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Hypofractionated post-prostatectomy radiotherapy for prostate cancer to reduce toxicity and improve patient convenience: A Phase I/II trial

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Abstract

Purpose: This is a multicenter, Phase I/II study of hypofractionated (HypoFX) prostate bed radiation therapy (RT) as salvage or adjuvant therapy. The Phase I portion of this study aimed to identify the shortest dose-fractionation schedule with acceptable toxicity. The Phase II portion aimed to assess the health-related quality of life (QoL) of utilizing this HypoFx regimen.

Methods and Materials: Eligibility included standard adjuvant or salvage prostate bed RT indications. Patients were assigned to receive one of three daily RT schedules: 56.6 Gy in 20 Fx, 50.4 Gy in 15 Fx, or 42.6 Gy in 10 Fx. Regional nodal irradiation and ADT were not allowed. Participants were followed for 2 years after treatment with outcome measures based on PSA levels, toxicity assessments (CTCAE v4.0), QoL measures (EPIC, EQ-5D), and out-of-pocket costs.

Results: There were 32 evaluable participants, and median follow-up was 3.53 years. The shortest dose-fractionation schedule with acceptable toxicity was determined to be 42.6 Gy in 10 FX, with most patients (n=23) treated with this schedule. Grade 3 GU and GI toxicities occurred in three patients and one patient, respectively. There was one grade 4 sepsis event. Higher dose to

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Conflicts of interest: None

the hottest 25% of the rectum was associated with increased risk of grade 2+ GI toxicity; no dosimetric factors were found to predict for GU toxicity. There was a significant decrease in the mean bowel, but not bladder, QoL score at 1 year compared to baseline. PSA failure occurred in 34.3% using a nadir plus 2 ng/mL definition. Metastases were more likely to occur in regional lymph nodes (5/7) than in bones (2/7). Mean out of pocket costs for patients during treatment, were $223.90.

Conclusions: We identified 42.6 Gy in 10 fractions as the shortest dose-fractionation schedule with acceptable toxicity in this Phase I/II study. There was a higher than expected rate of grade 2–3 GU and GI toxicity and a decreased EPIC bowel QoL domain with this regimen. Future studies are needed to explore alternative adjuvant/salvage HypoFx RT schedules following radical prostatectomy.

Keywords

prostate cancer; salvage radiation therapy; adjuvant radiation therapy; hypofractionated; post-prostatectomy

Introduction:

Radiation therapy (RT) is delivered after radical prostatectomy (RP) for patients with localized prostate cancer, either as adjuvant RT (ART) for men at high risk of recurrence based upon adverse pathological features[1–3] or as early salvage RT (eSRT) for men with a rising prostate specific antigen (PSA) level after RP.[4–6] The joint consensus statement from the American Urological Association and the American Society for Radiation Oncology recommends that patients with adverse pathological features after RP receive multidisciplinary discussion of the risks and benefits of ART.[7,8] Recent and emerging evidence from three randomized clinical trials of ART versus eSRT,[9–11] as well as a meta-analysis of these data,[12] suggests that ART may be omitted in favor of observation with selective use of eSRT for many men at higher risk of recurrence after RP.

Hypofractionated (HypoFx) RT is promising for the post-RP setting, since it may enhance convenience and reduce health care and travel costs for patients with potential associated improvements in patient experience as well as appropriate RT utilization. While HypoFx RT schedules have become standard of care in the primary treatment for localized prostate cancer,[13] the use of HypoFx RT in the adjuvant or salvage settings remains an emerging strategy.[14] The optimal dose-per-fraction and total dose for adjuvant or salvage HypoFx have not been established, but most studies to date with published results have delivered 2.2–3 Gy per fraction with total doses intended to deliver BEDs (assuming tumor α/β=1.5 Gy) in the range of 153 to 193 Gy with promising rates of biochemical control while maintaining acceptable GU and GI toxicities.[14–20]

In the current report, we describe a prospective trial of HypoFx post-RP RT to the prostate bed that evaluated 20-, 15-, and 10-fraction schedules, with the shortest schedule being 42.6 Gy in 10 fractions. This represents a more extreme hypofractionation range than in prior studies. The dose schedules were calculated from the initial reference point of a series of HypoFx post-prostatectomy RT reported by the University of Wisconsin.[21,22] They used

intensity-modulated RT (IMRT) with daily target localization and delivered 2.5 Gy fractions to a total dose of 65–70 Gy and observed low toxicity and favorable biochemical control rates. Our trial included treatment to the prostate bed only, without inclusion of regional nodes or androgen deprivation therapy (ADT), and was closed in 2019 based upon interim data that suggests benefit from short-term ADT and pelvic nodal irradiation,[23,24] which were not permitted in this study.

