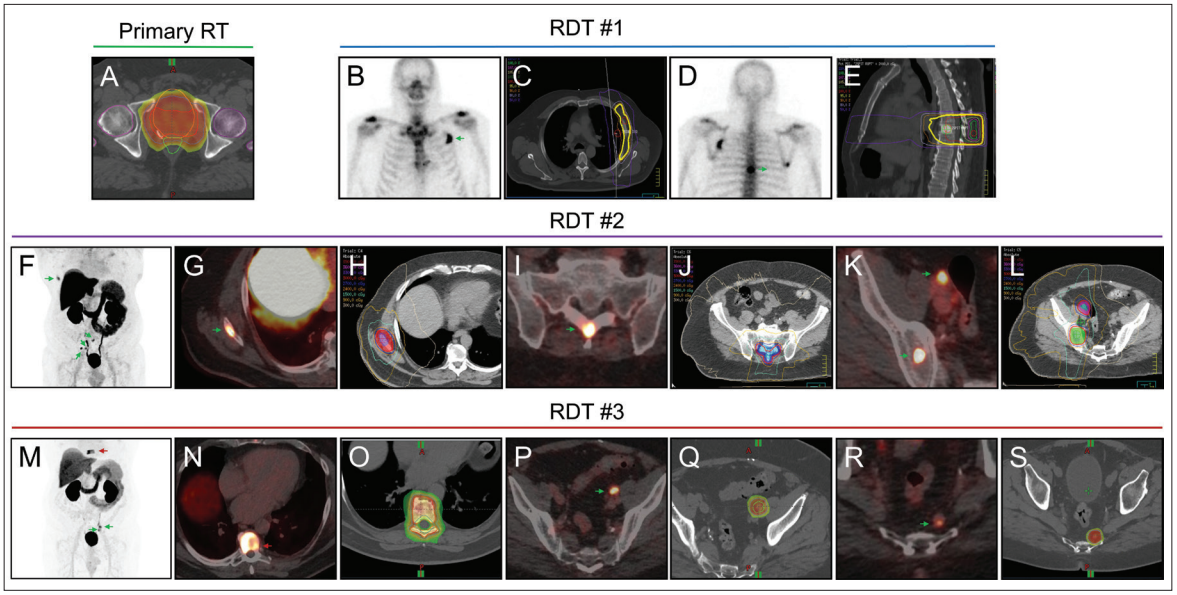

Figure 1. Imaging and radiotherapy (RT) plans for primary and metastatic prostate cancer. (A) Radiation plan for prostate bed treated in 2014. (B, D) Bone scan in June 2018 revealed metastatic foci in the third rib and T7 spine (green arrows). (C, E) Three-dimensional conformal radiation plans (2000 cGy in 5 fractions) for metastases in the T7 spine and third rib. (F) Prostate-specific membrane antigen positron emission tomography (PMSA-PET) scan in January 2020 showed complete response in previous metastases but identified several new sites (green arrows from top to bottom): Right scapula (G), sacrum (I), two right external iliac lymph nodes (one shown) and right ilium (K). Stereotactic body radiation therapy (SBRT) plans (3000 cGy in 5 fractions) for the metastatic sites at (H) right scapula, (J) sacrum, and (L) one of the right external iliac nodes and right ilium. (M) PSMA-PET scan in June 2022 showed disease recurrence at the T7 vertebra (red arrow; N), plus novel sites in the right external iliac lymph node (top green arrow; P) and perirectal lymph node (bottom green arrow; R). SBRT plans (3000 cGy in 5 fractions) for the re-treatment of T7 spine (O) and the treatment of the right external iliac lymph node (P) and perirectal lymph node (S).

