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ORIGINAL ARTICLE

Acute toxicity of hypofractionated intensity-modulated radiotherapy for prostate cancer

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ABSTRACT

Background

Dose-escalated hypofractionated radiotherapy (HFRT) using intensity-modulated radiotherapy (IMRT), with inclusion of the pelvic lymph nodes (PLNS), plus androgen suppression therapy (AST) in high-risk prostate cancer patients should improve patient outcomes, but acute toxicity could limit its feasibility.

Methods

Our single-centre phase II prospective study enrolled 40 high-risk prostate cancer patients. All patients received HFRT using IMRT with daily megavoltage computed tomography imaging guidance, with 95% of planning target volumes (PTV68 and PTV50) receiving 68 Gy and 50 Gy (respectively) in 25 daily fractions. The boost volume was targeted to the involved PLNS and the prostate (minus the urethra plus 3 mm and minus 3 mm from adjacent rectal wall) and totalled up to 75 Gy in 25 fractions. Acute toxicity scores were recorded weekly during and 3 months after radiotherapy (RT) administration.

Results

For the 37 patients who completed RT and the 3-month follow-up, median age was 65.5 years (range: 50–76 years). Disease was organ-confined (T1c–T2c) in 23 patients (62.1%), and node-positive in 5 patients (13.5%). All patients received long-term AST. Maximum acute genitourinary (GU) and gastrointestinal (GI) toxicity peaked at grade 2 in 6 of 36 evaluated patients (16.6%) and in 4 of 31 evaluated patients (12.9%) respectively. Diarrhea and urinary frequency were the chief complaints. Dose–volume parameters demonstrated no correlation with toxicity. The PTV treatment objectives were met in 36 of the 37 patients.

Conclusions

This HFRT dose-escalation trial in high-risk prostate cancer has demonstrated the feasibility of administering 75 Gy in 25 fractions with minimal acute GI and GU toxicities. Further follow-up will report late toxicities and outcomes.

KEY WORDS

Hypofractionated radiotherapy, intensity-modulated radiotherapy, androgen suppression, high-risk prostate cancer, acute toxicity

1. INTRODUCTION

In 2014 in North America, more than 250,000 men were expected to be diagnosed with prostate cancer, and approximately 1 in 8 men will develop prostate cancer during their lifetime[1,2]. For many, the disease will be indolent; however, high-risk prostate cancer will develop in 20%–30% of men presenting with localized disease[1,2]. The definition of high-risk prostate cancer generally includes a diagnosis of high-grade prostate adenocarcinoma, Gleason score 8 or greater, prostate specific antigen (PSA) 20 ng/mL or more, and locally advanced disease on clinical examination (cT3 or higher). One option that is considered standard treatment for high-risk disease includes the use of both external-beam radiotherapy (RT) and androgen suppression therapy (AST).

Dose escalation in the treatment of prostate cancer has improved freedom from failure, with acceptable toxicity[3,4]. Hypofractionation for prostate cancer is a radiobiologic concept of theoretical advantage demonstrated with an equivalent biologic effective dose delivered using more than 2.2 Gy per fraction[5]. Hypofractionated RT (HFRT) in the treatment of prostate cancer has demonstrated promising biochemical control and acceptable acute and late toxicity[6–9]. Clarity concerning the optimal dose and fractionation of HFRT and evidence of equivalent or

improved outcomes with toxicities comparable to those observed with standard fractionation could allow for an evidence-based shift in clinical practice.

The present single-centre phase II prospective trial tested the feasibility and safety of HFRT using intensity-modulated RT (IMRT) combined with AST in high-risk and pelvic lymph node (PLN)–positive prostate cancer. The study stems from a previous investigation of a HFRT regimen using 68 Gy in 25 fractions[10]. The present trial used further dose escalation to 75 Gy in 25 fractions to the boost volume, dose escalation to 50 Gy in 25 fractions to the PLNs, and smaller planning target volume (PTV) margins. Here, we report the acute toxicity associated with the new regimen; late toxicity and clinical outcomes will be reported when the data mature.

2. METHODS

2.1 Study Design

This single-institution phase II prospective clinical trial received ethics approval from the institutional research ethics board and obtained written informed consent from all patients before their enrolment into the study. The primary endpoint of the study was late rectal toxicity. Secondary endpoints included acute rectal toxicity, acute and late bladder toxicity, biochemical control, and disease-free and overall survival. This interim report describes the acute gastrointestinal (GI) and genitourinary (GU) toxicities.

