Low-Dose Hemibody Radiation, a Treatment Option for Recurrent Prostate Cancer: A Phase 2 Single-Arm Trial

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Abstract

Purpose: Nontargeted low-dose ionizing radiation has been proposed as a cancer therapeutic for several decades; however, questions remain about the duration of hematological changes and optimal dosing regimen. Early studies delivering fractionated low doses of radiation to patients with cancer used varying doses and schedules, which make it difficult to standardize a successful dose and scheduling system for widespread use. The aim of this phase 2 two-stage trial was to determine whether low-dose radiation therapy (LD-RT) reduced prostate-specific antigen (PSA) in patients with recurrent prostate cancer in efforts to delay initiation of conventional therapies that are known to decrease quality of life. The primary study outcome was reduction in PSA levels by at least 50%.

Methods and Materials: Sixteen patients with recurrent prostate cancer were recruited and received 2 doses of 150 mGy of nontargeted radiation per week, for 5 consecutive weeks, with 15 participants completing the study.

Results: A maximal response of 40.5% decrease in PSA at 3 months was observed. A total of 8 participants remained off any additional interventions, of whom 3 had minimal fluctuations in PSA for at least 1 year after treatment. The most common adverse event reported was mild fatigue during active treatment (n = 4), which did not persist in the follow-up period. No participants withdrew due to safety concerns or hematological abnormalities (ie, platelet ≤ 50 × 10^9/L, leukocyte ≤ 3 × 10^9/L, granulocyte ≤ 2 × 10^9/L).

Conclusions: Our study did not meet the primary objective; however, LD-RT may be a potential therapy for some patients with recurrent prostate cancer by stalling rising PSA. This study also demonstrates that low-dose radiation is well tolerated by participants with minimal toxicities and no change in quality of life.

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Data sharing statement: A complete deidentified patient-level data set will be made available to researchers for the purpose of meta-analysis or a newly proposed study. Following submission of a maximum 2-page proposal by the requestor, data will be made available, if acceptable, upon approval of the request by the trial steering committee. A signed data sharing access agreement will be required. Data will become available 1 year after publication of the initial study results and will end 4 years after publication of the initial study results. Data requests should be sent to parpia@mcmaster.ca.
Introduction

Prostate cancer is one of the most frequently diagnosed cancers in men.\(^1\) Even in patients whose primary cancer has been effectively treated with surgery and/or radiation, more than a third of patients with localized prostate cancer will recur within 10 years.\(^2\) Disease progression is clinically monitored with prostate-specific antigen (PSA). After initial local treatment for prostate cancer (ie, surgery or radiation therapy), PSA levels are low to undetectable. When PSA levels begin to rise, patients undergo frequent monitoring to determine when to initiate salvage treatment, such as androgen deprivation therapy (ADT).\(^3,4\) Between unwanted side effects and a finite window of therapeutic benefit before developing castrate-resistant prostate cancer, initiating ADT is often delayed for as long as possible.\(^5,6\) Low-dose radiation may be an option for these patients to further eliminate or delay the need to start ADT.

There is a considerable body of evidence supporting low-dose radiation as a cancer treatment\(^8,9\); however, its use has declined dramatically over the past several decades. The majority of reports from the 1970s and 1980s using total body irradiation (TBI) or hemibody irradiation have primarily involved patients with hematological malignancies such as chronic lymphocytic leukemia and non-Hodgkin lymphoma.\(^10-20\) Unfortunately, inconsistencies in how the low-dose radiation was administered make it difficult to develop a standard dosing regimen. Most of these early studies used a range of 50 to 500 mGy/fraction, delivered 3 to 5 times a week, sometimes with several rest periods of a few weeks to months to avoid bone marrow depression, where a cumulative dose for each patient would fall between 1000 and 4000 mGy.\(^10-14\)