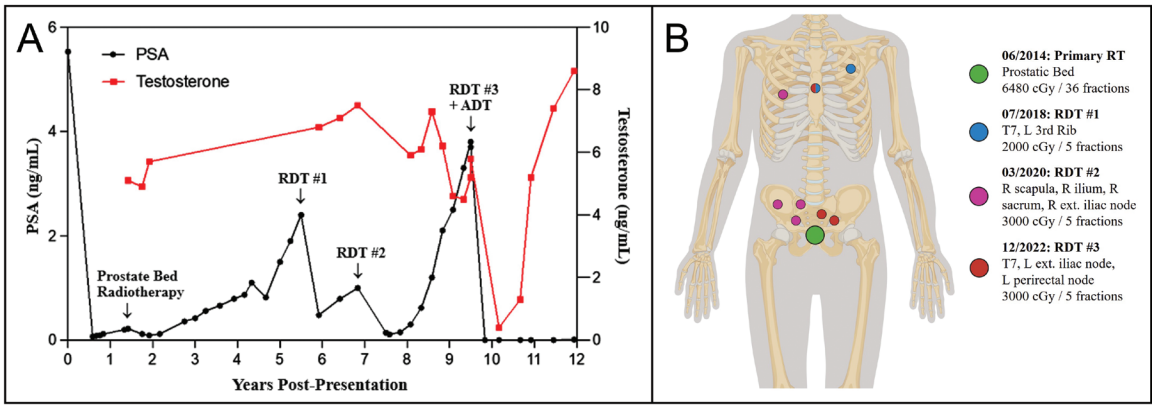

Figure 2. Summary of disease course, prostate-specific antigen (PSA) and testosterone measurements, and radiotherapy treatments. (A) Patient PSA and testosterone trends since diagnosis. (B) Summary of disease sites and corresponding treatment regimen.

for efficacy in managing metastatic lesions, prompting further consideration of the timing and necessity of ADT in certain clinical scenarios. Once systemic therapy was initiated in this patient, the combined use of ADT and SBRT yielded durable biochemical remission consistent with the synergy seen in studies.[5,6]

The intensification of systemic therapy with the addition of ARPIs to ADT ± chemotherapy has been elevated to the standard of care for de novo metastatic CSPC after recent studies demonstrated failure-free and overall survival (OS) benefit with their use.[7-9] Within this patient population, recent studies have identified an emerging role for consolidative ablative local radiotherapy to active disease sites in metastatic PCa.

The STAMPEDE and PEACE1 trials showed improved PFS and OS benefit with the addition of prostate radiotherapy to standard-of-care ADT in patients with low-volume mCSPC.[10,11] The ORIOLE and STOMP phase 2 randomized trials demonstrated that compared to surveillance, SBRT for oligo-metastases in metastatic PCa with ≤3 lesions improved PFS (61% vs. 19% at six months) and ADT-free survival (34% vs. 8% at five years), with few serious toxicity events.[5,12] These outcomes reflect the broader trend in oligo-metastatic cancer management. In this setting, the SABR-COMET phase 2 trial found patients with ≤5 metastases who received ablative therapy in addition to the standard-of-care saw enhanced five-year PFS (17% vs. 3%) and median OS (50 months vs. 28 months).[13]

In the absence of systemic therapy, metastasis-directed therapies alone, including SBRT and surgery, are capable of prolonging ADT-free survival in oligo-metastatic PCa.[14] The findings align with the broader objective of metastasis- and recurrence-directed therapy in advanced PCa: to prolong ADT-free survival, delay systemic treatment initiation and/or reduce systemic treatment duration, improving QoL while controlling disease progression.

Using a reversal of the conventional paradigm, studies have begun reporting RDT outcomes in oligo-metastatic CSPC with short-course ADT added as an adjunct treatment. Although there were no detected differences in the time to development of CRPC or eugonadal PFS rates, the randomized phase 2 trial RADIOSA showed significantly improved clinical and biochemical PFS with the addition of six-month ADT in patients with metachronous oligo-metastatic CSPC treated with SBRT.[15] Such findings support a growing emphasis on personalized approaches to RDT and ADT.

CONCLUSIONS

Overall, recurrence-directed SBRT has emerged as a promising and transformative tool to help manage early metastatic PCa. The case we present here suggests that SBRT, in combination with PSMA-PET imaging, may be a useful tool for long-term management of oligo-progressive CSPC that could help delay systemic therapy in certain clinical scenarios and/or complement short-term ADT as an approach to preserving QoL in patients with limited metastatic burden.

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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CORRESPONDENCE: Dr. Theos Tsakiridis, Radiation Oncology, Juravinski Cancer Center, Hamilton, ON, Canada; tsakirt@mcmaster.ca