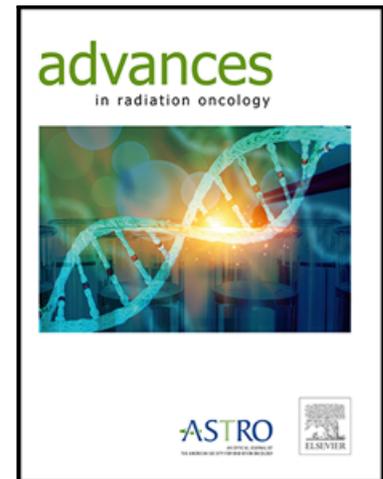


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A Phase I Trial of Highly Conformal, Hypofractionated Post-Prostatectomy Radiotherapy

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ABSTRACT

Purpose: This is a phase I trial aimed to identify the maximally tolerated hypofractionated dose schedule for post-operative radiotherapy (PORT) after radical prostatectomy. Secondary objectives included biochemical control and quality of life (QoL) measures.

Methods: Patients were treated on 1 of 3 dose levels (DL): 56.4Gy in 20 fractions (DL1), 51.2Gy in 15 fractions (DL2), and 44.2Gy in 10 fractions (DL3). Treatment was delivered to the prostate bed without pelvic nodal irradiation. Dose escalation followed a standard 3+3 design with an expansion for 6 additional patients at the maximally tolerated hypofractionated dose schedule. Acute dose limiting toxicity (DLT) was defined as grade 3 toxicity lasting >4 days within 21 days of PORT completion; late DLT was defined as grade 4 GI or GU toxicity.

Results: Between 01/2018 and 08/2019, 15 patients underwent radiation treatment: 3 on DL1, 3 on DL2, and 9 on DL3. The median follow-up was 24 months. There were no DLTs, and the maximally tolerated hypofractionated dose schedule was identified as DL3. Two of the 15 patients (13.3%) experienced biochemical failure (PSA > 0.1). Ten of 15 patients (67%) had grade 2+ acute toxicities, consisting of transient gastrointestinal (GI) toxicities. Three patients experienced late grade 2+ GI toxicity, and 5 patients experienced late grade 2+ genitourinary (GU) toxicity. Late grade 3 GU toxicity occurred in 2 patients. There were no grade 4+ acute or late toxicities. There were no significant differences in GI measures of QoL, however there was an increase in GU symptoms and corresponding decrease in GU QoL between 12 and 24 months.

Conclusions: The MTHDS for hypofractionated post-operative radiotherapy to the prostate bed was determined to be 44.2 Gy in 10 daily fractions. The most frequent clinically significant toxicities were late grade 2+ GU toxicities, which corresponded to a worsening of late GU QoL.

INTRODUCTION

Recently, there has been an increase in the rate of diagnosis of localized prostate cancer with high-risk features [1]. Over this same time period, there has been a trend towards an increase in the utilization of upfront surgical management of this risk stratum [2]. The co-occurrence of these two trends have created a growing population of men who will eventually require post-operative radiotherapy (PORT) [3]. This population experiences several barriers to completing radiotherapy including the length of a treatment course [4] and financial toxicity of treatment [5], providing a rationale for the development of novel hypofractionated dose schedules with the objectives of mitigating these barriers and maintaining oncologic efficacy without an undue decrement in long-term quality of life (QoL).

After several randomized trials verified the safety and efficacy of moderately hypofractionated radiotherapy (MHRT) in the treatment of intact prostate cancer [6-9], MHRT has been accepted as the new standard of care in this setting [10]. This change in the standard of care has improved convenience for patients and has decreased the financial burden of treatment [11]. Although recently presented studies of MHRT have suggested this approach compares favorably to conventional fractionation in regard to post-therapy QoL [12], a similar shift in the standard of care towards more compressed dose schedules has not yet been widely adopted as the standard of care in the post-operative setting, due to the lack of robust data to establish comparative efficacy and toxicity of such regimens. Due to the low α/β ratio of prostate cancer [13] and higher α/β ratio [14-16] of the surrounding normal tissues [14], hypofractionated PORT may allow for the compression of the standard post-operative dose schedule without significantly increasing rates of toxicity. Thus far, however, the optimal total dose and fractionation in this setting have yet to be established.

This report describes the findings of a prospective phase I trial investigating the safety of three isoeffective and increasingly hypofractionated dose-schedules to the prostate bed with the intention of defining the maximally hypofractionated dose schedule for future investigation.

METHODS AND MATERIALS

NCTxxxxxxx is a single-institution, phase I trial of highly conformal, hypofractionated, image guided post-prostatectomy radiotherapy designed to evaluate increasingly hypofractionated dose schedules for patients requiring radiotherapy after prostatectomy. The trial was conducted with approval from the institutional review board of the XXXXXXXXXXXXXXX, and all study participants provided written informed consent prior to enrollment. The trial included two cohorts run in parallel. The first, pending full accrual, included participants with evidence of local recurrence within the prostate fossa on imaging. The second, reported here, included participants without evidence of local recurrence on imaging and has been closed due to completion of accrual and protocol mandated follow-up.