Methods:

This was a multicenter, Phase I/II trial designed to evaluate HypoFX RT schedules for daily salvage prostate bed RT to identify the shortest schedule with acceptable GU/GI toxicity during Phase I, and then to evaluate the health-related quality of life (QoL) of that dose schedule during Phase II. The clinical trial (NCT 01868386) was conducted with approval from the Institutional Review Boards of all participating institutions, and all participants signed informed consent prior to participation. The design estimated a maximum accrual of 52 patients, but the study closed early as noted above. The complete clinical trial protocol is included in the Supplementary Materials.

Cohort:

Eligible patients included adult patients for whom postoperative prostate bed radiation therapy was recommended as either adjuvant or salvage therapy after RP for prostate adenocarcinoma. Treatment indications included either detectable PSA after RP or the presence of extracapsular extension, seminal vesicle invasion, or positive surgical margin in the surgical specimen. Previous ADT was allowed if it was completed at least 3 months prior to study treatment. Participants were enrolled at two academic medical centers (University of Virginia and Virginia Commonwealth University). Exclusion criteria included metastases to regional nodes or distant sites, prior pelvic radiation therapy or prior treatment with chemotherapy. Restaging studies were not mandated by protocol, since the primary objectives focused on toxicity and quality of life, but restaging abdominopelvic computed tomography (CT) imaging was performed for all patients per institutional practice. Positron emission tomography (PET) scans were not performed for staging.

Treatment:

Patients were assigned to daily RT at one of 3 dose levels of increasingly smaller number of fractions (Table 1). Dose schedules were calculated to maintain similar biological equivalent dose (BED) for prostate cancer, compared to 1.8 Gy (conventional) and 2.5 Gy (U. Wisconsin) schedules, with decreased BED for late normal tissue injury (α/β= 3Gy) with the goal of reducing toxicity. Participants were immobilized in the supine position and planning was performed based upon CT. The clinical target volume (CTV) was based upon consensus guidelines from the Radiation Therapy Oncology Group,[25] and a 5–7 mm margin was applied for the planning target volume (PTV). The rectum was contoured from sigmoid flexure to the bottom of the ischial tuberosities. The bladder, femoral heads, and penile bulb were also contoured as solid structures. IMRT planning was required, as was daily image-guidance with CT. Dosimetric objectives used during treatment planning for each dose level

are shown in Supplementary Tables 1-3. Treatment was delivered daily on consecutive weekdays (Monday through Friday).

Assessments:

Participants were followed for 2 years after study treatment for evaluation of primary and secondary objectives, and then periodically during clinical surveillance. Outcome measures included: toxicity using Common Terminology Criteria for Adverse Events (CTCAE v4.0), PSA levels, QoL using the Expanded Prostate Cancer Index Composite (EPIC)[26] and the European Quality of Life-5 Dimensions (EQ-5D) instruments,[27] the American Urological Association Symptom Index questionnaire,[28] and out of pocket costs using a short form developed for the study based on published work by Jayadevappa et al.[29] The schedule of assessments in shown in Supplementary Table 4. The EPIC instrument was administered pre-study, during the last week of RT, and between 4 – 6 weeks and at 3, 6, 12 and 24 months after RT. The EPIC questionnaire contains 50 items regarding urinary, bowel, hormonal and sexual domains. The primary focus of the use of the EPIC instrument was on bowel and urinary domains, which is comprised of 26 of the 50 items on the questionnaire. The EPIC scores were transformed to a 0 – 100 scale,[30] with higher scores indicating better health-related QoL.

Statistical Design:

The primary objective of Phase I was to determine the shortest dose-fractionation schedule with acceptable toxicity for evaluation in Phase II. The primary endpoint of Phase I was incidence of grade ≥3 acute GU or GI toxicity assessed by CTCAE v4.0. A dose-limiting toxicity (DLT) was defined as any treatment related grade ≥3 GU or GI toxicity, within 90 days of treatment. For escalation decisions, participants must have been observed for a minimum of 30 days after RT completion; however, any DLT observed through 90 days was used in the modeling stage of the Phase I design. Dose escalation was based on the two-stage continual reassessment method (CRM).[31] The first stage accrued participant cohorts of size 2 until a participant experienced a DLT, after which a model-based allocation (stage 2) began in cohorts of size 1. At study conclusion, the fractionation schedule with an estimated DLT rate closest to the target rate of 20% was considered the shortest dose-fractionation schedule with acceptable toxicity. Stopping rules for safety were defined based on DLT event rates.

