
# Low-dose hemi-body radiation: A treatment option for recurrent prostate cancer: a phase II single arm trial

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**Full Title**: Low-dose hemi-body radiation: A treatment option for recurrent prostate cancer: a phase II single arm trial

**Short Running Title:** Low-dose hemi-body radiation

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Ian Dayes: No conflict of interest to disclose.

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**Data Availability Statement for this Work:** A complete de-identified 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 one year after publication of the initial study results and will end four

years after publication of the initial study results. Data requests should be sent to parpia@mcmaster.ca.

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**Abstract**

Purpose: Non-targeted 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 cancer patients 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 II two-stage trial was to determine whether low-dose radiation therapy (LD-RT) reduced prostate specific antigen (PSA) in recurrent prostate cancer patients 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 two doses of 150 mGy of non-targeted 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 minor 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 (i.e. platelet ≤50 x $10^9$/L, leukocyte ≤3 x $10^9$/L, granulocyte ≤2 x $10^9$/L).

Conclusions: Our study did not meet the primary objective; however, LD-RT may be a potential therapy for some recurrent prostate cancer patients 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.

**Keywords:** prostate cancer, low-dose radiation, treatment, non-targeted, PSA, CBC

## Background

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). Following initial local treatment for prostate cancer (i.e. surgery or radiotherapy), 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[3,5–7]. 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 hemi-body irradiation (HBI) have primarily involved patients with hematological malignancies such as chronic lymphocytic leukemia and non-Hodgkin's lymphoma[10,11,20,12–19]. Unfortunately, inconsistencies in how the low-dose radiation was administered make it difficult to develop a standard dosing regime. Most of these early studies used a range of 50-500 mGy/fraction, delivered 3-5 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 1000-4000 mGy[10–14].

More recent studies have found that low dose TBI or HBI 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's lymphoma after low-dose TBI was delivered in two cycles of four daily fractions of 200 mGy (total dose of 1600 mGy)[22]. Another trial involving patients with non-Hodgkin's lymphoma concluded that 79% of patients achieved full remission in response to low dose TBI, compared to 60% who achieved a full response with LD-RT in combination with local irradiation[23]. Similarly, one study involving non-Hodgkin's 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, XXXXXX *et al* reported that a recurrent prostate cancer patient who received 30 weekly fractions of 150 mGy had PSA decline from >5 ng/mL to near non-detectable levels (0.085 ng/mL) after the sixth fraction, and remain 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 II 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 if non-targeted low-dose radiation therapy (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

### *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 XXXXXXX XXXXXXXXXX XXXXXXX XXXXXX XXXXX (XXXXX XXXXX) and was registered with the United States National Library of Medicine and National Institutes of Health (#XXXXXXXXXX).

Sample size estimation was calculated assuming the probability of response under the null hypothesis of $p<0.1$, and 0.25 under the alternate hypothesis (alpha = 0.15 and power = 0.80), determining the maximum sample size required was 21 patients. After 16 participants completed the study (stage 1), if 1 or fewer participants responded, the trial would be terminated. If more than 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 3 or fewer.

To be eligible, participants had a histological diagnosis of adenocarcinoma of the prostate, having undergone either prior prostate surgery or radiotherapy (or both), show evidence of recurrence in the disease by rising circulating PSA levels (nadir + 2 ng/mL) and have a minimum of one 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 below 50 x $10^9$/L, a leukocyte count below 3 x $10^9$/L or a granulocyte count below 2 x $10^9$/L were excluded. Once deemed eligible, informed consent was obtained.

*Radiation Intervention*

Participants received two doses of radiation each week over a span of five weeks at the XXXXXXXXXX XXXXXX XXXXX, XXXXXXXX, XXXXXXX. 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 by using anterior and posterior fields (i.e. 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 towards the patient standing at a distance approximately 3.7 m from the linear accelerator isocenter (Supplemental Figure 1A). The field size was individually tailored to participants by adjusting the superior-inferior beam edges to span from their suprasternal notch to their