Eligible patients were 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status 0-1 in whom adjuvant or salvage prostate bed radiotherapy was recommended. Treatment indications included high-risk surgical pathology (\geq pT3, pN1, positive surgical margins), persistent post-operative PSA, or biochemical recurrence, defined as a detectable post-operative verified by repeat measurement. Receipt of prior ADT was not an exclusion criterion, and occurred only prior to surgery in this trial. Patients were staged with a bone scan or 18 F-NaF PET/CT and a multiparametric MRI of the prostate bed. Individuals were considered ineligible if pre-treatment staging discovered diseases outside of the prostate bed, including nodal or osseous metastases.

TREATMENT PROTOCOL

Patients were treated with three increasingly abbreviated courses of radiotherapy as specified in **Table 1**. Each dose level was selected as the isoeffective dose schedule to a standard, conventionally fractionated prescription (68.4Gy in 38 fractions) at its respective treatment course length as determined by the linear-quadratic model with an α/β of 3Gy representing normal tissues. The initial course length of 20 fractions was selected as prior studies demonstrated the tolerability of a 26 fraction course of treatment [17]. The clinical target volume (CTV) was defined by the RTOG consensus definition [18]. A PTV margin of 7 mm was used concentrically with allowance for minimization to 5 mm posteriorly to meet dose constraints if necessary. The dose was prescribed to the 100% isodose line using intensity modulated radiation therapy (IMRT). The maximum heterogeneity allowed was a minimum of 95% and a maximum of 115% of the prescription dose within the PTV. Organs at risk (OARs) were contoured. Dose constraints were calculated as isoeffective to previously, widely established values for normal tissues using the linear-quadratic model and an α/β ratio of 3 as detailed in **Supplementary Table 1**. Treatments were delivered with daily fractionation, 5 days per week, using daily cone beam CT image guidance with physician approval of alignment prior to each fraction.

Androgen deprivation therapy (ADT) was allowed at the discretion of the treating physician. When clinically appropriate, 6 months of ADT was given with a depot GnRH antagonist with or without a run-in period of a nonsteroidal antiandrogen.

ASSESSMENTS

Subjects were followed for 24 months after completion of radiotherapy. Patients with biochemical progression during follow-up were removed from study. Adverse events (AEs) were classified using Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) and were scored weekly during treatment and at each follow-up visit. After the completion of treatment, patients were followed every 3 months while enrolled on study and outcome measures were assessed including PSA, testosterone, and AEs. AEs were classified as acute if occurring from the start of treatment to 90 days after treatment and late if occurring > 90 days after treatment.

Patient reported QoL was assessed with the Expanded Prostate Cancer Index Composite Short Form (EPIC-26), Sexual Health Inventory for Men (SHIM), American Urologic Association-Symptom Index (AUA-SI), Patient-Reported Outcomes Measurement Information System (PROMIS) Psychosocial Illness Impact-Positive (PII), PROMIS Anxiety (PROMIS-A), PROMIS Depression (PROMIS-D), and Decision Regret Scale (DRS). All patient reported QoL instruments were collected at baseline and at the 6-, 12-, 18-, and 24-month timepoints.

STATISTICAL DESIGN

The primary objective of this study was to determine the maximally tolerated hypofractionated dose schedule in the post-prostatectomy setting. Acute dose limiting toxicity (DLT) was defined as a grade 3 or higher in-field, physician-assessed toxicity which did not resolve to grade 2 or less within 4 days and occurred during the treatment course or within three weeks after completion of treatment. As an additional safety measure, a late DLT constraint was also included in the trial. A late DLT was defined as a grade 4 or higher gastrointestinal (GI) or genitourinary (GU) toxicity occurring after the DLT assessment period (more than 3 weeks after completion of therapy). Both acute and late DLTs were considered in regard to escalating dose levels.

Three patients were allocated sequentially to each dose level. If none of the three patients experienced a DLT during the assessment period, escalation to the next dose level was initiated. If one of three participants experienced a DLT at any dose level, three additional patients would be enrolled at that dose level. If two participants experienced a DLT at any dose level, that DL would be considered the maximally tolerated hypofractionated dose schedule. If no DLT was observed at the most hypofractionated dose level, that level was considered the maximally tolerated hypofractionated dose schedule.

Secondary objectives were an evaluation of the safety and tolerability of the investigational treatment, the rate of biochemical control (defined as a PSA < 0.1) at 12- and 24-months post-treatment, and patient-reported outcomes (PROs) measured with the SHIM, AUA-SI, and EPIC-26 instruments. Exploratory objectives included additional psychometric testing with the PROMIS-PII, PROMIS-A, PROMIS-D, and DRS.