More recent studies have found that low dose TBI or hemibody irradiation improves outcomes for several cancer types.\(^21-23\) A complete remission rate of 29% and a 2-year progression-free survival of 32% was reported from 35 patients with relapsed and/or chemotherapy resistant non-Hodgkin lymphoma after low-dose TBI was delivered in 2 cycles of 4 daily fractions of 200 mGy (total dose of 1600 mGy).\(^22\) Another trial involving patients with non-Hodgkin lymphoma concluded that 79% of patients achieved full remission in response to low-dose TBI, compared with 60% who achieved a full response with low-dose radiation therapy (LD-RT) in combination with local irradiation.\(^23\) Similarly, one study involving non-Hodgkin lymphoma patients who received low-dose TBI as their first-line treatment reported a 5- and 10-year relapse-free survival of 32% and 27%, respectively.\(^24\)

More recently, Kojima et al reported that a patient with recurrent prostate cancer who received 30 weekly fractions of 150 mGy had a PSA decline from >5 ng/mL to near nondetectable levels (0.085 ng/mL) after the sixth fraction and remained low until treatment was completed.\(^25\) However, there was no report on how long PSA remained lower in this patient after radiation sessions ended.

To date, the small sample size of these trials and the inconsistent dosing regime has limited generalizability. Herein we report the results of a phase 2 clinical trial investigating the use of low-dose radiation for prostate cancer using a uniform treatment regime in patients with recurrent prostate cancer. The purpose of this study was to determine whether nontargeted LD-RT could reduce PSA levels by 50% in men with recurrent prostate cancer with minimal adverse events, hematological changes, or alterations in quality of life.

Methods and Materials

Study design

Patients with recurrent prostate cancer were recruited from a single institution for a Simon 2-stage design study. The study protocol and all supporting documents were approved by the local hospital and Hamilton Integrated Research Ethics Board (HiREB #2706) and was registered with the United States National Library of Medicine and National Institutes of Health (#NCT03196778).

Sample size estimation was calculated assuming the probability of response under the null hypothesis of \(P < .1\), and \(P < .25\) under the alternate hypothesis (alpha, 0.15; power, 0.80), and the maximum sample size required was determined to be 21 patients. After 16 participants completed the study (stage 1), if \(\leq 1\) participants responded, the trial would be terminated. If >1 participant responded in stage 1, then the trial would continue to enroll an additional 5 patients. With the completion of 21 patients, therapy is to be rejected if the total number of responding patients is \(\leq 3\).

To be eligible, participants must have had a histologic diagnosis of adenocarcinoma of the prostate, undergone either prior prostate surgery or radiation therapy (or both), shown evidence of recurrence in the disease by rising circulating PSA levels (nadir +2 ng/mL), and had a minimum of 1 year’s worth of PSA data. Patients who had received prior treatment with chemotherapy, abiraterone, enzalutamide, or radium-223; were taking any immunosuppressive medications; or had a platelet count \(<50 \times 10^9/L\), a leukocyte count \(<3 \times 10^9/L\), or a granulocyte count \(<2 \times 10^9/L\) were excluded. Once deemed eligible, informed consent was obtained.
Radiation intervention

Participants received 2 doses of radiation each week over a span of 5 weeks at the Juravinski Cancer Centre, Hamilton, Ontario. Treatments were scheduled at least 2 days apart and delivered to the hemi body field using 6 MV x-rays. At each LD-RT session, a radiation dose of 150 mGy was delivered to the midplane using anterior and posterior fields (ie, 75 mGy/field), at a dose rate of approximately 1 Gy/min. Treatment planning was performed for each participant based on a clinical set-up. The machine gantry was rotated to direct the beam horizontally toward the patient standing at a distance approximately 3.7 m from the linear accelerator isocenter (Fig. E1A). The field size was individually tailored to participants by adjusting the superior-inferior beam edges to span from their suprasternal notch to their lowest fingertips when hands were placed at their sides, and the lateral beam edges to include the width of the participant, including arms (Fig. E1B). Each patient received a cumulative weekly dose of 300 mGy and a total study dose of 1500 mGy. Although multiple dosing regimens can be found in the literature, this schedule was chosen as it is the most commonly reported.17,18,21 As a result, it was felt that following this regimen would result in fewer unexpected toxicities. For optimal dosimetry and ease of patient set-up and comfort, we chose the previously discussed standing technique. Admittedly, this does not result in total body radiation. However, only the head and lower legs were excluded, sites in which distant disease is much less likely in comparison to the axial skeleton and lymph nodes, which were included in the irradiated fields. To verify treatment planning doses, thermoluminescent dosimetry was performed for the first 2 participants on their first treatment visit.