lowest finger tip when hands were placed at their sides, and the lateral beam edges to include the width of the participant, including arms (Supplemental Figure 1B). Each patient received a cumulative weekly dose of 300 mGy and a total study dose of 1500 mGy. While 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 above 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 two 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 pre-treatment study visit and the first day of LD-RT, prior to receiving radiation, to determine eligibility and capture baseline PSA. Blood was similarly collected at the last day of scheduled LD-RT, and at 1 month, 3 months, 6 months and 12 months following 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 pre-treatment visit for a complete blood count (CBC) as previous studies reported a decrease in platelets and leukocyte numbers[10,11,19]. At the beginning of each treatment week, prior to radiation treatment, participants had a CBC to monitor hematological parameters, as treatment was to be withheld if platelet counts were below 50 x $10^9$/L, leukocyte counts were below 3 x $10^9$/L or if granulocyte counts were below 2 x $10^9$/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 (FACT-P) survey assessed physical well being, social well being, emotional well being, functional well being as well as a prostate cancer sub-score, with questions specific to a prostate cancer diagnosis. Scores were normalized by dividing the total score by the number of answered questions, to accommodate for missing answers. A general FACT score (FACT-G) 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-G. Finally, a treatment outcome index (TOI) was measured by adding the physical well being, the function well being and the prostate cancer subscore 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 0-100, 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 pre-treatment visit and repeated on the last LD-RT visit, 1 month 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, nauseas, 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 (NCI-CTCAE) 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 (DSMB) was established and met at mid-accrual 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 XXXX – November XXXX. In total, 24 patients were approached for study enrollment, with a consent rate of 67.7% (n=16). Reasons for non-enrollment are outlined in Supplemental Table 1. Enrolled participants were on average 76.5±7.3 years of age and were primarily Caucasian (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 3.0-62.0 ng/mL with a median value of 8.8 ng/mL (Table 2).

The Eastern Cooperative Oncology Group (ECOG) 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 pre-disease; and a max score of 4 measuring functional status as completely disabled and cannot carry on with selfcare, often confined to a bed. Participants recruited to the study

scored either 0 (n=8, 50.0%) or 1 (n=8, 50.0%) reporting restrictions with strenuous physical activities but are 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). Mean time since primary tumour treatment was 8.4±3.5 years (Table 1). Primary treatment for initial prostate cancer diagnosis was heavily weighted towards patients receiving radiotherapy as their primary tumour 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 radiotherapy, and one 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 15/16 (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 DSMB and was determined to have not been related to treatment.



*Clinical Outcomes*

An overview of individual participant PSA trajectories is presented in Figure 1. None of the study participants had reached the primary outcome of a 50% decrease in PSA. Following treatment, PSA continued to increase in 10 participants over the follow

up stage of the study. Consequently, seven of these participants started a systemic therapy 3-8 months after treatment due to progression (Figure 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 (Figure 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 (Figure 1B). Three of these patients had succumbed to disease after the follow up period of the study by March XXXX. One additional death was reported within the same time frame, due to a respiratory disease.

Of the 8 patients who did not progress to needing systemic therapy, three (Figure 1B&D) had PSA lower, or an increase of less than 25% from baseline at 12 months after LD-RT (Figure 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% (Figure 1E). Overall, no significant changes were seen in absolute PSA or testosterone levels as a result of LD-RT (Figure 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 following 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 following LD-RT, and was resolved by 3 month following 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 following the last fraction of LD-RT. It is important to note that the two cases of gynecomastia occurred in one patient who was currently taking ADT, and in a second patient with a history of ADT. Hot flashes and hematospermia was reported by one 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=12/15) experienced a decrease in platelet levels to between 75-150 x $10^9$/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 50-75 x $10^9$/L (Grade 2) (Table 3). Platelet levels remained depressed in a third of participants 1 month following the final fraction, but by 12 months all but 4 participant platelet counts had recovered.

A decrease in leukocyte count to 3.0-4.0 x $10^9$/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 following 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=12/15) of participants (Table 3) to between 0.8-1.5 x $10^9$/L (Grade 1) as early as after 1 week of LD-RT. Three participants had lymphocyte numbers decrease to between 0.5-0.8 x $10^9$/L (Grade 2). One month following 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, 4 had below-normal levels at baseline (Table 3). Absolute neutrophil counts were not affected during treatment (Table 3), however, neutrophil counts decreased between 1.5-2.0x$10^9$/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=5/15) had a decrease in hemoglobin between 100-130 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 one participant between 80-100 g/L (Grade 2) 6 months following LD-RT. Hemoglobin levels recovered for most participants by the 12 month visit.

