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CLINICAL INVESTIGATION

Hypofractionated, Dose Escalation Radiation Therapy for High-Risk Prostate Cancer: The Safety Analysis of the Prostate Cancer Study-5, a Groupe de Radio-Oncologie Génito-Urinaire de Quebec Led Phase 3 Trial

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Purpose: The low $\alpha\backslash\beta$ ratio of 1.2 to 2 for prostate cancer (PCa) suggests high radiation-fraction sensitivity and predicts a therapeutic advantage of hypofractionated (HF) radiation therapy (RT). To date, no phase 3 randomized clinical trial has compared moderately HF RT with standard fractionation (SF) exclusively in high-risk PCa patients. We are reporting the safety of moderate HF RT in high-risk PCa in an initially noninferiority-designed phase 3 clinical trial.

Methods and Materials: From February 2012 to March 2015, 329 high-risk PCa patients were randomized to receive either SF or HF RT. All patients received neoadjuvant, concurrent, and long-term adjuvant androgen deprivation therapy. Standard fractionation RT consisted of 76 Gy in 2 Gy per fraction to the prostate, where 46 Gy was delivered to the pelvic lymph nodes.

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This protocol is registered with ClinicalTrials.gov and may be viewed online at ClinicalTrials.gov; identifier: NCT01444820.

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The raw data of the study at present is not available for sharing.

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Hypofractionated RT included concomitant dose escalation of 68 Gy in 2.72 Gy per fraction to the prostate and 45 Gy in 1.8 Gy per fraction to the pelvic lymph nodes. The coprimary endpoints were acute and delayed toxicity at 6 and 24 months, respectively. The trial was originally designed as a noninferiority with a 5% absolute margin. Given the lower-than-expected toxicities in both arms, the noninferiority analysis was completely dropped.

Results: Of the 329 patients, 164 were randomized to the HF and 165 to the SF arms. In total, there were more grade 1 or worse acute gastrointestinal (GI) events in the HF arm, 102 versus 83 events in the HF and SF arm, respectively ($P = .016$). This did not remain significant at 8 weeks of follow-up. There were no differences in grade 1 or worse acute GU events in the 2 arms, 105 versus 99 events in the HF and SF arm, respectively ($P = .3$). At 24 months, 12 patients in the SF arm and 15 patients in the HF arm had grade 2 or worse delayed GI-related adverse events (hazard ratio, 1.32; 95% CI, 0.62-2.83; $P = .482$). There were 11 patients in the SF arm and 3 patients in the HF arm with grade 2 or higher delayed genitourinary (GU) toxicities (hazard ratio, 0.26; 95% CI, 0.07-0.94; $P = .037$). There were 3 grade 3 GI and one grade 3 GU delayed toxicities in the HF arm and 3 grade 3 GU and no grade 3 GI toxicities in the SF arm. No grade 4-toxicities were reported.

Conclusions: This is the first study of moderate HF dose-escalated RT in exclusively high-risk patients with prostate cancer treated with long-term androgen deprivation therapy and pelvic RT. Although our data were not analyzed as a noninferiority, our results demonstrate that moderately HF RT is well-tolerated, similar to SF RT at 2 years, and could be considered an alternative to SF RT.

Introduction

Prostate cancer is the second most common cancer in men worldwide, with a GLOBOCAN estimation of 1.4 million prostate cancer diagnoses in 2020,[1] and the third leading cause of cancer mortality in men in North America[2,3] and fifth worldwide.[1]

Treatment options for localized prostate cancer range from expectant management or surgery to radiation therapy (RT). Radiation therapy includes external beam radiation therapy, brachytherapy, or a combination of these approaches. Multiple large database analyses involving populations in the United States and Canada demonstrate that between 26.9% and 42.5% of patients with prostate cancer receive RT within a year of diagnosis.[4] Although RT, with or without androgen deprivation therapy (ADT), is one of the recommended treatment options for men with adenocarcinoma of the prostate,[5,6] one important limiting factor is the radiation exposure of late-reacting normal tissues. Advances in radiation delivery techniques have improved the accuracy of anatomic targeting and dose conformality, allowing dose escalation to the target while reducing dose spillage to surrounding tissues.[7-10]