2.2 Patient Characteristics

Between June 2009 and July 2012, the trial enrolled 40 patients, among whom 37 were eligible for participation. Inclusion criteria included a histologic diagnosis of high-risk prostate cancer (any one or a combination of cT3/4, N0/1, M0; a Gleason score of ≥8; or a pre-treatment PSA ≥20 ng/mL). Patients with PLN involvement or radiologic features of pelvic metastasis were eligible for participation. Patients were excluded if there was evidence of distant metastasis; a prior history of inflammatory bowel disease, anal stenosis, colorectal surgery, or repeated endoscopic examinations or interventions related to anorectal diseases; a history of prostatectomy, transurethral resection of prostate on more than one occasion, or previous pelvic radiotherapy; a history of androgen suppression for 4 months or more; or malignancy within preceding 5 years, except for nonmelanoma skin cancer or highly curable malignancy with a cure prognosis exceeding 80%.

2.3 Patient Evaluation

Pre-treatment evaluation of all patients included a complete history and physical examination, including a digital rectal examination, routine blood work, baseline pre-treatment PSA, diagnostic computed tomography (CT) of abdomen and pelvis, and a whole-body bone scan within 6 months of the RT start date.

During treatment, patients were assessed weekly, and GI and GU toxicities were recorded using the *Common Terminology Criteria for Adverse Events,* version 3.0. Post-treatment follow-up was arranged for 3 months after the last day of RT and included a physical exam, repeat PSA, repeat routine blood work, and toxicity reporting.

2.4 RT

Non-contrast CT simulation images were used to delineate organs at risk and target volumes. All RT was delivered as IMRT using the helical tomotherapy (HT) method. Daily megavoltage CT imaging was performed before treatment for verification. During CT simulation and treatment, patients were positioned in a supine position on the flat table couch, with a full bladder and empty bowels. Immobilization devices were used to keep the pelvis straight, with a sponge under the patient's knees and the patient's hands positioned on the chest, per the institutional standard for CT simulation and treatment. Digital images were transferred to an Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, U.S.A.) via a DICOM system with a maximum image slice thickness of 3 mm.

The Eclipse planning system was used to manually define targets, the prostate gland and seminal vesicles, PLNs, the clinical target volume (CTV)/PTV50, CTV/PTV68, boost volume, and planning organs at risk volume–urethra onto each CT slice. The prostate gland and seminal vesicles were delineated on each slice for all images, and the PLNs were delineated per the Radiation Therapy Oncology Group PLN volumes for prostate cancer. The CTV50 represented the PLNs and seminal vesicles and, with a 10-mm uniform margin in all directions (except for a 6-mm inferior margin), created the PTV50. The CTV68 represented the prostate and, with an 8-mm uniform margin in all directions (except for a 3 mm posterior and inferior margin), created the PTV68. The boost volume, 75 Gy, represented the prostate plus involved clinically positive lymph nodes, with a 3-mm subtraction from adjacent rectum, minus the planning organs at risk volume–urethra, which was defined as the urethra plus a 3-mm uniform margin. (At the time of CT simulation, a Foley catheter is used to improve the accuracy of target definition.) The Eclipse planning system was also used to manually define all organs at risk onto each CT slice. The bladder was drawn as a solid volume from the dome of the bladder to the base. The rectum was drawn from the anal canal to the rectosigmoid flexure (Figure 1).

Treatment was delivered as dynamic IMRT using the HT technique with a photon beam [5.7 MV high-dose source (nominal dose rate of 850 cGy/min,

1.5 mm point source)]. Quality assurance checks of the machine were performed per institutional standard, with quality assurance of the HT plan being performed before the start of RT in each patient. Table I highlights the treatment goals, and dose–volume (V) constraints included rectum ($V_{60} \leq 30\%$, $V_{50} \leq 55$ Gy), bladder ($V_{65} \leq 30\%$, $V_{50} \leq 60$ Gy), peritoneal cavity or bowel (maximum dose ≤ 54 Gy), femurs (maximum dose ≤ 52 Gy), and unspecified tissue (median dose ≤ 75 Gy).

2.5 Treatment Verification

Megavoltage CT images obtained daily during treatment were compared with the images from the planning CT imaging. Axial, sagittal, and coronal images were used for verification. Necessary table shifts were applied for each treatment after manual 3-dimensional correction at the prostate–rectum interface.