Clinical outcomes

The study aimed to determine the efficacy of LD-RT as a treatment for recurrent prostate cancer. Blood was collected at the pretreatment study visit and the first day of LD-RT, before receiving radiation, to determine eligibility and capture baseline PSA. Blood was similarly collected at the last day of scheduled LD-RT and at 1, 3, 6, and 12 months after treatment. As per Prostate Cancer Clinical Trials Working Group guidelines, the primary outcome was a decrease in PSA following treatment of 50%.

A separate blood draw was collected from the pretreatment visit for a complete blood count as previous studies reported a decrease in platelets and leukocyte numbers.10,11,19 At the beginning of each treatment week, before radiation treatment, participants had a complete blood count to monitor hematological parameters, as treatment was to be withheld if platelet counts were <50 × 10^9/L, leukocyte counts were <3 × 10^9/L, or granulocyte counts were <2 × 10^9/L. Treatment was to resume once measurements returned above the safety threshold. Blood was collected at the 1-, 3-, 6-, and 12-month follow-up visits to monitor long-term status of hematological parameters following LD-RT.

Quality of life and mood assessment

Health-related quality of life data assessed the physical and mental health of participants over the course of LD-RT. The Functional Assessment of Cancer Therapy for Prostate survey (FACT-P) assessed physical, social, emotional, and functional well-being as well as a prostate cancer subscore, with questions specific to a prostate cancer diagnosis. To accommodate for missing answers, scores were normalized by dividing the total score by the number of answered questions. A general FACT score was obtained by summing the normalized physical, emotional, social, and function well-being scores. A prostate cancer FACT score (FACT-P) was measured with the addition of the prostate cancer subscore to the FACT-General. Finally, a treatment outcome index was measured by adding the physical well-being, functional well-being, and prostate cancer subscores together.

The 36-item Short-Form Health Survey (SF-36) is a self-reported measure of health-related quality of life.26,27 This survey covers 9 domains: physical function, body pain, limitations due to physical health problems, limitations due to personal/emotional problems, emotional well-being, social functioning, energy/fatigue, general health perception, and general health changes. This survey scores each domain ranging from 0 to 100, with a higher score defining a more favorable health status. If a question on the survey was missed by a participant, the domain score was adjusted accordingly.

The FACT-P and SF-36 were administered at the pretreatment visit and repeated on the last LD-RT visit and 1 and 12 months after treatment to determine changes in quality of life over the study period.

Adverse events

Patients were assessed weekly to monitor for adverse events, specifically regarding diarrhea, nausea, vomiting, fatigue, any hair loss or skin changes within the beam field, or any urinary or bladder changes. Adverse events were classified using National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0), which is widely accepted as the standard classification and severity grading scale for adverse events in cancer therapy, clinical trials, and other oncology settings.28 An independent Data Safety Monitoring Board was established and met at midaccrual to alert the investigators of any patient safety concerns.
Statistical analysis

Statistical analysis was performed in GraphPad Prism 9. The predicted trajectory PSA values (pre- and post-treatment) were determined by linear regression. Quality-of-life data was tested using mixed effects models using Geisser-Greenhouse corrections.

Results

Participant enrollment

Participant recruitment occurred between September 2017 and November 2019. In total, 24 patients were approached for study enrollment, with a consent rate of 67.7% (n = 16). Reasons for nonenrollment are outlined in Table E1. Enrolled participants were, on average, 76.5 ± 7.3 years of age and were primarily White (93.8%) (Table 1). The median number of medical comorbidities was 2 (range, 0-7). Hypertension was the most commonly reported comorbidity (62.5% of participants), and cardiac conditions were reported in 25% of participants (Table 1). PSA values at the beginning of the study ranged from 3.0 to 62.0 ng/mL with a median value of 8.8 ng/mL (Table 2).