Cell-type specific responses to RT dose are described using a linear quadratic model, with its α/β value indicating the cell killing rate in the context of tumor control and normal tissue complications. The α/β ratio is the dose where the linear and quadratic components cause the same amount of cell killing.[11] Therefore, cells with a low α/β ratio are particularly sensitive to dose fractionation, with a larger dose rate conferring a more effective cell kill. Most carcinomas and rapidly dividing normal tissues have a high α/β ratio of approximately 10 Gy, whereas slowly dividing cancers and late-reacting normal tissues commonly have a low α/β ratio of 3 to 5 Gy.[11,12] Tumors with a high α/β ratio can therefore be reasonably treated with conventionally fractionated RT of 1.8 to 2.0 Gy per fraction. A number of studies, including large database studies and meta-analyses, have recognized the α/β ratio for prostate cancer to be 1.2 to 2.0 Gy.[13-17] This is far lower than many other cancers, suggesting that hypofractionated (HF) RT (ie, fewer doses of radiation, each at a higher fraction of the total dose per treatment course) may be especially effective in this setting. Furthermore, the α/β ratio of prostate cancer cells (1.5 Gy) is lower than that of the rectum and the bladder (3-5 Gy),[13] suggesting that HF may provide a therapeutic gain with no change in late toxicity.[18]

The safety of moderate HF RT in patients with low, intermediate, or mixed-risk prostate cancer has been confirmed in multiple phase 3 trials.[19-25] We report the primary safety analysis of the first randomized trial of moderate HF RT with concurrent long-term ADT for exclusive patients with high-risk prostate cancer.

Methods and Materials

Study design and participants

This is a multicentric phase 3 trial. The patients included in this study were high-risk prostate patients, defined as histology-proven localized adenocarcinoma with at least one of the following features: T stage ≥3a, Gleason score ≥8, or a baseline prostate-specific antigen (PSA) of >20 ng/mL. The patients were randomized into one of 2 treatment arms. The control arm comprises the standard fractionation (SF) schedule of 76 Gy in 38 fractions over 7.5 weeks. Patients in the experimental arm received an HF schedule of 68 Gy in 25 fractions over 5 weeks.

Study population

Patient recruitment began on February 6, 2012, and was closed to recruitment on March 25, 2015. There were 12 participating institutions across 2 provinces in Canada.

Histologic confirmation of adenocarcinoma of the prostate was done within 6 months before randomization, and all patients had high-risk PCa. Metastatic disease was ruled out for all patients with a computer tomography (CT) scan or magnetic resonance imaging of the abdomen and pelvis and a total body bone scan performed within 12 weeks before randomization. Baseline blood included complete blood count, liver, and kidney function tests, which were done within 28 days before randomization. Bone densitometry was performed for all patients at baseline and 36 months post-randomization to assess castration-induced bone loss in the presence of prescribed calcium and vitamin D supplement, which was reported separately.[26] Patients receiving 5-alpha-reductase inhibitors (eg, Finasteride) for benign prostate hyperplasia discontinued their treatment at least 4 weeks before the PSA level was performed.

Patients were excluded if they had any history of other malignancies (except for nonmelanoma skin cancer), the presence of small cells, neuroendocrine or transitional-cell carcinoma in the biopsy specimen, or previous systemic therapy for carcinoma of the prostate. Patients with prior surgical prostate carcinoma treatment, including transurethral resection of the prostate or previous bilateral orchiectomy, were also excluded. Other exclusions included contraindication to pelvic radiation therapy, including, but not limited to, previous pelvic radiation therapy, inflammatory bowel disease, severe bladder irritability, and for technical reasons, patients with bilateral hip replacement prostheses. Patients with serious nonmalignant disease resulting in a life expectancy <3 years, or other serious illnesses, that would not permit the patient to be managed according to the protocol or not fit for the treatment regimen were also excluded. Patients with an Eastern Cooperative Oncology Group performance status of 3 or higher were excluded. Patients with baseline hemoglobin ≤100 g/L, absolute neutrophils $\leq 1.5 \times 10^9$/L, platelets ≤100, aspartate transaminase or alanine transaminase ≥1.5 times the upper limit of normal (ULN), alkaline phosphatase ≥2.5 times the ULN, total bilirubin ≥ ULN, and serum creatinine ≥ ULN were excluded from the study.