LD-RT did not affect the quality of life in any reported measures on FACT-P (Figure 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 (Figure 3B).

## Discussion

This study is the first aimed to explore if LD-RT has a role in men with recurrent prostate cancer by reducing PSA in an effort to delay initiation of conventional salvage therapies. While 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 and likely led to a delay in initiating further treatments (Figure 1D). Future studies with LD-RT involving prostate cancer patients 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 (Figure 1D), while 2 of these participants have remained off ADT for over two years (data not shown). One patient not on ADT during the time of LD-RT was placed on ADT 9 months following LD-RT by his urologist after discovering a local recurrence despite a stable and actually lower than study baseline PSA level (Figure 1C). Furthermore, rather than 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 8/15 participants for 12 months without the need of salvage therapy (Figure 1B,D). 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 nor SF-36 scores (Figure 3A,B) suggesting it may be preferable to some patients over current options.

LD-RT has been suggested as a method to prime the body prior to a larger dose of radiation used as a cancer treatment with the premise that multiple doses of LD-RT would stimulate the immune system for improving overall response and survivorship[18,19,22,24,31]. 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 and required 1 month before returning to normal (Table 3). Fluctuations in leukocyte and granulocyte numbers were minimal during treatment and only decrease 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 showing 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 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 prostate cancer patients.

In addition to testosterone supporting the growth of prostate cancer cells, many studies support androgens having a suppressive effect on immune cells[34–36]. Patients currently on ADT (n=4) did not appear to respond to LD-RT as their PSA values continued to rise (Figure 1A,B) whereas patients not on ADT had mixed responses to the treatment (Figure 2C,D). 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 detectible 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 pre-treatment levels after therapy (Figure 2A) ensuring that LD-RT was not indirectly altering PSA levels by influencing circulating androgen levels. With our small sample size strong inferences can not 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 two 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[37]. Increasing heat treatments to three times per week markedly improved the effectiveness of the treatments presumably by further inducing and maintaining the mechanisms responsible. In addition, it is unknown if further treatments can help maintain the remission effect in patients who responded to our initial treatment. A second, smaller sub-study is currently underway to explore this possibility. Given that the current protocol was tested in recurrent prostate cancer patients, 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 hemi-body 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. Pre-clinical models for LD-RT suggest a possible immune-mediated mechanism. The study treatment is readily available, inexpensive, requires minimal radiation planning and is well tolerated by patients. Participants were closely followed for 12 months post-treatment for PSA response, toxicity, hematological status and quality of life. Even following 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 for a reduction in the 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, prior to the use of ADT, hopefully delaying 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 recurrent prostate cancer patients for at least 12 months, further delaying the need to initiate ADT, which is associated with unwanted side effects and 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 to 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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**Figure Captions**