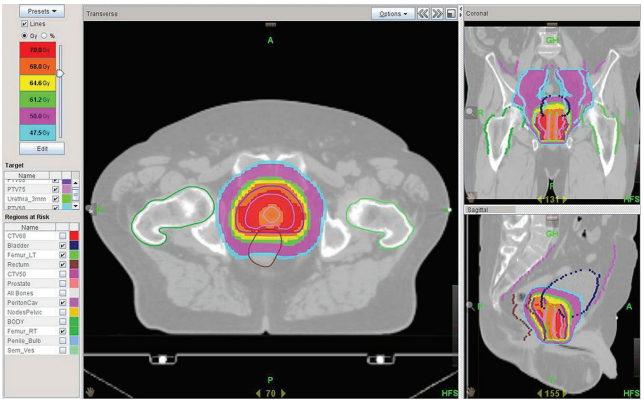


FIGURE 1 Representative intensity-modulated radiotherapy plan for high-risk prostate cancer, with the planning target volumes (lilac, 75 Gy; blue, 68 Gy; and turquoise, 50 Gy) contoured on the transverse slice. Critical structures include the femurs (outlined in green, transverse and coronal), the rectum (outlined in brown, transverse and sagittal), and the bladder (outlined in navy, coronal and sagittal). Colourwash indicates dose (red, 70 Gy; orange, 68 Gy; magenta, 50 Gy).

2.6 AST

Neoadjuvant, concurrent, or adjuvant leuprolide acetate by injection or subcutaneous depot was prescribed to each patient for a total duration of 2–3 years (duration of neoadjuvant AST was ≤4 months). Antiandrogen therapy scheduling, dose, and duration were at the discretion of the patient's physician.

2.7 Statistical Analysis

Descriptive statistics were generated for patient characteristics. Means and standard deviations were calculated for continuous variables; frequencies and percentages are reported for the categorical variables of GU and GI toxicity. Mean, standard error of the mean, and range are reported for volume and dose variables. A p value less than 0.05 was considered statistically significant. The SAS software application (version 9.3: SAS Institute, Cary, NC, U.S.A.) was used for performing the statistical analyses.

3. RESULTS

Of 40 high-risk prostate cancer patients enrolled, 3 were ineligible for therapy or analysis. One had a large volume of nodal disease, and his physician removed him from study. Another patient failed to report a hip prosthesis during screening, and the third patient withdrew consent. Of the 37 eligible patients, more than 50% had a Gleason score of 8 or 9, and more than 90% of the patients were clinically staged T2 or greater. Table II presents additional characteristics.

All patients received leuprolide 22.5–45 mg subcutaneously every 3–6 months for a mean duration of 23.83 ± 1.56 months (range: 4.0–41.47 months). Neoadjuvant AST was administered to all 37 patients, beginning on average 78.81 ± 6.19 days (range: 23–264 days) before the start of RT.

All treatment objectives for the PTV were satisfied (Table I), except in 1 patient whose minimum dose

TABLE I Hypofractionated intensity-modulated radiotherapy for prostate cancer: prescription and treatment goals

Target	*Total dose (Gy)*	*Fractions (n)*	*Dose per fraction (Gy)*	*Days per week (n)*	*Treatment goals*		
					1	*2*	*3*
PTV75	75	25	3	5	—	≤2 cm^2 to receive ≤68 Gy (cold spot)	Max dose ≤78.75 Gy [105% of 75 Gy (hot spot)]
PTV68	68	25	2.72	5	95% of PTV68 to receive 68 Gy	≤2 cm^2 to receive ≤64.6 Gy (95% of 68 Gy)	Max dose ≤75 Gy [107% of 68 Gy (hot spot)]
PTV50	50	25	2	5	95% of PTV50 to receive ≥50 Gy	≤2 cm^2 to receive ≤47.5 Gy (95% of 50 Gy)	Max dose ≤68 Gy (or 75 Gy if PTV75 is close)

PTV = planning target volume.