The Eastern Cooperative Oncology Group performance status was used to measure functional status of each participant recruited, where a score of 0 is indicative of no restrictions to daily activities with performance similar to predisease and a maximum score of 4 measuring functional status is indicative of being completely disabled and unable to engage in self-care, often confined to a bed. Participants recruited to the study scored either 0 (n = 8; 50.0%) or 1 (n = 8; 50.0%). They reported restrictions with strenuous physical activities but were ambulatory and able to carry out light work (Table 1). Just over half of the participants (n = 9) had an intermediate-risk prostate cancer at initial presentation, with Gleason score ≥7 (Table 1). The mean time since primary tumor treatment was 8.4 ± 3.5 years (Table 1). Primary treatment for initial prostate cancer diagnosis was heavily weighted toward patients receiving radiation therapy as their primary tumor treatment (n = 10; 62.5%) (Table 1). Approximately a third (n = 5; 31.3%) of the participants previously had a radical prostatectomy in conjunction with radiation therapy, and 1 participant received brachytherapy (Table 1). At the time of accrual, 7 (43.8%) participants had never received ADT, 4 (25.0%) participants had a previous history of intermittent ADT but were in an “off” phase during the study period, and 5 participants (31.3%) were currently undergoing ADT (Table 1).

Study compliance was high, with 15 of 16 (93.8%) patients completing the 5-week treatment. One participant with an extensive cardiac history experienced a significant cardiac event during the weeks of LD-RT resulting in death. This event was reported to the local ethics committees in addition to being reviewed by an independent Data Safety Monitoring Board and was determined to have not been related to treatment.

Clinical outcomes

An overview of individual participant PSA trajectories is presented in Fig. 1. None of the study participants had reached the primary outcome of a 50% decrease in PSA. After treatment, PSA continued to increase in 10 participants over the follow-up stage of the study. Consequently, 7 of these participants started a systemic therapy 3 to 8 months after treatment due to progression (Fig. 2B). Interestingly, of the 11 participants not on ADT during time of LD-RT, 7 avoided salvage therapy by the end of the 12-month follow-up period (Fig. 1D). This ratio was much higher than observed in patients who were on ADT during the time of LD-RT, where 1 patient out of those 4 patients avoided salvage therapy (Fig. 1B). Three of these patients had succumbed to disease after the follow-up period of the study by March 2021. One additional death, due to a respiratory disease, was reported within the same time frame.

Of the 8 patients who did not progress to needing systemic therapy, 3 had PSA lower (Fig. 1B, 1D) or an increase of less than 25% from baseline at 12 months after LD-RT (Fig. 2B). The largest decrease in PSA levels was a 40.5% reduction from baseline at the 3-month follow-up visit, and 3 patients experienced a reduction in PSA by at least 25% (Fig. 1E). Overall, no significant changes were seen in absolute PSA or testosterone levels as a result of LD-RT (Fig. 2A).

Adverse events

Adverse events reported over LD-RT are outlined in Table 2 and were all reported as grade 1. The most commonly reported adverse event during active treatment was mild fatigue (n = 4) which was earliest reported after 1 week of LD-RT (n = 1). This resolved by 6 months after the last dose of LD-RT. Mild nausea was reported by 1 participant after 1 week of LD-RT and in a second participant after 4 weeks of LD-RT. Both incidents were resolved shortly after radiation ended. A mild rash was reported by 1 participant 2 weeks into LD-RT and resolved by the following week. One report of chest hair loss was documented 1 month after LD-RT and was resolved by 3 months after LD-RT. Bladder changes, specifically an increased urinary frequency, was reported in 1 participant after 3 weeks of LD-RT. By 3 months post-LD-RT increased urinary frequency was reported by 4 participants and did not resolve in 2 of them by the end of the
12-month follow-up period. Other adverse events reported by participants during LD-RT were gynecomastia (n = 2), mild constipation (n = 3), and headaches (n = 1), all resolved by 1 month after the last fraction of LD-RT. It is important to note that the 2 cases of gynecomastia occurred in 1 patient who was currently taking ADT and in a second patient with a history of ADT. Hot flashes and hematospermia was reported by 1 participant at the 12-month follow-up visit, which also coincided with initiation of ADT. No medical intervention was required as all events were mild and self-limiting.