**Table 1:** Baseline characteristics of the trial participants.

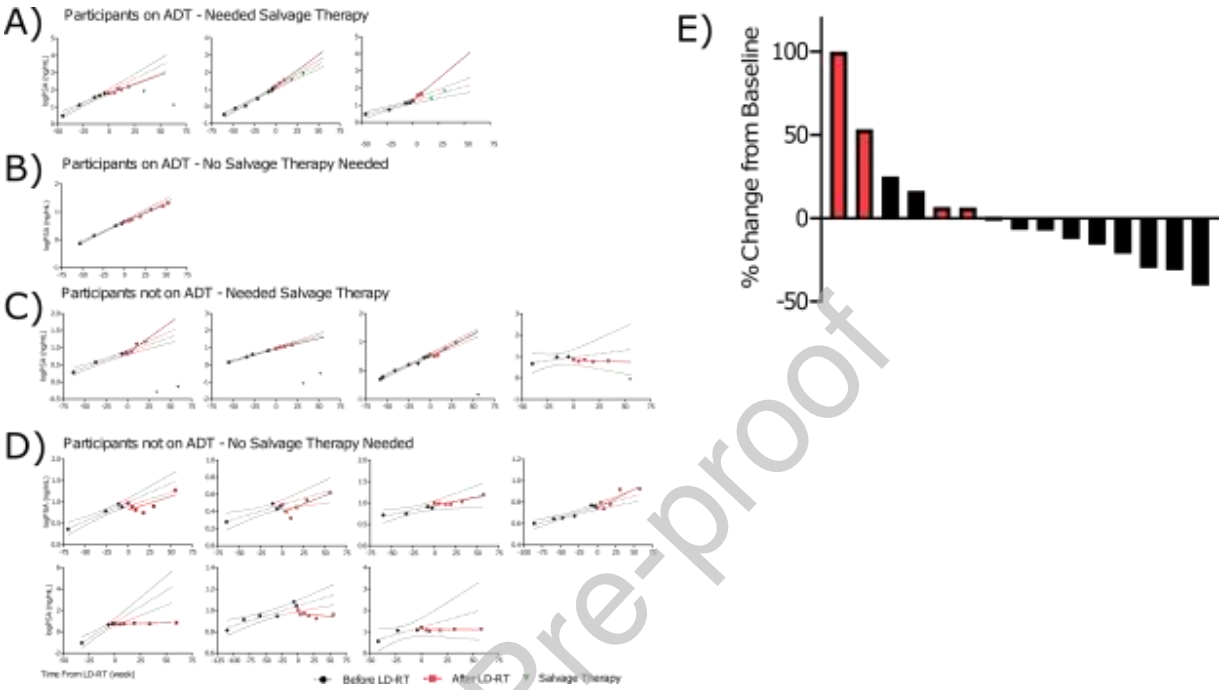


**Figure 1:** Trajectory of each participant's PSA over the course of LD-RT. The predicted trajectory for 52 weeks of logPSA values (black dotted line with 95% confidence interval shown in grey) was determined for each participant utilizing their PSA data available from 12 months prior to LD-RT (black data points). logPSA measured during the study period is represented in red data points, as well as the change in PSA trajectory following LD-RT (red solid line). If a participant started salvage therapy during the follow up period of this study, their further PSA values were highlighted (green) and excluded from PSA trajectory calculations. Each graph represents an individual participant. **A)** Participants on ADT who started additional salvage therapy during the follow up phase of the study. **B)** Participants on ADT who did not proceed to salvage therapy. **C)** Participants initially not on ADT but who commenced ADT during the follow up phase of

the study. **D)** Participants not on ADT and remained off during the study period. **E)** Waterfall plot for the best percentage change in PSA from baseline. Patients taking ADT while being treated with LD-RT are outlined in red.

A)

| **Absolute PSA (ng/mL) [median(min-max)]** | | |
|---|---|---|
| | **Before treatment** | **1 month after LD-RT** |
| Participants on ADT | 17 (4.5-62) | 41 (5.2-111) |
| Participants not on ADT | 7.24 (3.0-16) | 7.1 (2.1-12.9) |
| All Study Participants | 8.8 (3.0-62) | 9.3 (2.1-111) |
| **Testosterone (ng/mL) [median(min-max)]** | | |
| | **Before treatment** | **End of LD-RT** |
| **Participants on ADT** (n=4) | | |
| Testosterone, ng/mL | Below level of detection | Below level of detection |
| **Participants not on ADT** (n=7) | | |
| Testosterone, ng/mL | 8.03 (3.21-12.0) | 7.9 (6.45-12.2) |

B)

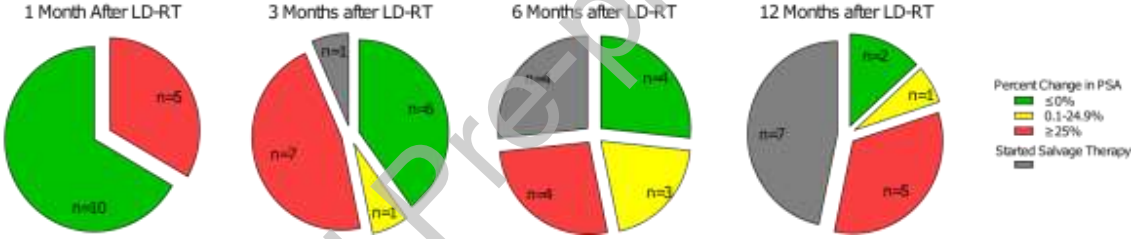


**Figure 2:** PSA and testosterone monitoring before and after LD-RT (n=15). **A)** Absolute PSA and testosterone before and after LD-RT. **B)** Frequency distribution of percent change in PSA from baseline within the patient population at 1,3, 6 and 12 months after LD-RT.