TABLE II Characteristics of the study patients

Characteristic	*Value*
Age (years)	
Median	66.0
Range	50–77
Initial PSA (ng/mL)	
Median	13.5
Range	1.1–82.3
Gleason score [*n* (%)]	
≤7	15 (40.5)
8–9	22 (59.5)
Clinical stage [*n* (%)]	
T1	3 (8.1)
T2	20 (54.1)
T3-T4	14 (37.8)
N1 nodal status [*n* (%)]	5 (13.5)
High risk[a] [*n* (%)]	37 (100)
Biopsy cores positive (%)	
Median	58.3
Range	16.7–100
Perineural invasion [*n* (%)]	24 (64.9)

[a] Radiation Therapy Oncology Group criteria.
PSA = prostate-specific antigen.

to the boost volume was 67.3 Gy rather than 68 Gy. Other dosimetric parameters not met included bladder V_{50} (<60% in 4 patients) and peritoneal cavity maximum $D_{1\%}$ (<54 Gy in 5 patients). All other dosimetric parameters for organs at risk were met (Table III).

Patients were assessed for urinary frequency, cystitis, urinary incontinence, GU obstruction, and GU hemorrhage within the GU toxicity category, and for diarrhea, anal incontinence, proctitis, and GI hemorrhage within the GI toxicity category. Within each category, the highest grade of toxicity experienced by a patient at each time point was designated their maximum cumulative toxicity.

The maximum cumulative grade 2 or greater GI toxicity occurred in 4 of 31 evaluated patients (12.9%, Figure 2), and GU toxicity, in 6 of 36 evaluated patients (16.6%, Figure 3). No grade 3 toxicity was reported. Urinary frequency and diarrhea were the most frequent symptoms. Furthermore, maximum GI toxicity was recorded from week 3 to week 5 (Figure 2), and peak GU toxicity was recorded at week 4 (Figure 3).

Five patients had node-positive disease, and they did not differ from the remaining patients in dose delivered or toxicity experienced.

4. DISCUSSION

Since the early 2000s, to further improve local disease control in prostate cancer, multiple studies[6–10] have explored the feasibility and efficacy of HFRT based on the concept that prostate cancer cells have a low α:aab ratio (0.8–1.5). A low ratio theoretically demonstrates a therapeutic gain with the use of HFRT[5]. A progressive movement toward dose escalation has since occurred, with dose per fraction increasing to 3.5 Gy from 2.2 Gy in HFRT (Table IV). Dose escalation has been achieved with advances in conformal technology, allowing for increasing conformality of RT with a safe reduction in margins[8,9,13,21,31].

Here, we reported the results of a prospective phase II trial showing that, for high-risk prostate cancer, HFRT by IMRT, combined with PLN RT and long-term AST, is well tolerated, with low rates of grade 2 and greater acute toxicity. Despite conformal PLN irradiation and a relatively high dose per fraction (3 Gy), rates of acute GI and GU toxicity (Figures 2 and 3) are comparable to rates in other published accounts of HFRT.

The studies summarized in Table IV have used a variety of RT techniques and parameters, making meaningful comparisons of acute toxicity rates difficult. Key parameters include dose per fraction (median: 2.875 Gy; range: 2.5–3.65 Gy), overall treatment time (median: 5 weeks; range: 3.8–6.4 weeks), $EQD2_{\alpha/\beta=1.5\ Gy}$ for tumour control (median: 80 Gy; range: 61.9–96.4 Gy), and $EQD2_{\alpha/\beta=10\ Gy}$ (median: 69.4 Gy; range: 55.2–81.3 Gy).

In those studies, acute GI toxicity of grade 2 or greater is reported in 0%–37% of patients (median: 18.5%), with limited reports of acute grade 3 toxicity (0%–10%). Acute GU toxicity of grade 2 or greater has been reported in 2.3%–47% of patients (median: 34%), with acute grade 3 GU toxicity being reported to range between 0% and 9.2%.

Our study, with its potential to improve clinical outcomes, is benefited by the inclusion of only high-risk prostate cancer patients and its intensification of treatment with PLN coverage and a simultaneous integrated boost to involved nodes and the primary site. We tested the delivery of HFRT, 75 Gy in 25 fractions, for high-risk patients exclusively. In contrast, a study by Pollack *et al.*[8] compared IMRT 76 Gy in 38 fractions with 70.2 Gy (2.7 Gy/fraction) in both intermediate- and high-risk patients. In that study, approximately one third of the patients in the hypofractionation arm were considered high-risk (52 of 151), and they also received PLN RT and AST. The report described acute grade 2 or greater GI and GU toxicity of 18% and 40% respectively in the HFRT arm (compared with 12.9% and 16.6% in the present study). The difference in GI toxicity was nonsignificant ($p = 0.379$), but the lower incidence of GU toxicity reached significance (chi-square $p = 0.020$).