Changes to PROs from baseline to each follow-up visit were tested by the Wilcoxon signed-rank test. Changes with respect to ADT use and castrate level of testosterone (< 50 ng/mL) for overall sexual function of EPIC and overall SHIM score were compared by Kruskal rank test. In evaluating these measures, the minimally important difference (MID), or threshold beyond which changes in PRO measurements are considered clinically relevant, was defined based on previously used values for the AUA-SI [19], EPIC [20], PROMIS-A [21], PROMIS-D [22], and DRS [23]. As previous work has shown the MID to be dependent on the baseline SHIM score, the MID was variably defined as 2 for mild (score 0-10), as 5 for moderate (score 11-16), and 7 for severe erectile dysfunction (score 17-25) [24]. P-values < 0.05 were considered statistically significant. As these analyses were exploratory in nature, no adjustment for multiple comparisons was made.

RESULTS

Patient Characteristics

From January 29, 2018 to August 9, 2019, a total of 15 patients were enrolled. All participants were followed until 24 months or until removal from protocol after biochemical failure. The median follow-up was 24 months. The median age was 69.9 years (range: 46.8-76.0 years). The majority patients were treated in the salvage setting for biochemical persistence or recurrence (n=14/15). Twelve of the 15 patients (80%) had margin negative resections at time of prostatectomy, and most patients (60%) had NCCN high-risk disease defined by pathologic staging. The remainder of the key patient characteristics are summarized in **Table 2**.

Primary Objective and Toxicity

The maximal tolerated hypofractionated dose schedule was found to be 44.2 Gy in 10 daily fractions over two weeks (DL3) on which 9 of the 15 patients were treated. No acute or late DLTs were encountered at any dose level. Adverse events possibly, probably, or definitely related to radiation are summarized in **Table 3**. Overall, the most common acute adverse events were grade 1 GU toxicity and grade 2 GI toxicity each occurring in 60% of the patient population. The most common acute grade 2 GI toxicity was proctitis, occurring in 7 patients. A single patient encountered acute grade 3 proctitis that resolved to grade 2 within 3 days with medical management and did not meet the pre-specified criterion for a DLT due to its duration. No other acute grade 3 toxicity was observed. Two late grade 3 toxicities occurred. These consisted of one episode of noninfective cystitis that

resolved after 11 weeks in one patient on DL2 and an increase of baseline post-operative incontinence from grade 2 to grade 3 which developed 6 months after treatment and was ongoing at 24 months of follow-up in one patient on DL3. No grade 4 or 5 adverse events were observed.

One notable toxicity occurred in a patient treated on DL3 after removal from the protocol for biochemical progression, which occurred 14 months after the completion of treatment. This patient experienced intermittent, gross hematuria adjudicated to likely be treatment-related. After infectious causes were excluded, imaging revealed left ureteral and renal pelvis dilation. Cystoscopy with biopsies of the prostatic urethra and bladder trigone revealed necroinflammatory debris from the former and reactive appearing urothelium from the latter. There was no evidence of prostate or bladder cancer. Unilateral ureteral stenosis was addressed with a combination of balloon dilation and temporary stent placement. As this event occurred after removal from the protocol, it is not reported in **Table 3**.

Oncologic Outcomes

Of the 15 patients in this study, a single patient met the pre-specified definition for biochemical failure (PSA > 0.1, confirmed on subsequent measurement) by 12 months and a second patient met these criteria for biochemical failure by 24 months. This corresponded to a 12-month rate of biochemical control of 93% and a 24-month rate of 86%. Of the two biochemical failure events, the first exhibited no PSA response to treatment with a PSA trajectory which continued to rise on all post-treatment measurements. The second biochemical failure occurred after an initial PSA response at 22 months post-treatment in a patient who also received ADT. While initial restaging at time of biochemical failure did not detect any recurrent disease in either case, PSMA PET/CTs obtained at PSA values of > 1.0 ng/mL did eventually document an out-of-field pattern of failure and did provide radiographic verification of in-field disease control.

Genitourinary Patient Reported Outcomes

AUA-SI

The baseline AUA-SI was evenly distributed between no/mild burden of urinary symptoms (score: 0-7; 47%) and a moderate burden of urinary symptoms (score 8-19; 53%). The mean baseline AUA-SI score was 7.6 (median 8,

range: 0-17). There was a trend toward continued deterioration of urinary function from baseline over the follow-up period with statistically significant changes at the 12-, 18-, and 24-month timepoint (**Figure 1A**). The increase in the mean AUA-SI score at 24-month follow-up was below the MID at 4.9 points higher than baseline. Throughout the follow-up period, 6 patients had elevations of their AUA-SI score above the MID threshold, however only 4 of these patients had an elevation above the MID threshold by final follow-up. As expected, the resultant AUA-SI QoL score showed a trend towards an increase over time, corresponding to a worse rating of QoL as seen in **Figure 1B**. The average difference was significant only at 24 months ($p=0.049$) with an absolute difference of 0.9 points on a 7-point scale.