The primary objective of Phase II of the trial was to assess the health-related QoL of the recommended shortest dose-fractionation schedule by determining whether or not there is a significant reduction in 1-year disease specific QoL, as compared to baseline, on this schedule. Therefore, additional eligible patients were accrued to the estimated shortest acceptable dose-fractionation schedule. Secondary objectives included evaluation of incidence of acute and late GU and GI toxicity, PSA failure rate at 2 years, out of pocket costs (survey included in Supplementary Materials) during treatment (e.g., co-pays and transportation costs), and change in QoL scores in the Sexual and Hormonal domains at 1 year after treatment.

Sample size and power: Using data from 570 patients in a previously published study,[30] we estimated the standard deviation of the differences between baseline and 1-year scores for both the bowel and urinary domains. Based on these estimates, we considered, for the current study, a drop in 0.5 of a standard deviation (i.e. approximately 4 points in the urinary domain and 3.5 points in the bowel domain) to be a significant reduction in mean EPIC score from baseline to 1-year.

The overall type I error rate for this study is controlled at 10%, so that for each endpoint (urinary and bowel), we used a 5% significance level for a one-sided paired t-test. Assuming a type II error rate of 10%, the ability of the test to detect a reduction of 4 points in the urinary domain and 3.5 points in the bowel domain in the mean EPIC score from baseline to 1-year requires accrual of 36 total eligible patients at the recommended shortest dose-fractionation schedule. In order for the one-sided paired t-test to detect a reduction of 1 standard deviation in each domain (8 points in urinary and 7 points in bowel), the study would require 11 patients at the estimated dose-fractionation schedule.

Data analysis:

GI and GU EPIC domains were evaluated separately. For each patient, the difference between baseline and 1-year EPIC score was generated. The mean and standard deviation of these differences was calculated and used in conducting a one-sided paired t-test at the 5% level of significance for each domain. Similar methods were used to estimate the change in Sexual and Hormonal domains of EPIC at 1 year as secondary endpoints, as well as to estimate the change between baseline and 2-year QoL scores for each domain. We also evaluated rates of minimal clinically important change (MCIC) in EPIC scores for each domain as described by Martell and colleagues in their report: any decline in EPIC score by more than 0.5 standard deviation of the baseline score was considered a MCIC.[14] Estimates and 95% exact binomial confidence intervals were calculated for the proportion of patients experiencing acute and late GU/GI toxicity and the proportion of patients experiencing PSA failure at 2 years.

We also performed an exploratory analysis of the associations between dosimetric factors and GU and GI toxicity events, with statistical significance estimated using Fisher’s Exact test. For the dosimetric analysis, we adjusted doses in Gy to percentage of prescription doses to allow analysis of all dose levels together. Estimates and 95% confidence intervals were generated for total out-of-pocket costs incurred by patients during treatment.

Results:

From April 16, 2013 and January 25, 2019, a total of 33 patients were enrolled on the study. One patient chose to be removed from the study immediately after treatment, providing a total of 32 evaluable participants. The shortest dose-fractionation schedule with acceptable toxicity was estimated to be 42.6 Gy in 10 fractions, and most patients (23/32) were treated at this dose level (see Table 1). Table 2 shows key patient characteristics. Although the study allowed adjuvant therapy, all but one patient enrolled on the trial were treated with salvage intent with detectable PSA at time of registration. A total of 1 DLT (3.1%; 95% C.I. (0%, 16.2%)) was observed within 90 days of treatment, a grade 3 diarrhea occurring at dose level

2 (50.4 Gy in 15 fractions). During the follow up period, late grade 3 GU events were observed in three participants (9.4%), including cystitis with hematuria in two patients, and urinary incontinence in one patient. Both of the cystitis with hematuria events were observed on dose level 2 (50.4 Gy in 15 fractions), and the urinary incontinence event was observed on dose level 3 (42.6 Gy in 10 fractions). These three events occurred beyond 90 days (230 and 499 days for cystitis with hematuria; 604 days for urinary incontinence) from completion of RT and thus did not contribute to dose escalation as DLT events, which highlights the challenges in conducting radiation studies where significant toxicities can arise outside of the DLT observation period. On dose level 2 (50.4 Gy in 15 fractions), there was one grade 4 sepsis event that occurred during management of grade 3 cystitis. Grade 2 GU and GI toxicities were observed in three (9.4%; 95% C.I. (2%, 25%)) and 15 (46.9%; 95% C.I. (29.1%, 65.3%)) participants, respectively. All three of the Grade 2 GU toxicities occurred on dose level 3 (42.6 Gy in 10 fractions). The number of Grade 2 GI toxicities on dose levels 1, 2, and 3 were 1, 4, and 10, respectively. The 15 grade 2 GI toxicities included 9 diarrhea, 3 proctitis, 1 fecal incontinence, and 2 rectal hemorrhage events, all of which occurred within the first 30 days of treatment (median 15 days).