In addition, advancements in image guidance have fundamentally altered the concept of PTV with a margin for set-up and inter- and intrafraction motion, which has progressively been shrinking. That change is demonstrated in the current study, with its safe reduction in PTV68 margins (compared with

TABLE III Dosimetric data

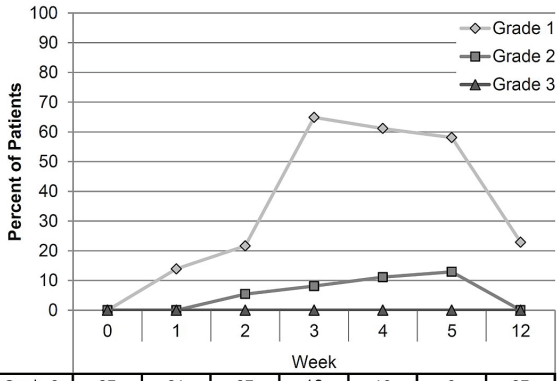
Target or organ	*Mean*	*SEM*	*Range*	*Interquartile range*
PTV75				
Volume (cm^2)	49.6	2.9	21.4–81.6	36.1–62.4
$D_{1\%}$ (Gy)	75.0	0.4	69.8–78.4	73.4–76.6
$D_{50\%}$ (Gy)	72.1	0.2	68.8–74.2	71.3–73.2
$D_{99\%}$ (Gy)	69.2	0.1	67.3–70.4	68.7–69.7
V_{70} (%)	82.5	3.4	0.3–100.0	76.8–94.5
PTV68				
Volume (cm^2)	115.4	6.3	44.8–191.7	88.1–148.1
$D_{1\%}$ (Gy)	74.5	0.4	70.3–78.2	72.7–76.2
$D_{99\%}$ (Gy)	67.0	0.1	66.2–67.7	66.7–67.4
PTV50				
Volume (cm^2)	736.4	27.9	392.2–1173.8	616.9–845.1
$D_{1\%}$ (Gy)	65.8	0.4	61.2–74.8	64.7–66.9
$D_{99\%}$ (Gy)	49.5	0.1	47.2–51.3	49.2–50.1
Bladder				
Volume (cm^2)	421.9	36.6	144.9–1052.5	245.7–560.8
$D_{1\%}$ (Gy)	71.0	0.2	70.0–73.1	70.2–71.6
$D_{50\%}$ (Gy)	47.7	0.6	32.0–53.4	35.0–50.3
V_{50} [% (goal: <60%)]	44.3	2.5	17.7–100.0	35.0–51.8
V_{65} [% (goal: <30%)]	9.1	0.7	2.1–18.6	6.4–12.2
V_{70} [% (goal: <20%)]	2.7	0.3	0–7.5	1.3–3.2
Rectum				
Volume (cm^2)	81.6	5.3	47.5–208.8	57.7–88.9
$D_{1\%}$ (Gy)	70.4	0.2	68.0–72.7	69.7–71.2
$D_{50\%}$ (Gy)	45.9	0.4	40.8–49.4	43.9–47.9
V_{50} [% (goal: <55%)]	38.2	1.1	24.4–47.6	33.2–43.9
V_{60} [% (goal: <30%)]	16.7	0.9	8.0–30.0	11.8–20.6
V_{65} (%)	9.7	0.6	3.3–16.4	7.0–12.1
V_{70} (%)	1.8	0.2	0–4.8	0.7–3.2
Peritoneal cavity				
Volume (cm^2)	1441.4	103.5	549.5–2939.5	889.7–1821.6
$D_{1\%}$ [Gy (goal: <54 Gy)	53.0	0.5	51.1–65.6	51.6–42.7

SEM = standard error of the mean; PTV = planning target volume.

those in our previous study[10]) to 8 mm, except for 3 mm posterior, because of the use of modern image guidance, including daily megavoltage CT. Clearly, some studies in Table IV, using larger margins and similar techniques, experienced higher rates of GU toxicity (2.3%[20] vs. 47.0%[32]) and GI toxicity (2.3%[29] vs. 37%[24]). Minimization of the PTV margin should theoretically lower the frequency and severity of toxicity and is feasible as cited by Shirato *et al.*[33], who reported accuracy of 1-mm margin expansion for static targets and 1.5-mm margin expansion for moving targets (long-term outcome results are pending).