### Patient safety and hematology

None of the participants had hematologic values fall below pre-established study safety levels, and no treatment visits were withheld for safety concerns. Most participants (n = 12 of 15) experienced a decrease in platelet levels to between $75 \times 10^9/L$ and $150 \times 10^9/L$ (grade 1) (Table 3). Decreases in platelet counts were observed as early as after 2 weeks of LD-RT, and lowest levels were generally observed after 4 weeks. Two participants experienced a decrease in platelets levels between $50 \times 10^9/L$ and $75 \times 10^9/L$ (grade 2) (Table 3). Platelet levels remained depressed in one-third of participants 1 month after the final fraction, but by 12 months, all but 4 participant platelet counts had recovered.

A decrease in leukocyte count of $3.0 \times 10^9/L$ to $4.0 \times 10^9/L$ (grade 1) occurred in 2 participants during LD-RT (Table 3). Two additional participants (26.7% of total cohort) had a decrease in leukocyte count 1 month after the last LD-RT dose. These decreases were transient as levels returned to normal in all participants by the second follow-up visit (3 months). A decrease in absolute lymphocyte count was observed in 80% (n = 12 of 15) of participants (Table 3) to between $0.8 \times 10^9/L$ and $1.5 \times 10^9/L$ (grade 1) as early as after 1 week of LD-RT.
| Adverse events reported* | During treatment | After treatment | Total study period |
|--------------------------|------------------|-----------------|-------------------|
|                          | After 1 wk | After 2 wk | After 3 wk | After 4 wk | Month 1 | Month 3 | Month 6 | Month 12 | Visit 1-15 |
| Diarrhea                 | 0 (0.0)    | 1 (6.67)   | 0 (0.0)    | 0 (0.0)    | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 1 (6.67)   |
| Nausea/vomiting          | 1 (6.67)    | 1 (6.67)   | 2 (13.3)   | 2 (13.3)   | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 1 (6.67)   |
| Fatigue                  | 1 (6.67)    | 2 (13.3)   | 2 (13.3)   | 2 (13.3)   | 2 (13.3)  | 2 (13.3)  | 1 (7.14)  | 4 (26.6)  | 1 (6.67)   |
| Hair loss                | 0 (0.0)     | 0 (0.0)    | 0 (0.0)    | 0 (0.0)    | 1 (6.67)  | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 1 (6.67)   |
| Skin changes             | 0 (0.0)     | 1 (6.67)   | 0 (0.0)    | 0 (0.0)    | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 1 (6.67)   |
| Urinary/bladder changes  | 0 (0.0)     | 0 (0.0)    | 1 (6.67)   | 1 (6.67)   | 1 (6.67)  | 2 (13.3)  | 0 (0.0)   | 2 (14.3)  | 4 (26.6)   |
| Other                    |              |            |            |            |         |         |         |         |           |
| Gynecomastia             | 2 (13.3)    | 2 (13.3)   | 2 (13.3)   | 2 (13.3)   | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 2 (13.3)   |
| Constipation             | 0 (0.0)     | 1 (6.67)   | 1 (6.67)   | 1 (6.67)   | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 1 (7.14)  | 3 (20.0)   |
| Headaches                | 0 (0.0)     | 0 (0.0)    | 0 (0.0)    | 1 (6.67)   | 1 (6.67)  | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 1 (6.67)   |
| Hot flashes              | 0 (0.0)     | 0 (0.0)    | 0 (0.0)    | 0 (0.0)    | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 1 (7.14)  | 1 (6.67)   |
| Hematospermia            | 0 (0.0)     | 0 (0.0)    | 0 (0.0)    | 0 (0.0)    | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   | 1 (7.14)  | 1 (6.67)   |

*All results are given as the number (percentage) of participants.