An exploratory analysis of the association between toxicity and dosimetric parameters (>median vs ≤ median) is summarized in Supplementary Tables 5 and 6. Higher dose to the hottest 25% of the rectum was associated with increased probability of grade 2+ toxicity events. Doses higher than a median of 77.2% of the prescription dose was associated with statistically significant higher rate of toxicity events than below the median (53.3% vs 12.5%; Fisher's exact test p=0.023). No other significant associations were observed for GI toxicity, and there were no predictors of GU toxicity.

Quality of Life:

For the primary analysis in Phase II, mean EPIC score in the urinary domain did not significantly decrease from baseline (mean score 79.89) to 1-year (mean score 78.23) at the estimated shortest dose-fractionation schedule (Figure 1; p=0.2895). However, mean EPIC score in the bowel domain significantly decreased from baseline (mean score 92.08) to 1-year (mean score 85.80) at the estimated shortest dose-fractionation schedule (Figure 1; *p=0.0261*). For the sexual domain, mean EPIC score in the sexual domain increased from baseline (mean score 23.35) to 1-year (mean score 30.43) at the estimated shortest dose-fractionation schedule (Figure 2), with estimated mean difference of −5.08 (95% C.I. (−9.45, −0.72)). Mean EPIC score in the hormonal domain slightly decreased from baseline (mean score 91.35) to 1-year (mean score 91.28) at the estimated shortest dose-fractionation schedule (Figure 2), with a small estimated mean difference of 0.077 (95% C.I. (−3.17, 3.33)). The decline in mean EPIC score for the bowel domain and the increase in mean EPIC score for the sexual domain meet pre-specified estimates of clinical significance. Mean EPIC score in the urinary and bowel domains at 2-years was 75.92 and 87.59, respectively, at the shortest dose-fractionation schedule (Figure 3). Mean EQ-5D score in the sexual and hormonal domains at 2-years was 31.24 and 86.79, respectively, at the shortest dose-fractionation schedule (Figure 4).

Disease Outcomes:

A total of 11 of 32 participants (34.3%; 95% C.I. (18.6%, 53.2%)) experienced a PSA failure defined as nadir plus 2 ng/mL and 14 of 32 participants (43.8%; 95% C.I. (26.4%, 62.3%)) experienced PSA failure defined as three consecutive rises in PSA. A total of 11 of 32 participants also experienced a PSA failure defined as PSA ≥ 0.4 ng/mL and rising. This endpoint requires that the PSA is detectable and rising for at least two values with the second value at 0.4 ng/mL or greater. Among the 27 participants for which distant metastasis data were available, 7 participants developed distant metastasis (25.9%; 95% C.I. (11.1%, 46.3%)), more commonly in regional lymph nodes only (5/7) than in bones (2/7).

Out of Pocket Costs:

The estimated mean out of pocket costs (i.e., copays and transportation due to prostate cancer) during the month prior to treatment was $35.13 (95% C.I. ($8.79, $61.47)). The estimated mean out of pocket costs during treatment was $224.90 (95% C.I. ($130.29, $319.52)).

Discussion:

In this multicenter, Phase I/II study of HypoFX prostate bed RT as salvage or adjuvant therapy, we enrolled a total of 32 evaluable participants, identified 42.6 Gy in 10 fractions in Phase I as the shortest dose-fractionation schedule with acceptable toxicity for evaluation in an expansion cohort, and treated a total of 23 patients at this dose level. Only 1 DLT was observed within 90 days after treatment. However, we observed grade 3 GU and GI events in 9.4% and 3.1% of participants, respectively, as well as grade 2 GU and GI events in 9.4% and 46.9% of participants, respectively, during the follow-up period. Most events occurred beyond 90 days after treatment. We also observed a decline in bowel QoL, but not urinary QoL, from baseline to 1 year after treatment that met pre-specified criteria for clinical significance. The results from this study for grades 2–3 GU/GI toxicity and bowel QoL were worse than we expected, and our primary conclusion from the current study is that alternative dose schedules should be explored in future trials (rather than 42.6 Gy in 10 fractions). We recommend additional prospective studies to evaluate and optimize late GU and GI toxicity rates before adopting HypoFx RT as a standard approach in the post-RP setting. Furthermore, future regimens will need to address inclusion of ADT and/or regional lymph nodes in the treatment field, which was not included in our trial. Given the small sample size and the potential impact of patient selection through restaging imaging, as well as nodal irradiation and androgen deprivation therapy (which were not included in this study), we do not recommend drawing conclusions from the observed rates of PSA failure and distant metastasis in the current study.