EPIC-26 GU

While there was no significant difference in the distribution of EPIC-26 Overall GU score at 6 and 12 months ($p > 0.05$) from baseline (mean: 66.7), there was a significant worsening from baseline at the 18 month (mean: 46.2, $p = 0.02$) and 24-month timepoint (mean = 41.1, $p = 0.013$) which exceeded the MID in magnitude. These results are shown in **Figure 1C**.

Gastrointestinal Patient Reported Outcomes

EPIC-26 GI

The baseline average EPIC-26 GI score was high with a mean of 93.3 (median: 100), indicating favorable QoL amongst this cohort. At each subsequent timepoint, the mean was lower than baseline, however these differences did not reach statistical significance at 6, 12, 18, or 24 months ($p > 0.05$) as shown in **Figure 1D**.

Sexual Health Patient Reported Outcomes

SHIM

The majority of patients had low SHIM scores at baseline (mean: 5.9, median: 2), with most patients being classified as having severe erectile dysfunction ($n=12$). At 24 months there was a decrease in average SHIM score (mean: 2, median: 1) with an increase in the number of patients classified as having severe erectile dysfunction ($n=14$) from baseline. The change in mean score from baseline was not significantly different at the 6-, 12-, and 18-month timepoint. This change, however, did reach significance at the 24-month timepoint ($p=0.029$)

as shown in **Figure 2A**. The change in SHIM score from baseline was not found to correlate with the receipt of ADT or castrate testosterone level. Of the 14 evaluable patients at 24-month follow-up, two patients (14.2%), who initially had mild ED, experienced a clinically significant decline with change from baseline above the MID.

EPIC-26 Sexual Health

Similarly, the mean EPIC-26 overall sexual function score was low with a value of 31.7 at baseline. There were nominal improvements in the change in mean sexual function from baseline reported at 6, 12, and 18 months (range: +7.7 to +11.7) and a nominal decrement at 24 months (-5.4 points); changes from baseline at all timepoints did not exceed the MID and were not statistically significant ($p > 0.05$) as shown in **Figure 2B**. Further, differences from baseline did not correlate with the receipt of ADT or castrate levels of testosterone in those who had received ADT at any timepoint ($p > 0.05$), potentially due to low baseline sexual function.

Psychometric

Psychological Health

The average change from baseline in psychological health on the PROMIS-D (**Figure 3A**), and PROMIS-A (**Figure 3B**) at 6, 12, 18, and 24 months ranged from 0.9 to 3.4 and 0.4 to 3.8, respectively; none of these changes were statistically significant ($p > 0.05$) nor did they exceed the MID. Likewise, the average change in PROMIS-P11 ranged from -2.6 to -1.3. These changes were not statistically significant ($p > 0.05$) and are summarized in **Figure 3C**.

Decision Regret

At baseline, patients reported a low level of regret regarding their prior prostate cancer treatment (score: 8/25). At final follow-up, 2 patients had reduced regret from baseline, 4 patients had no change from baseline, and 9 patients had increased amounts of decision regret. Decision regret was not correlated with PSA failure.

DISCUSSION

In this prospective, phase I trial evaluating three increasingly hypofractionated, isoeffective dose schedules in patients without gross locally recurrent disease, we found that the maximally tolerated hypofractionated dose schedule was 44.2 Gy in 10 daily fractions. No DLTs were observed, however the crude rate of grade 3 toxicities was significant. In the entire cohort, there was a single acute grade 3 toxicity (6.7%), a GI toxicity in dose level 3, and two late grade 3 toxicities (13.3%), both of which were GU toxicities that occurred in patients treated on dose level 2 and dose level 3. As a secondary measure, the efficacy of this regimen appeared to compare favorably to conventionally fractionated PORT in contemporary trials [25, 26].

Quality of Life

There were two key findings from our QoL analysis. First, there was no significant change in GI QoL from baseline at any timepoint during the study period. This finding is in contrast to the results from a previous phase I/II trial from Wages et al. [27], which investigated three similar hypofractionated PORT regimens delivered in 20, 15, and 10 fractions and found a statistically significant decrease at the 1-year timepoint (92.08 vs. 85.80, $p = 0.026$) in EPIC GI QoL. While the mean difference from baseline to 1-year was very similar between our trial and this previous trial (-5.36 vs. -6.28 points), a difference in the mean change from baseline did emerge at 2 years between the two studies (-16.07 vs. -4.49 points). As the treatment volume in the prior study was the same as that employed in the current study, and our rectal planning constraints were slightly more permissive than those in the prior study, the differences in these findings are likely explained by patient-related or technical factors, such as subtle differences in treatment planning or delivery. Future larger follow-up studies are needed to further profile the impact of hypofractionated PORT on GI QoL.