† n = 14.
Three participants had lymphocyte numbers decrease to between 0.5 × 10^9/L and 0.8 × 10^9/L (grade 2). One month after the last fraction of LD-RT lymphocyte numbers had not returned to normal; however, by 12 months, half of these participants had lymphocyte counts fully restored. Of those 6 participants who did not have lymphocytes, numbers return to normal levels by the end of the study period, and 4 had below-normal levels at baseline (Table 3). Absolute neutrophil counts were not affected during treatment (Table 3); however, neutrophil counts decreased between 1.5 × 10^9/L and 2.0 × 10^9/L (grade 1) in 2 participants during follow-up visits. Absolute monocyte counts did not differ during the study period (Table 3).

A third of participants (n = 5 of 15) had a decrease in hemoglobin between 100 and 130 g/L (grade 1) during the 14-month study period (Table 3). Measurable decreases in hemoglobin started as early as after 1 week of LD-RT and was more frequently observed after 3 weeks. Hemoglobin continued to decrease for 1 participant between 80 and 100 g/L (grade 2) 6 months after LD-RT. Hemoglobin levels recovered for most participants by the 12-month visit.

**Quality of life**

LD-RT did not affect the quality of life in any reported measures on FACT-P (Fig. 3A). Further analysis revealed there was no relationship between PSA response and quality of life, suggesting similar patient experiences independent of individual outcome. Similar null results were found with the SF-36, where no statistical difference was found on any of the 9 domains within the SF-36 (Fig. 3B).
Discussion

This study is the first aimed to explore whether LD-RT has a role in men with recurrent prostate cancer by reducing PSA in an effort to delay initiation of conventional salvage therapies. Although optimal timing to initiation ADT upon recurrence remains unknown, a tactic such as LD-RT may delay exposure to the toxicity associated with androgen suppression and potentially delay the time to castrate resistance.29,30 Although none of the participants met our criteria of a PSA level decrease by 50%, 3 participants had their PSA levels plateau for ≥12 months, suggests a potential cytostatic response to LD-RT, which likely led to a delay in initiating further treatments (Fig. 1D). Future studies with LD-RT involving patients with prostate cancer may therefore want to evaluate the role of other outcomes. Of the 11 participants not on ADT during time of LD-RT, 7 avoided salvage therapy by the end of the 12-month follow-up period (Fig. 1D), whereas 2 of these participants remained off ADT for >2 years (data not shown). One patient not on ADT during the time of LD-RT was placed on ADT 9 months after LD-RT by his urologist after discovering a local recurrence despite a stable PSA that was actually lower than the study’s baseline (Fig. 1C). Furthermore, rather than the primary endpoint being measured in a reduction in PSA, future studies might be better designed to examine the time to salvage treatment as an indicator of response, particularly in comparison to a control group.

Without intervention, when PSA levels surpass the nadir +2 ng/mL threshold, indicating biochemical failure, the patient will likely continue on that trajectory of progression. Our LD-RT schedule was able to maintain PSA levels in 8 of 15 participants for ≥12 months without the need of salvage therapy (Fig. 1B, 1D). In addition to an extensive list of unwanted toxicities, ADT has been shown to reduce patient quality of life.3,5-7 Our LD-RT regime has demonstrated no changes in FACT-P or SF-36 scores (Fig. 3A, 3B) suggesting it may be preferable to some patients over current options.

LD-RT has been suggested as a method to prime the body before a larger dose of radiation used as a cancer treatment with the premise that multiple doses of LD-RT would stimulate the immune system to improve overall response and survivorship.18,22,24,31 LD-RT has also been used as a primary cancer treatment.11,13,14,16,32 Hematologic abnormalities such as thrombocytopenia, leukopenia, and a decrease in granulocytes have commonly been reported and often result in interruptions during scheduled therapy.13,15,18,19,33 Interpretation of these hematological abnormalities is complicated when patients are currently taking or have recently finished chemotherapy agents, which frequently suppress the immune system. Our data show that platelet count was most often decreased after an accumulation of 900 mGy of radiation