The published outcomes for various HypoFx post-prostatectomy RT schedules, mostly in the 2.2–3 Gy-per-fraction range, have been mostly favorable.[32] However, the reported late toxicity rates do vary widely, with a recent review showing that late grade 3 GU toxicity rates ranged from 0–46.5% and late grade 4 rates from 0–4%.[32] In the current study, the rates of grades 3 and 4 late GU and GI toxicities were within these reported ranges, but higher than we anticipated. Most patients in our trial were treated at the shortest dose-

fractionation schedule of 42.6 Gy in 10 fractions, a relatively high dose-per-fraction compared to most reports in the published literature. Tandberg and colleagues found that moderate HypoFx using 2.5 Gy per fraction was not associated with greater GU toxicity rates than conventional fractionation in the post-prostatectomy setting.[33] Results are forthcoming from a prospective, multicenter randomized trial from NRG Oncology that will provide more evidence for clinical outcomes after HypoFx using 2.5 Gy per fraction (NRG GU-003). However, there is less evidence available in the literature regarding post-prostatectomy HypoFx using larger fraction sizes, and limited data regarding late toxicity rates. Martell and colleagues observed no late grade 3–4 toxicities and 31% rate of biochemical failure after 51 Gy in 17 fractions (3 Gy/fraction) to the prostate bed in a Phase I/II trial of 30 patients.[14] The Martell study used a smaller margin for PTV (4 mm vs 5–7 mm) than in the current study, as well as a lower BED.[14] In addition, Ballas et al observed no grade 3 or higher acute toxicity after post-prostatectomy stereotactic body radiation therapy (SBRT) using a dose of 35.5 Gy in 5 fractions,[34] but the follow up was short and only 12 participants were treated at that dose level. Sampath and colleagues observed no grade 3 or higher late GI toxicity and a 15% rate of grade 3 or higher late GU toxicity in their trial of prostate bed SBRT to doses of 35 Gy, 40 Gy and 45 Gy in 5 fractions.[35] Our experience with 10 daily fractions of 4.26 Gy/fraction provides information regarding late toxicity events and suggests that alternative HypoFx schedules, employing lower dose-per-fraction or lower total dose, may be more promising for further investigation in this setting than the schedules we evaluated. Although beyond the scope of the current study, we hypothesize that the higher than expected toxicity rates observed in our study may relate to the substantial volume of bladder and adjacent digestive organs located within or near the target volume in the post-prostatectomy pelvis, in contrast to prostate SBRT in the setting of primary prostate cancer treatment.

Much has been written about the alpha-beta ratio for prostate cancer as it pertains to HypoFx RT, but most large analyses of alpha-beta ratio have excluded patients receiving post-RP RT.[36,37] In the post-RP setting, with the vesico-urethral anastomosis being the most likely site of recurrence and the bladder neck located within the target volume, it is essential to consider the alpha-beta ratio of organs-at-risk when considering HypoFx schedules.[38,39] Cozzarini and colleagues observed a higher than expected rate of late urinary toxicity after moderately hypofractionated post-RP RT, and hypothesized that the bladder may be more sensitive to RT in the postoperative setting.[39] Radiobiological modelling of their data suggests that the high rate of late urinary toxicity could be explained by a bladder alpha-beta ratio less than 1 Gy.[40] Such a low alpha-beta ratio is even lower than estimates for prostate cancer,[37] suggesting caution is warranted when choosing candidate HypoFx RT schedules to evaluate after prior RP. In contrast, Martell and colleagues observed no grade 3–4 GU or GI toxicities with a dose of 51 Gy in 17 fractions to the prostate bed,[14]which is a lower dose than used ineither the Cozzarini et al study or the current trial. These anatomical and dose considerations may explain in part the observation of a high rate of late toxicities in the current trial.

Financial toxicity is a significant concern for prostate cancer patients, with out-of-pocket costs affecting patients over the long term during and after RP and RT.[29,41] In the current study, we used a survey (see Supplementary Materials) designed for the study by adapting

information from a published report from Jayadevappa et al.[29] We found that a 10-fraction RT schedule resulted in a relatively small impact on out-of-pocket costs, supporting the potential for HypoFx RT regimens to minimize financial toxicity for prostate cancer patients. Costs reported in our study were less than reported with conventional RT regimens.[29,42] It should be noted that the timing of our survey collection was such that patient-reported costs do not reflect copays related directly to the bills for RT itself. Our findings substantiate the logical conclusion that HypoFx RT regimens reduce direct health care costs and may reduce patient out-of-pocket costs associated with cancer treatment, as has been highlighted elsewhere.[43]