**Table 2**: Adverse events reported over the study period. *n=14

**Table 3:** Frequency of reported changes in hematological parameters, as outlined on a complete blood count report over the study period n=15.

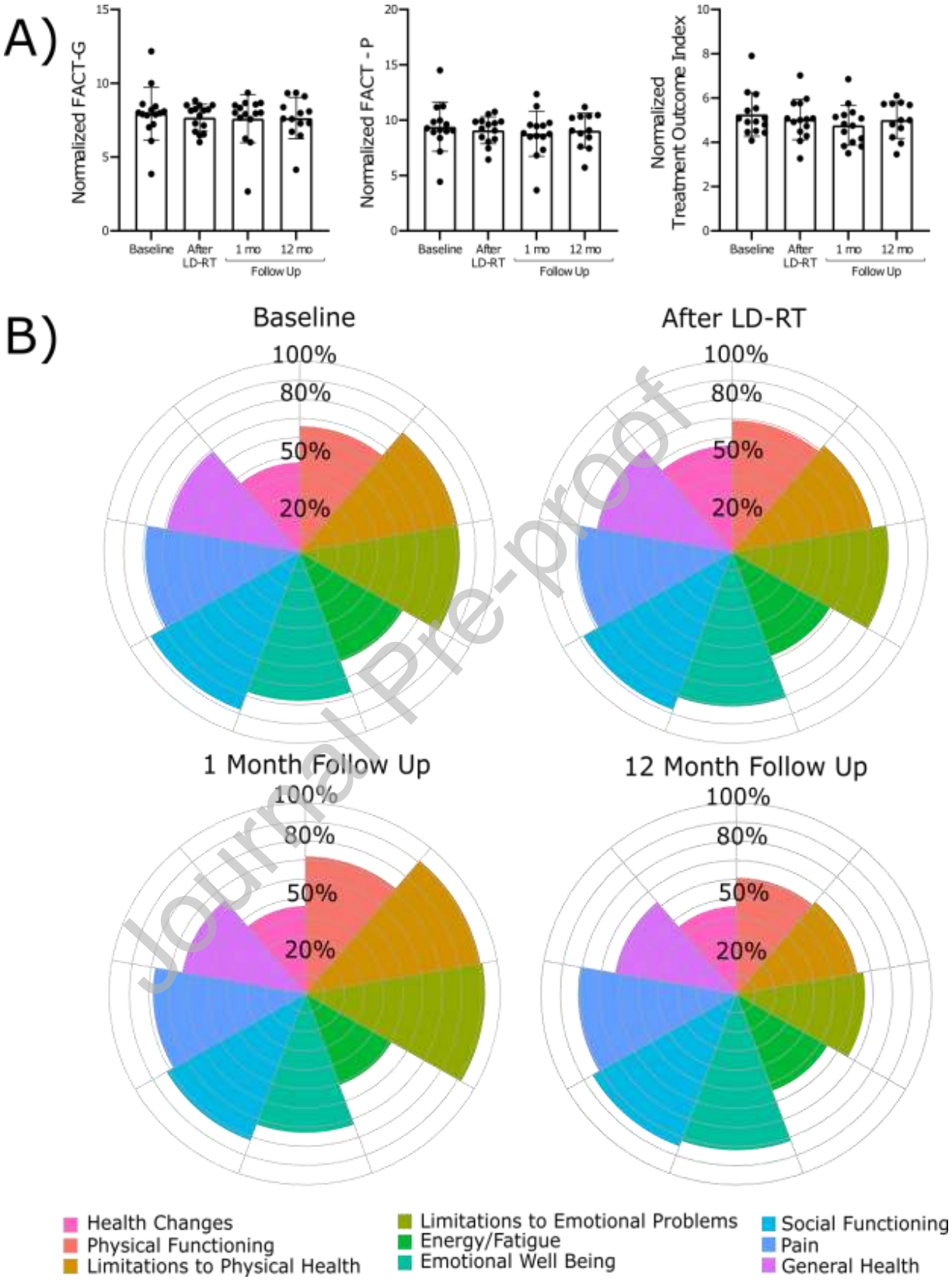




**Figure 3:** Participant quality of life as measured by FACT-P and SF-36 **A**) Functional

Assessment of Cancer Therapy - general score (FACT-G), - prostate specific score (FACT-P) and Treatment Outcome Index (TOI) was measured in the self-reported survey. Mixed effects analysis shows no statistical significance between each collection time point, data is shown as mean ± standard deviation **B):** Self-reported 36-item Short Form Health Survey (SF-36) by participants revealed no statistical differences in the 9 available health scales measured with the survey. Data is shown in a forest plot, with each SF-36 scale identified by a unique colour, with the mean score (n=15) graded from 0-100%

**Supplemental Table 1:** Reasons for non-enrollment of approached patients

**Supplemental Figure 1:** Delivery of hemi-body low-dose radiation **A)** Beams are directed toward the participant standing 3.7 meters from the source. **B)** Each participant had the field size tailored unique to their body profile. The field covered from the suprasternal notch to the mid-thigh, to just cover the fingertips (figure made with BioRender.com).

**Table 1:**

| Participant Characteristics | |
|---|---|
| Age in years, mean (SD) | 76.5 (7.3) |
| Max (years) | 84.5 |
| Min (years) | 59.5 |
| Race, frequency (%) | |
| Caucasian | 15 (93.8) |
| Asian | 1 (6.3) |
| Weight in kg, mean (SD) | 93.9 (16.9) |
| Max | 123.7 |
| Min | 70.2 |
| Smoking Status, frequency (%) | |
| Never | 9 (56.3) |
| Former | 5 (31.2) |
| Current | 2 (12.5) |
| Medical Comorbidity, median | 2 |
| Max | 7 |
| Min | 0 |
| Medical Comorbidity, frequency (%) | |
| Cardiac | 4 (25.0) |
| Hypertension | 10 (62.5) |

| | |
|---|---|
| Neurological | 2 (12.5) |
| Renal | 1 (6.25) |
| Hepatic | 0 (0.0) |