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**Figure 2** Prostate-specific antigen (PSA) and testosterone monitoring before and after low-dose radiation therapy (LD-RT) (n = 15). A, Absolute PSA and testosterone before and after LD-RT. B, Frequency distribution of percentage change in PSA from baseline within the patient population at 1, 3, 6, and 12 months after LD-RT.
| Table 3  | Frequency of reported changes in hematological parameters, as outlined on a complete blood count report during the study period (n = 15) |
|----------|----------------------------------------------------------------------------------------------------------------------------------|
|          | **During LD-RT**                                                                                                                 | **Follow-up period**                                                                 |
|          | **Baseline** | **After 2 doses** | **After 4 doses** | **After 6 doses** | **After 8 doses** | **1 mo after LD-RT** | **3 mo after LD-RT** | **6 mo after LD-RT** | **12 mo after LD-RT** |
| Leukocytes | G1 | 0 | 0 | 0 | 1 | 1 | 4 | 0 | 0 | 0 |
|           | Cumulative | 0 | 0 | 0 | 1 | 2 | 4 | 4 | 4 | 4 |
|           | Missing | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 3 |
| Hemoglobin | G1 | 2 | 3 | 2 | 3 | 3 | 4 | 5 | 2 | 3 |
|           | G2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
|           | Cumulative | 2 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 6 |
|           | Missing | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 3 |
| Platelet | G1 | 2 | 2 | 2 | 7 | 10 | 5 | 4 | 3 | 4 |
|           | G2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
|           | Cumulative | 2 | 3 | 3 | 7 | 12 | 12 | 12 | 12 | 12 |
|           | Missing | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 3 |
| Mean platelet volume | G1 | 4 | 5 | 3 | 1 | 4 | 5 | 4 | 5 | 2 |
|           | Cumulative | 4 | 5 | 5 | 5 | 6 | 7 | 7 | 8 | 8 |
|           | Missing | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 5 |
| Abs neutrophil count | G1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
|           | Cumulative | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 |
|           | Missing | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 3 |
| Abs lymphocyte count | G1 | 4 | 7 | 9 | 9 | 9 | 9 | 5 | 8 | 7 |
|           | G2 | 0 | 2 | 2 | 3 | 3 | 2 | 3 | 3 | 0 |
|           | Cumulative | 4 | 9 | 11 | 12 | 12 | 12 | 12 | 12 | 12 |
|           | Missing | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 3 |
| Abs monocyte count | G1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|           | Cumulative | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|           | Missing | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 3 |

**Abbreviations:** Abs = absolute; LD-RT = low-dose radiation therapy.
Figure 3  Participant quality of life as measured by the Functional Assessment of Cancer Therapy for Prostate survey (FACT-P) and 36-item Short-Form Health Survey (SF-36). A, FACT-General score, FACT-P, and the treatment outcome.
and required 1 month before returning to normal (Table 3). Fluctuations in leukocyte and granulocyte numbers were minimal during treatment and only decreased 1 month after the last dose of radiation. This suggests that a total dose of 1500 mGy of radiation is the threshold before changes in leukocytes and granulocytes numbers would be observed (Table 3). However, these cell types returned to normal levels by the next study visit and showed no long-term side effects. Interestingly, several patients experienced decreased erythrocytes over the study period (most often after 900 mGy of radiation), and these numbers remained decreased in most patients until the end of the 12-month follow-up period (Table 3), suggesting some possible changes in erythrocyte production. It is important to note that these decreased values in hematological parameters were largely mild with no observed clinical consequences and were self-limiting. As no treatments were halted due to safety hematological thresholds, this study demonstrates that 150 mGy LD-RT twice a week for 5 weeks is well tolerated within patients with prostate cancer.

In addition to research showing that testosterone supports the growth of prostate cancer cells, many studies support androgens having a suppressive effect on immune cells. Patients currently on ADT (n = 4) did not appear to respond to LD-RT as their PSA values continued to rise (Fig. 1A, 1B) whereas patients not on ADT had mixed responses to the treatment (Fig. 2C, 2D). To ensure that radiation did not alter circulating androgens in the participants not on ADT, testosterone levels were monitored before and after LD-RT. As expected, testosterone levels in participants undergoing ADT were not detectable before LD-RT, and consequently there was no change after treatment. Furthermore, testosterone levels in the participants not on ADT did not show any changes from pretreatment levels after therapy (Fig. 2A) ensuring that LD-RT was not indirectly altering PSA levels by influencing circulating androgen levels. With our small sample size strong inferences cannot be made about the role of androgens in response to LD-RT; however, further research is warranted to highlight the mechanisms that differ between these 2 groups.