The current study has limitations that warrant consideration, beyond the typical small sample size of a Phase I/II study. Most importantly, the study treatment did not allow pelvic nodal irradiation or ADT, which does not reflect contemporary standards based on recent findings from clinical trials.[23,24] This may limit comparison of biochemical control and toxicity rates with other published results, particularly since lymph nodes were the predominant site of metastases in our study. Patients enrolled in our trial had lymphadenectomy at time of RP and no evidence of lymph node metastasis on imaging. Although restaging was not mandated by the trial protocol, all patients had routine nodal staging with CT prior to treatment. The lack of PET staging in our trial may have resulted in inclusion of subjects with metastases at time of RT, and may limit the applicability of our observed disease outcomes to contemporary practice. Given the low pre-RT PSA values for patients enrolled in our trial, the effect of a lack of PET staging on outcomes may be tempered by the fact that most patients reported to have PET-detected findings in the recurrent setting have PSA > 1 ng/mL[44,45] and sensitivity of PET/CT for staging is dependent upon PSA level.[46] It should be noted that the use of HypoFx RT in the post-prostatectomy setting does not preclude the elective treatment of at-risk pelvic lymph nodes, and simultaneous integrated boosts can be utilized to treat the prostate bed at a higher dose per fraction while treating nodal volumes at 1.7 to 1.9 Gy per fraction.[19,20] However, more trials are needed to evaluate HypoFx RT approaches that include nodal irradiation. The current study evaluated only three dose schedules, and alternative dose schedules should be investigated, particularly given the concerning toxicity rate observed in our study. Finally, our CRM for dose schedule allocation focused on events that occurred within 90 days of treatment. Similar future studies should strive to incorporate late events into the model based upon the timeline of observed events in our study and the clinical significance of late GU and GI events, although this may present challenges to accrual feasibility, external validity due to interim secular trends, funding concerns, and delays in receiving interpretable results.

In conclusion, we identified 42.6 Gy as the shortest dose-fractionation schedule with acceptable toxicity, based upon pre-specified evaluations of toxicity events over a 90-day post-treatment period, in a Phase I/II study of prostate bed HypoFx RT. However, we observed a higher than expected rate of late grade 2–3 GU and GI toxicity in this study, mostly after the 90-day observation period for DLTs, and a decline in bowel QoL from baseline to 1 year after RT. We recommend that future trials explore alternative dose schedules for HypoFx post-prostatectomy RT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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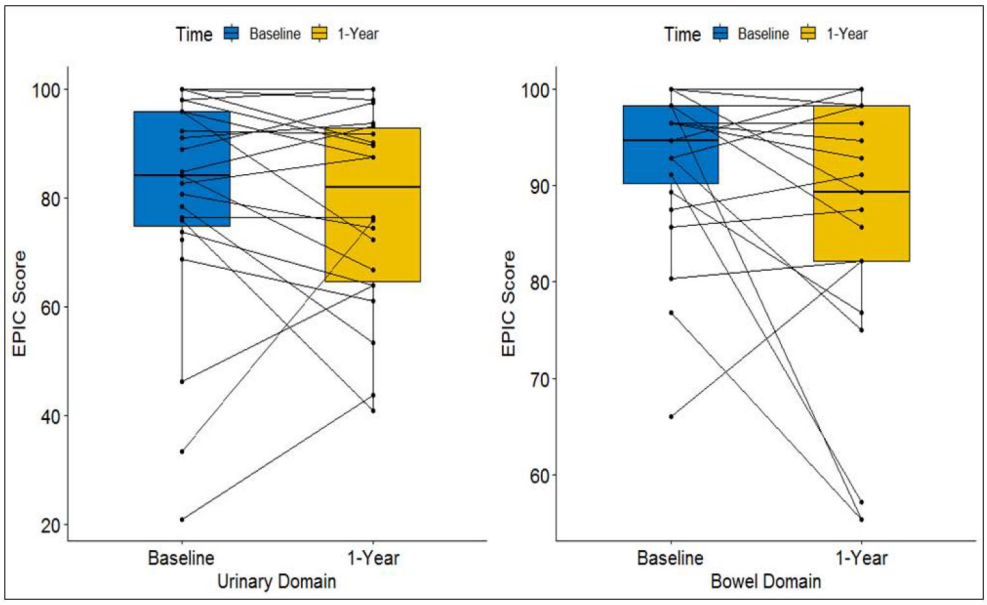

Figure 1:

Dot and box plot of EPIC scores in urinary and bowel domains at baseline and 1 year after RT treatment at 4.26 Gy × 10 = 42.6 Gy [2 weeks].