The second key finding was that there is a substantial increase in patient reported GU symptom burden as indicated by higher scores on the AUA-SI and corresponding worse GU QoL as measured by changes in the AUA-SI QoL score and EPIC-26 overall GU score. In a previous, detailed, prospective study of PORT delivered via standard fractionation, similar decrements in GU QoL as measured by the EPIC-26 inventory were not seen in

long term follow-up [28]. Further, of note, this finding also differs from that of the previous trial examining a hypofractionated dose schedule [27]. In the prior study [27], the phase II endpoint was the change in the EPIC-26 QoL subdomain scores at 1 year from baseline. In that study, no significant change in this measure of GU QoL was seen at this timepoint. Our trial corroborated these findings up to 1 year follow-up, showing no significant differences in GU QoL at 6 or 12 months. However, a noticeable decrement on GU QoL became apparent with later follow-up. At the 18- and 24-month timepoints, a statistically significant and clinically meaningful decrement in GU QoL emerged emphasizing the necessity of long-term follow-up to uncover the full QoL burden of hypofractionated PORT schedules on patient reported QoL.

Toxicity

Hypofractionated PORT may also increase the objective rates of GU toxicity. Overall, 2 of the 15 patients (13.3%) enrolled on our trial experienced a late grade 3 GU toxicity. These consisted of one patient with self-resolving cystitis and a second with an exacerbation of baseline grade 2 incontinence. This rate of late toxicity is higher than that expected for conventional fractionation; contemporary phase III trials such as SAKK 09/10 [25] and RTOG 0534 [29] report rates of late grade 3+ GU toxicity within the range of 5.3% to 7.9% in patients undergoing post-operative, prostate bed-directed, salvage radiotherapy. The preliminary results of a recent phase III non-inferiority trial, NRG GU003, designed to compare the 2-year EPIC-26 QoL scores of a more protracted hypofractionated regimen than in our trial (62.5Gy in 25 fractions) and a conventionally fractionated regimen (66.6Gy in 37 fractions) also showed a possible signal of grade 3 adverse events in the hypofractionated arm with a 4.7% rate of grade 3 cystitis as compared to 0% in the conventionally fractionated arm [12]. The aforementioned trial by Wages et al. reported a rate of late grade 3 GU toxicity of 9.4% at 24 months, but were unable to find any statistically significant dosimetric predictors of grade 2+ or grade 3+ GU toxicity on exploratory analysis [27]. Additionally, 4 of the 26 patients (15.4%) in a separate phase I five-fraction dose escalation trial encountered late grade 3 GU toxicity [30] with exploratory analysis revealing a candidate pool of dosimetric predictors of late GU toxicity [31]. These findings from our study and the prior available reports underscore the need for further study of predictors of late GU toxicity in patients who receive PORT. Given that serious GI toxicity appears to be rare, a modification in the dosimetric objectives for treatment planning to prioritize sparing of bladder dose at the expense of higher integral doses to GI structures may produce a superior therapeutic index.

Implications

Similarly, our findings may argue for a modification of treatment volumes. Current recommendations for the definition of a post-operative clinical target volume (CTV) are based primarily on the principle of encompassing the entirety of the surgical field and the inclusion of the most frequent sites of local failure [18, 32-35]. Another implicit criterion used in the definition of the planning target volume (PTV) is the feasibility of delivering a therapeutic dose to a certain treatment volume without undue toxicity. While this is common in routine clinical practice, formal evidence of this directive is provided by the specification of anisotropic PTV margins used in several clinical trials which recommend more conservative posterior margins [25, 36] despite the lack of evidence that setup uncertainty or internal organ motion is lower in magnitude posteriorly at the rectal interface [37, 38]. Furthermore, in other reports of hypofractionated PORT there has been some heterogeneity in PTV margin definitions from as low as 2mm [30] or 3mm [39] to as high as 7mm [27] despite the use of daily image guidance in all cases.

Based on the observation that hypofractionated PORT appears to have a more substantial impact on late grade 3+ GU toxicity as compared to GI toxicity as well as higher rates of GU toxicity as compared to prior conventionally fractionated treatments [12, 25], the risk-benefit ratio of the inclusion of various post-prostatectomy anatomic zones in the treatment volume is likely different than in conventionally fractionated radiotherapy. Current CTV recommendations have been reported to inadequately provide coverage of the area posterior to the vesicourethral anastomosis (VUA) [40] and in the posterolateral aspect of the treatment field at the anorectal interface [41]. Based on the possibility that serious late GI toxicity appears less frequent than corresponding rates of serious late GU toxicity when delivering treatment with a hypofractionated as compared to a standard dose schedule, expansion the posterior aspect of the treatment volume to ensure adequate coverage of the VUA and posterolateral anorectal recess may improve oncologic control without substantial cost in terms of GI toxicity.