These findings have brought about further questions. Increasing the frequency of LD-RT treatments to shorten the time between exposures may enhance and maintain the magnitude of the cellular responses induced by the radiation exposures. In a previous clinical trial using heat stress to treat psoriasis, it was determined that a treatment frequency of twice per week was insufficient to maintain optimal response kinetics. Increasing heat treatments to 3 times per week markedly improved the effectiveness of the treatments presumably by further inducing and maintaining the mechanisms responsible. In addition, it is unknown whether further treatments can help maintain the remission effect in patients who responded to our initial treatment. A second, smaller substudy is currently underway to explore this possibility. Given that the current protocol was tested in patients with recurrent prostate cancer, future studies are needed to determine whether LD-RT may have similar or superior outcomes in other clinical settings.

Study strengths include the fact that it is the first report on low doses of hemibody radiation for recurrent prostate cancer. The study protocol was adapted from older reports, largely in patients with lymphoma. Depending on the source of radiation used in these previous studies, challenges using LD-RT lie with the inability to offer an even distribution of energy across the body in addition to an absence of dosimetry confirming accuracy in dosing at these lower levels. It is common in these previous studies to report an estimated cumulative dose rather than an accurate number reported for each fraction or patient. Our study is the first to accurately examine the tolerability of delivering 150 mGy of LD-RT twice per week in such a population. The mechanism of action behind this low-dose treatment remains undetermined. However, substantial data on cellular and humoral factors were collected and will be reported in a subsequent publication. Preclinical models for LD-RT suggest a possible immune-mediated mechanism. The study treatment is readily available and inexpensive, requires minimal radiation planning, and is well tolerated by patients. Participants were closely followed for 12 months posttreatment for PSA response, toxicity, hematological status, and quality of life. Even after the 12-month study period, patients continue to be followed clinically, with some showing an extended response, long past protocol follow-up.

Limitations of this study include the lack of a control group and differences in ADT status, leading to some heterogeneity within the study population, hampering the strength of our findings. In addition, this study was performed at a single institution, limiting generalizability. With a small number of subjects and relatively short follow-up, our primary outcome was limited to PSA response and does not address more important clinical endpoints, such as overall survival or time to metastatic disease. All subjects were asymptomatic at time of enrollment, so there was no opportunity to observe improvements in symptoms, performance status, or quality of life, although there was no evidence of a reduction in the

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index was measured in the self-reported survey. Mixed effects analysis shows no statistical significance between each collection time point. Data are shown as mean ± standard deviation. B, Self-reported SF-36 by participants revealed no statistical differences in the 9 available health scales measured with the survey. Data are shown in a forest plot, with each SF-36 scale identified by a unique color, with the mean score (n = 15) graded from 0% to 100%.
latter. This study also does not well address the role of such a treatment in the ever-expanding armamentarium against recurrent prostate cancer. However, from our results, any value it may have likely lies in the early phase of recurrence, before the use of ADT, to delay both the commencement of androgen deprivation and the initiation of castrate resistance. Whether the systemic nature of this treatment limits any future role for cytotoxic therapy remains unknown.

Conclusion

In summary, LD-RT emerges as a promising, readily available method for managing PSA kinetics in patients with recurrent prostate cancer for at least 12 months, further delaying the need to initiate ADT, which is associated with unwanted side effects and a decreased quality of life. Deferral of ADT may potentially delay onset of castrate resistance, in addition to avoidance of its related toxicity. Based on our data, LD-RT appears safe, has minimal toxicity compared with current standard options, and does not alter quality of life. With further research and optimization, LD-RT has the potential to become an effective treatment option for managing recurrent prostate cancer and possibly other forms of malignant disease.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ado.2022.101066.

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