| Auto-immune | 0 (0.0) |
| Diabetes | 1 (6.25) |
| Other | 11 (68.8) |
| ECOG Performance | |
| 0 | 8 (50.0) |
| 1 | 8 (50.0) |
| Time Since Primary Treatment, mean (SD) | 8.4 (3.5) |
| Max (years) | 15.4 |
| Min (years) | 3.6 |
| Prostate Cancer Characteristics | Frequency (%) |
| Gleason Score | |
| 6 | 7 (43.8) |
| 7 | 7 (43.8) |
| 8 | 2 (12.5) |
| T Stage | |
| T1 | 8 (50.0) |
| T2 | 7 (46.6) |
| T3 | 1 (6.3) |
| Previous Local Treatment | |
| Radiotherapy as Primary Treatment | 10 (62.5) |
| Radical Prostatectomy Followed by Radiotherapy | 5 (31.3) |
| Brachytherapy | 1 (6.2) |
| Hormone Deprivation Therapy Status | |
| Never Received | 7 (43.8) |
| Previously Received | 4 (25.0) |
| Currently Taking | 5 (31.3) |

**Table 2:**

| | Adverse Events Reported [frequency(% participants)] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | During Treatment | | | | Following Treatment | | | | Total Study Period |
| | After 1 week | After 2 weeks | After 3 weeks | After 4 weeks | 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) | 1 (6.67) | 2 (13.3) | 1 (6.67) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (13.3) |
| Fatigue | 1 (6.67) | 2 (13.3) | 2 (13.3) | 2 (13.3) | 2 (13.3) | 2 (13.3) | 2 (13.3) | 1 (7.14) | 4 (26.6) |
| 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) |

**Table 3:**

| | | During LD-RT | | | | Follow Up Period | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | After 2 doses | After 4 doses | After 6 doses | After 8 doses | 1 month post-LD-RT | 3 months post-LD-RT | 6 months post-LD-RT | 12 months post-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 | 0 | 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 | 0 | 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 | 0 | 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 | 0 | 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 | 0 | 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 | 0 | 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 | 0 | 1 | 1 | 0 | 0 | 3 |