A final implication of these findings is that hypofractionated PORT may be most appropriate in a select patient population in whom rational field reduction strategies may be employed. One such group of these patients may be those in whom recurrent or residual disease can be radiographically detected within the prostate bed. In such a population, treatment volume reduction to the area of visible recurrence may be a viable strategy to control disease while limiting the volume of normal tissue exposure and consequent toxicity of treatment. A recent multi-institutional report of patients undergoing 5-fraction PORT to a limited CTV defined as gross disease with a 2mm margin supports this conclusion [42]. This study reported a favorable rate of biochemical remission in patients who did not receive ADT despite otherwise unfavorable baseline characteristics such as a mean pre-salvage PSA of 2.3 ng/mL. These results are somewhat more favorable than older, small, retrospective series reporting on the efficacy of focal brachytherapy in the salvage setting [43, 44] likely owing to the sensitivity of PET imaging to detect local recurrences earlier in their natural history in the contemporary reports.

LIMITATIONS

Our trial cohort was comprised mostly of patients with high-risk disease with 60% of our patient cohort being comprised of patients with high-grade surgical pathology (ISUP grade group 3-5). Unsurprisingly, both treatment failures occurred in this subset of the patient population with evidence of at least one patient having out-of-field relapse at time of treatment as judged retrospectively by PSA trend. While our study was not designed to establish a high confidence estimate of biochemical control, the 2-year rates for this population compares favorably to recent phase III data [25, 26] with all patients except one recovering testosterone to non-castrate levels by protocol completion. While the rate of biochemical control is encouraging, the patient population is small, owing to the phase I design of the trial. Additional investigation is required to provide high confidence estimates of the toxicity and oncologic efficacy of a ten-fraction dose schedule.

Secondly, our treatment protocol included daily cone-beam CT image guidance with pre-treatment approval by a GU-specialized radiation oncologist. This level of image guidance may not be practical in routine clinical practice. Further work is needed to determine if the same toxicity and quality of life profile can be maintained in more routine practice settings.

Finally, emerging data appears to suggest a benefit for pelvic nodal irradiation in some patients with prostate cancer. The preliminary results of RTOG 0534 (SPPORT) reported an increased freedom from progression at a median follow-up of 8.2 years with the inclusion of pelvic lymph node irradiation and short-term ADT to PORT [29]. In the current trial, no patients underwent pelvic nodal irradiation. The incorporation of pelvic nodal radiotherapy to hypofractionated treatment is an ongoing area of investigation, and several small prospective trials have been reported in the setting of intact prostate [45, 46]. Other reports, however, have identified concerning safety signals with unacceptable rates of severe GI toxicity [46], and thus these hypofractionated dose schedules should be cautiously applied to patients in whom nodal irradiation is planned.

CONCLUSION

In conclusion, our study identified the maximally hypofractionated tolerated dose schedule of the dose schedules investigated for post-prostatectomy radiotherapy to be 44.2 Gy in 10 daily fractions with daily image guidance. This regimen was found to be safe by our pre-specified criteria with acceptable rates of physician reported toxicity. The most frequent clinically significant toxicities were late grade 2+ GU toxicities which translated into a worsening of GU QoL demonstrated only after the 12-month timepoint. While our early oncologic outcomes are promising, further prospective validation via randomized trials are required to demonstrate equivalent efficacy of this treatment regimen as compared to standard dose schedules prior to widespread adoption for routine clinical use.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure Captions

Figure 1 Caption: Box plots of quality of life scores for the (A) AUA-SI, (B) AUA-SI, quality of life subdomain, (C) EPIC-26 overall GU subdomain, and (D) EPIC-26 Overall GI subdomain at 0 months (baseline), 6 months, 12 months, 18 months, and 24 months.