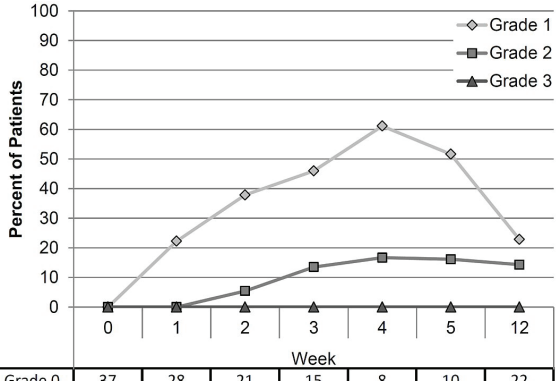
Unlike our previous study[10], which demonstrated a correlation between V_{60} rectum and rectal acute toxicity, the present study did not find statistical correlations of acute GU and GI toxicity with dosimetric and volumetric parameters of RT ($p = 0.085$). The previously reported correlation could be a consequence of a larger PTV margin expansion.

Important to advancements in RT are the establishment of evidence-based dose constraints with a strong foundation based on the reporting of dosimetric parameters used in HFRT regimes. Currently, data are being extrapolated from older, conventionally fractionated studies. For instance, Kupelian *et al.*[12] illustrated that, for the rectum, a V_{70} of less than 10 cm^3 correlated with lower rectal toxicity, and other HFRT studies reported that important dosimetric parameters for rectal toxicity include mean rectal dose, V_{25}, and V_{30}[17,18,28]. For acute GU toxicity (specifically of the bladder), the V_{65}[18] and V_{50}[8] have been reported to be statistically significant. In addition, in multivariate analysis, Macias *et al.*[18] illustrated that the bladder volume receiving 65 Gy or more (V_{65})



Number of Patients	0	1	2	3	4	5	12
Grade 0	37	31	27	10	10	9	27
Grade 1	0	5	8	24	22	18	8
Grade 2	0	0	2	3	4	4	0
Grade 3	0	0	0	0	0	0	0
Total	37	36	37	37	36	31	35

FIGURE 2 Maximum acute gastrointestinal toxicity. Peak toxicity was recorded in week 5, with 58.1% of patients experiencing grade 1 toxicity; 12.9%, grade 2 toxicity; and no patients, grade 3 toxicity.



Number of Patients	0	1	2	3	4	5	12
Grade 0	37	28	21	15	8	10	22
Grade 1	0	8	14	17	22	16	8
Grade 2	0	0	2	5	6	5	5
Grade 3	0	0	0	0	0	0	0
Total	37	36	37	37	36	31	35

FIGURE 3 Maximum acute genitourinary toxicity. Peak toxicity was recorded in weeks 3–5, with 61.1% of patients experiencing grade 1 toxicity; 16.6%, grade 2 toxicity; and no patients, grade 3 toxicity.

is associated with an increased risk of GU complications ($p = 0.017$), and that the mean rectal dose and total dose are significantly related to GI toxicity ($p = 0.013$ and $p = 0.019$ respectively). Future analysis of data from phase I/II studies will provide dose–volume histogram safety parameters for HFRT, with ranges of dose and fractionation.

As already mentioned, HFRT in prostate cancer could offer a therapeutic advantage, but concerns have been raised that the delivery of fractions exceeding 2 Gy could potentially precipitate increased acute toxicity and subsequent late permanent side effects, as demonstrated in a recent Dutch trial, HYPRO, in which acute toxicity strongly predicted late toxicity[29,34]. Lock *et al.*[22] also reported that acute GI toxicity of grade 2 or greater predicted late toxicity of grade 2 or greater ($p < 0.001$), and patients experiencing acute toxicity had an almost-tripled risk of late toxicity (32% vs. 12%, $p = 0.0001$). Furthermore, in multivariate analysis, a study by Jereczek–Fossa *et al.*[21] demonstrated that hypofractionated image-guided RT and higher PSA correlate with higher acute urinary toxicity ($p = 0.001$ and $p = 0.046$ respectively), although no independent factor correlates with acute rectal toxicity.