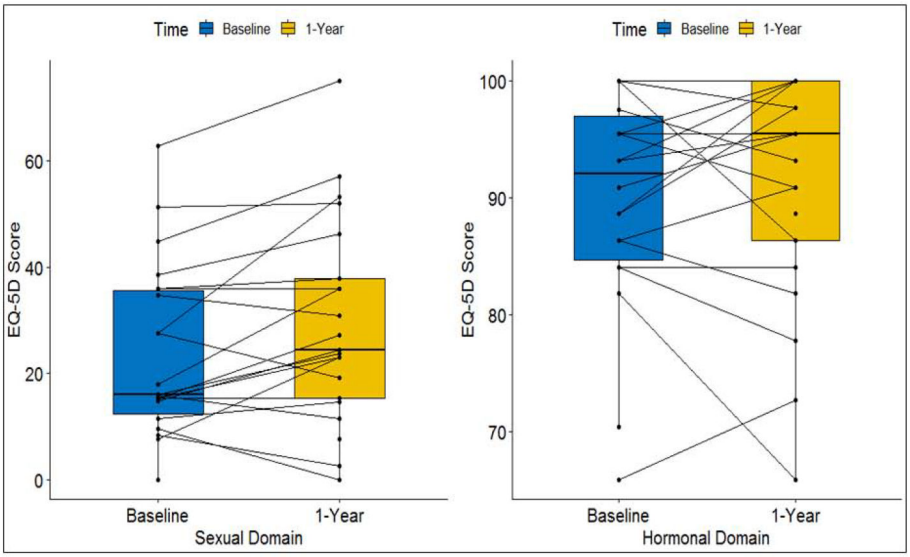

Figure 2:

Dot and box plot of EQ-5D scores in sexual and hormonal domains at baseline and 1 year after RT treatment at 4.26 Gy × 10 = 42.6 Gy [2 weeks].

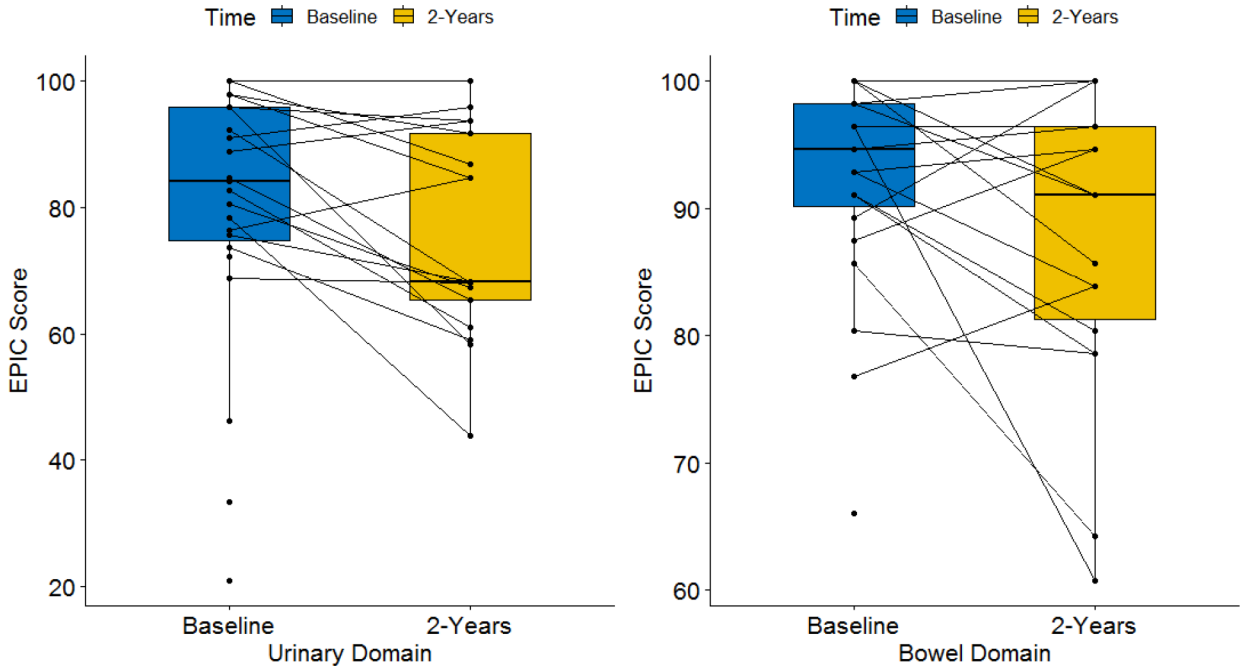

Figure 3:

Dot and box plot of EPIC scores in urinary and bowel domains at baseline and 2 years after RT treatment at 4.26 Gy × 10 = 42.6 Gy [2 weeks].