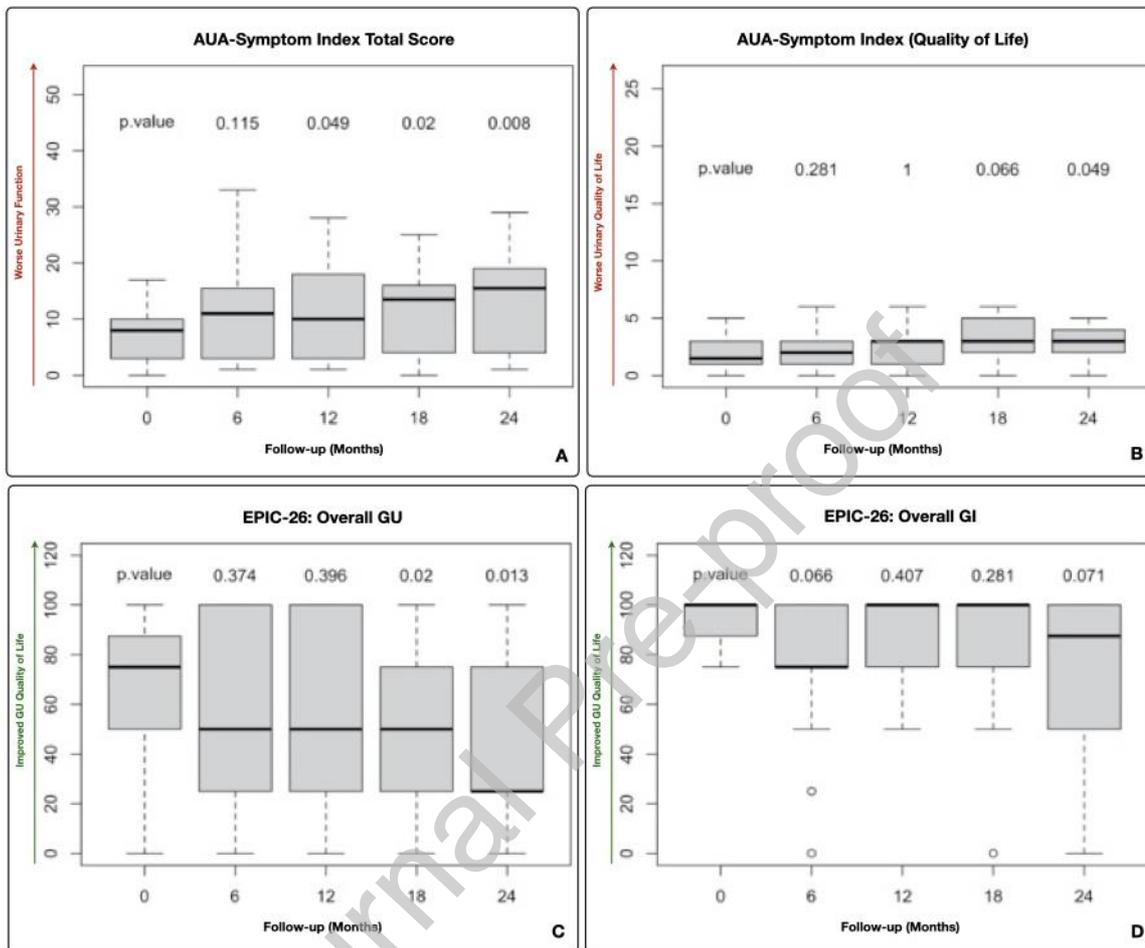


Figure 1. Patient Reported GU and GI Outcomes

Figure 2 Caption: Box plots of quality of life scores for the (A) SHIM, (B) EPIC-26 Overall Sexual Function subdomain at 0 months (baseline), 6 months, 12 months, 18 months, and 24 months.

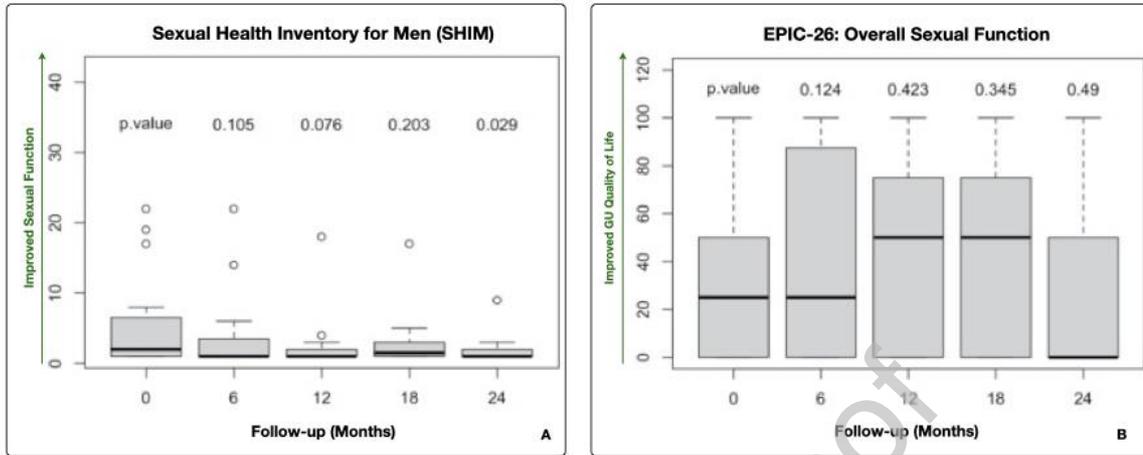


Figure 2. Patient Reported Sexual Function Outcomes

Figure 3 Caption: Box plots of quality of life scores for the (A) PROMIS Depression, (B) PROMIS Anxiety, and (C) PROMIS Psychosocial Illness Impact Inventory at 0 months (baseline), 6 months, 12 months, 18 months, and 24 months.