Interestingly, GU toxicity peaked at 4 weeks of HFRT in our study, declining thereafter; GI toxicity peaked at week 3 and declined slowly through week 5. The GI and GU toxicity had both greatly improved by 12 weeks after RT. Those toxicity patterns resemble the patterns reported in a study by Dearnaley *et al.*[20], in which acute GI and GU toxicity peaked at 4–5 weeks in the hypofractionated treatment arm. In comparison, patients in the control arm, which used conventionally fractionated RT, experienced toxicity peaking at weeks 7–8[20]. In another prospective study[18] that delivered 70.2 Gy in 27 fractions, the highest degree of acute toxicity occurred at 4–5 weeks. Grade 2 or greater GU toxicity was found in 32.6% of patients, and grade 2 or greater GI toxicity was seen in 10% of patients. Also, results from a phase I/II feasibility study of HFRT for localized prostate cancer showed that maximal acute toxicity was reached in weeks 4–5 and resolved within 4 weeks after RT in 82% of the patients[14]. Given that the pattern of toxicity with HFRT appears to peak earlier[14,18,20], we would recommend a more thorough assessment for signs of acute toxicity during weeks 3–5 of RT.

The safety and feasibility of HFRT for prostate cancer has been established, with more than 5 years of available follow-up data; clinical outcome results will be confirmed when ongoing studies are reported (search for NCT00304759, NCT00667888, and NCT00331773 at http://ClinicalTrials.gov/). Currently, HFRT is being encouraged because of safety and feasibility, and it is logistically attractive given its potential for noninferior clinical outcomes. Technological advances such as IMRT, HT, volumetric modulated arc therapy ("rapid arc"), and stereotactic body RT have allowed for HFRT to be used in the treatment of prostate cancer with acceptable acute and late toxicity profiles. A study by Yuen *et al.*[35] supports the use of those technological advancements, having demonstrated that HFRT using tomotherapy-based dynamic IMRT is superior to 3-dimensional conformal RT in dose delivery and critical structure–sparing in high-risk prostate cancer. Alternative treatments, such as proton therapy, have also advanced in recent years, resulting in better sparing of rectum and bladder[36]; however, such treatments are still cost-prohibitive compared with HFRT. Currently, no consensus has been reached concerning the superiority of one technique over another (volumetric modulated arc therapy vs. IMRT vs. tomotherapy).

TABLE IV Prospective studies of hypofractionated radiotherapy (RT) reporting acute toxicity