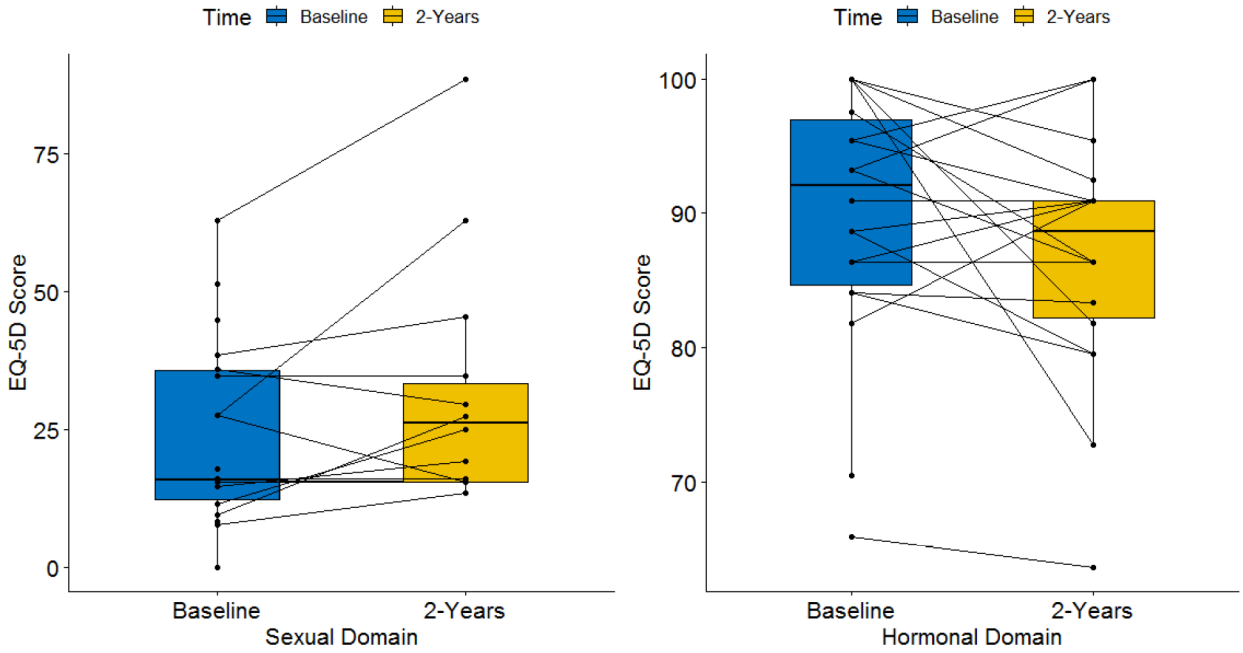

Figure 4:

Dot and box plot of EPIC scores in sexual and hormonal domains at baseline and 2 years after RT treatment at 4.26 Gy × 10 = 42.6 Gy [2 weeks].

Table 1.

Dose schedules used in the Phase I/II trial of postoperative prostate bed radiation therapy. The right-most column shows the distribution of subjects by dose schedule.

	Dose Escalation Schedule					
Dose Schedule	**$BED_{1.5}$ (Gy)**	**$EQD2Gy_{1.5}$(Gy)**	**BED_3 (Gy)**	**$EQD2Gy_3$ (Gy)**	**Dose Level**	**Participant total N (%)**
2.5Gyx26=65Gy (5.2 weeks)	*173.0*	74.3	*119.2*	71.5	*−1*	N=0 (0%)
2.83Gyx20=56.6Gy (4 weeks)	163.4	70.2	110.0	66.0	1	N=4 (12.5%)
3.36Gyx15=50.4Gy (3 weeks)	163.3	70.0	106.8	64.1	2	N=5 (15.6%)
4.26Gyx10=42.6 Gy (2 weeks)	163.6	70.1	103.1	61.9	3	N=23 (71.9%)
	Total					**N=32**

Table2.

Patient characteristics

Characteristic	Overall n=32
Age (mean (sd))	63.3 (6.31)
Ethnicity (%)	
Non-Hispanic	31 (96.9%)
Unknown	1 (3.1%)
Race (%)	
African American	10 (31.2%)
White	21 (65.6%)
Other	1 (3.1%)
Gleason score	
6	3 (9.4%)
7	20 (62.5%)
8	4 (12.5%)
9	5 (15.6%)
T Stage	
T2a	1 (3.1%)
T2c	17 (53.1%)
T3a	8 (25%)
T3b	6 (18.8%)
Positive Surgical Margin (n=28)	20 (71.4%)
Pre-RT PSA (mean (sd))	0.33 (0.71)
Median follow-up for those still alive (years (range))	3.78 (1.06 – 6.55)