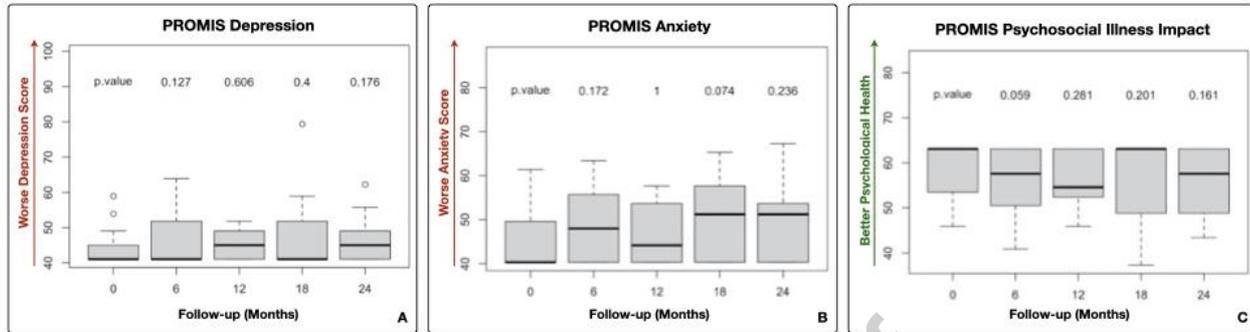


Figure 3. Patient Reported Psychometric Outcomes

Tables

Dosing Scheme	Number of Fractions	Dose per fraction	Total Dose	EQD2	BED	EQD2	BED	Number of Patients
				$\alpha \cdot d^2 \cdot m$				
Dose Level 1	20	2.82 Gy	56.4 Gy	65.6 Gy ₃	109.4 Gy ₃	60.3 Gy ₁₀	72.3 Gy ₁₀	3
Dose Level 2	15	3.41 Gy	51.2 Gy	65.6 Gy ₃	109.4 Gy ₃	57.2 Gy ₁₀	80.3 Gy ₁₀	3
Dose Level 3	10	4.42 Gy	44.2 Gy	65.6 Gy ₃	109.3 Gy ₃	53.1 Gy ₁₀	63.7 Gy ₁₀	9

Table 1. Hypofractionated Dose Schema Used in NCTxxxxxxx, Arm 2
Abbreviation: EQD2 = Equivalent Dose in 2 Gy Fractions

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Category	Subcategory	n	%
Age (Median, Range)			69.9 (46.8-76.0)
Ethnicity			
	<i>Hispanic</i>	0	0.0%
	<i>Non-Hispanic</i>	15	100.0%
Race			
	<i>Black / Other</i>	3	20.0%
	<i>White</i>	12	80.0%
Pathologic ISUP Grade Group			
	<i>GG1</i>	0	0.0%
	<i>GG2</i>	6	40.0%
	<i>GG3</i>	4	26.7%
	<i>GG4</i>	3	20.0%
	<i>GG5</i>	2	13.3%
Pathologic T-stage			
	<i>T2</i>	7	46.7%
	<i>T3a</i>	7	46.7%
	<i>T3b</i>	1	6.7%
Resection Status			
	<i>R0</i>	12	80.0%
	<i>R1</i>	3	20.0%
Extra-prostatic Extension			
	<i>Yes</i>	8	53.3%
	<i>No</i>	7	46.7%
Seminal Vesicle Invasion			
	<i>Yes</i>	1	6.7%
	<i>No</i>	14	93.3%
NCCN Risk Group (pre-op)			
	<i>Low Risk</i>	1	6.7%
	<i>Low-Intermediate Risk</i>	5	33.3%
	<i>High-Intermediate Risk</i>	4	26.7%
	<i>High-Risk</i>	5	33.3%
	<i>Very High-Risk</i>	0	0.0%
NCCN Risk Group (post-op)			
	<i>Low Risk</i>	0	0.0%
	<i>Low-Intermediate Risk</i>	3	20.0%
	<i>High-Intermediate Risk</i>	2	13.3%
	<i>High-Risk</i>	9	60.0%
	<i>Very High-Risk</i>	1	6.7%
CAPRA-S Risk Group			
	<i>Low Risk</i>	3	20.0%
	<i>Intermediate Risk</i>	10	66.7%
	<i>High Risk</i>	2	13.3%
Indication			
	<i>Adjuvant</i>	1	6.7%
	<i>Salvage</i>	14	93.3%
Nadir PSA			
	<i><0.02</i>	10	66.7%

PSA prior to salvage RT	<i>0.02 - 0.10</i>	5	33.3%
	<i><0.02</i>	1	6.7%
	<i>0.02 - 0.10</i>	5	33.3%
	<i>0.10 - 0.20</i>	5	33.3%
	<i>0.20 - 0.50</i>	3	20.0%
	<i>0.50</i>	1	6.7%
Concurrent ADT	Yes	9	60.0%
	No	6	40.0%

Table 2. Patient Characteristics

Abbreviations: PSA = prostate specific antigen

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	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)	Total (n)
Acute GI	3	9	1	13
Acute GU	9	0	0	9
Acute Other	5	0	0	5
Late GI	3	3	0	6
Late GU	3	3	2	8
Late Other	2	1	0	3

Table 3. Maximum Physician Reported Adverse Events During Protocol Follow-up

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