Reference	RT technique	Total dose (Gy)	Fr. (n)	Dose per fraction (Gy)	EQD2 (α/β=1.5)	EQD2 (α/β=10)	Margins (mm)	RT duration (weeks)	WPRT Dose (Gy)	WPRT Fr. (n)	RTOG/CTCAE acute toxicity grade (%)					
											Gastrointestinal		Dosimetric	Genitourinary		Dosimetric
											II	III		II	III	
Kitamura *et al.*, 2003[11]	IMRT, IGRT	70	28	2.5	80.0	72.9	1 post, 3 rest	5.6	—	—	0	0	—	5.8	0	—
Kupelian *et al.*, 2005[12]	IMRT, IGRT	70	28	2.5	80.0	72.9	4 post, 5 to 8	5.6	50.4	28	19	0	Vr_{70}: <10 cm^3	15	0	—
Lukka *et al.*, 2005[7]	2DRT	52.5	20	2.62	61.9	55.2	10 to 15	4	—	—	15	4.3	—	NA	9.2	—
Soete *et al.*, 2006[13]	3DCRT, IMRT	56	16	3.5	80.0	63.0	3 to 10	4.2	—	—	36	0	—	44	0	—
Junius *et al.*, 2007[14]	IMRT, IGRT	66	25	2.64	78.1	69.5	5 to 10	5	—	—	16	0	—	26	0	—
Martin *et al.*, 2007[15]	IMRT, IGRT	60	20	3	77.1	65.0	7 to 10	4	—	—	11	1	—	25	0	—
Leborgne and Fowler, 2008[16]	3DCRT	60	20	3	77.1	65.0	5–8 to 11	6.4	—	—	4.5	NA	—	23	NA	—
		63	20	3.15	83.0	69.0					29			29		
McCammon *et al.*, 2009[17]	IMRT	70	28	2.5	80.0	72.9	5 to 10	5.6	50.4	28	20	3.3	V_{25}	36.7	0	—
Macias *et al.*, 2013[18]	3DCRT	70.2	27	2.6	83.8	73.7	7 to 12	5.4	45	25	10.0	0	Mean R	32.0	0.6	V_{65}
Pervez *et al.*, 2010[10]	HT IMRT	68	25	2.7	82.0	72.1	5, 10	5	45	25	35.0	0	$V_{60rectum}$	36.7	3.33	—
Arcangeli *et al.*, 2010[19]	3DCRT	62	20	3.1	81.5	67.7	6 to 10	4	—	—	35	0	—	47	1	—
Dearnaley *et al.*, 2012[20]	IMRT	57	19	3	73.3	61.8	5 or 10	3.8	—	—	2.3	7.0	—	2.3	7.6	—
		60	20	3	77.1	65.0		4								
Jereczek–Fossa *et al.*, 2011[21]	3DART, IGRT	70.2	26	2.7	84.0	74.3	3 to 7	5.2	—	—	11.2	1.1	—	39.1	5.0	—
Lock *et al.*, 2011[22]	IMRT, IGRT	63.2	20	3.16	84.1	69.3	7.5	4.4	—	—	25	10	—	34	9	—
Pollack *et al.*, 2011[23]	IMRT	70.2	26	2.7	82.2	73.7	3 and 7	5.2	—[b]	—[b]	18	0	V_{65}	40	8	V_{50}
Quon *et al.*, 2011[24], Quon *et al.*, 2012[25], Valeriani *et al.*, 2011[26]	IMRT	67.5	25	2.7	80.5	71.1	4 to 10	5	45	25	37	0	—	39	4	—
	IGRT	54.75	15	3.65	80.6	62.3	NA	5	—	—	22.6[c]	0	—	51.6[c]	0	—
Yeoh *et al.*, 2011[27]	2DRT	55	20	2.75	66.8	58.4	15	4	NA	NA	NA	—	—	NA	—	—
Adkison *et al.*, 2012[28]	imrt	70	28	2.5	80.0	72.9	3 to 5	5.6	56	28	32	0	V30	38	0	—
Aluwini *et al.*, 2012[29]	IMRT	64.6	19	3.4	90.4	72.1	7	NA	NA	NA	NA	NA	NA	NA	NA	NA
Drodge *et al.*, 2013[30]	HT IMRT	75	25	3.0	96.4	81.3	3 post, 8 all	5	50	25	6.5	0	—	16.7	0	—
PROFIT trial[d]	IMRT	60	20	3	77.1	65.0	NA	4	NA	NA	NA	NA	NA	NA	NA	NA

[a] Only when statistically significant.
[b] Hazard ratio only (56 Gy in 28 fractions).
[c] Grades 1 and 2 combined.
[d] Visit http://clinicaltrials.gov/ct2/show/NCT00304759.

Fr. = fractions; WPRT = whole-pelvis RT; RTOG = Radiation Therapy Oncology Group; CTCAE = Common Terminology Criteria for Adverse Events; IMRT = intensity-modulated RT; IGRT = image-guided RT; 2DRT = two-dimensional RT; NA = not available; 3DCRT = three-dimensional conformal RT; HT = helical tomotherapy.

Our interim analysis shows that HFRT delivering 75 Gy in 25 fractions for treatment of high-risk prostate cancer is well tolerated, with minimal acute GI and GU toxicities. After further follow-up, late toxicities and outcomes will be reported.

5. CONCLUSIONS

Our study highlights the utility of hypofractionation and dose escalation in the treatment of high-risk prostate cancer. The delivery of 68 Gy to the prostate PTV and up to 75 Gy in 25 fractions to the prostate over 5 weeks of hypofractionated pelvic IMRT was associated with acceptable GU and GI acute toxicity that peaked at 4 weeks and declined thereafter. Dosimetric analysis did not demonstrate any correlation between the irradiated volume and GU or GI grade 2 or greater toxicity. The future role of HFRT in the treatment of prostate cancer will be determined by long-term outcome and toxicity results from ongoing studies, and the establishment of evidence-based dose constraints.

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7. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: MBP reports grants from the Alberta Cancer Foundation during the conduct of the study, and grants from the Canadian Partnership Against Cancer outside the submitted work. NP reports grants from the Alberta Cancer Board during the conduct of the study, and grants from Alberta Innovates: Health Solutions, from the Canadian Breast Cancer Foundation–Prairies/NWT, and from the Noreen Fraser Foundation outside the submitted work. The remaining authors declare that they have no conflicts of interest.

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