Randomization was conducted centrally by the Coordinating Center of Groupe de radio-oncologie génito-urinaire de Quebec, located at the Jewish General Hospital, Montreal, Quebec. A computer-generated randomization schedule allocated patients to the standard treatment or experimental arm on a 1:1 ratio. For allocation concealment, the standard method of sequentially numbered, opaque, sealed envelopes was used to protect the randomization process so that the treatment allocated was not known before the patient entered the study.

Patient consent was obtained according to local Institutional or University Human Experimentation Committee requirements. All participating investigators obtained the necessary clearance at their institution and indicated in writing that such clearance had been obtained before the commencement of the trial at their respective centers.

Treatment

Radiation therapy began 12 to 16 weeks after randomization. The study mandated 28 months of luteinizing hormone-releasing hormone (LHRH) agonist with 14 days of biclutamide, 50 mg per day, starting on day 1 of the first LHRH agonist injection only. Patients also received calcium and vitamin D supplements (calcium 500 mg/d 400 IU twice a day) for the duration of the LHRH agonist. Luteinizing hormone-releasing hormone agonist was to start within 2 weeks of randomization.

For the conventional radiation therapy (control) arm, a phase 2 technique was used. The first phase treated the whole pelvis, including the prostate, 1 cm of the seminal vesicles (the whole seminal vesicles ([SV] if T3b), and regional lymph nodes with 46 Gy in 23 fractions. The second phase was a boost of 30 Gy in 15 fractions to the prostate and the proximal 1 cm SV. For patients with T3b disease, the whole SV was treated to 76 Gy. The patients were treated with either 3-dimensional conformal radiation therapy or intensity-modulated RT (IMRT) techniques.

For the experimental arm, a one-phase technique was used. The treatment was delivered with a concomitant boost. Centers using IMRT used the dose painting technique to treat the prostate and proximal 1 cm SV with 68 Gy in 25 fractions, and the pelvic lymph nodes received 45 Gy in 25 fractions. For patients with T3b disease, the whole SV was treated with 68 Gy. Institutions using 3-dimensional conformal radiation therapy delivered the required dose of 45 Gy to the pelvic volume (including pelvic lymph nodes and boost volume) and a concomitant boost to the prostate and proximal 1-cm SV (or the whole SV if T3b) to 68 Gy. The daily dose to the pelvic lymph nodes was 1.8 Gy and 2.72 Gy to the boost volume.

Statistical assumption and analysis

The primary objective was to compare the safety of a shorter course of radiation therapy (68 Gy in 25 fractions over 5 weeks) with a conventional fractionation course (76 Gy in 38 fractions over 7.5 weeks). Thus, this trial was originally designed as a noninferiority trial, with the coprimary outcomes being gastrointestinal (GI) and genitourinary (GU) acute and delayed toxicities. Toxicity was measured with Common Terminology Criteria for Adverse Events version 4. In the original protocol, acute toxicity was defined as occurring ≤90 days from radiation therapy and late toxicity as occurring >90 days after the start of radiation. However, after trial commencement, it was decided to change the definition of acute and late toxicities to those occurring ≤6 months and >6 months, respectively, after the start of radiation to have comparable methods with other major randomized controlled trials.[27]

The sample size calculation was based on the original statistical analysis plan to calculate a risk difference between arms, using a combined GI and GU late toxicity outcome.

In the previous Italian study by Arcangeli et al,[24] the risks of delayed grade 2 or higher GI and GU toxicities were 17% and 16%, respectively, with 30% (25%-33%) of patients with toxicity having both GI and GU toxicities.[24] Based on this, we assumed an expected risk of late grade 2 or higher combined GI and GU toxicity of 28% in the standard arm and 18% in the hypofractionation arm. A sample size of at least 150 patients per arm was determined to be necessary to exclude a noninferiority margin of 5% difference, with a power of 90% and an alpha level of 5%. Allowing for dropouts, the intended sample size was increased by 10% for a total of 329 patients.

However, subsequently, to the publication of the CHHiP trial,[27] the statistical analysis plan was revised to increase the comparability of methods and outcomes with similar trials. Therefore, GI and GU outcomes were analyzed separately as coprimary outcomes rather than as a combined outcome. Instead of risk differences, the statistical analysis plan was revised to estimate odds ratios (OR) and hazard ratios (HR) of acute and late GI and GU toxicities by study arm. Logistic regression models were used to compare the ORs of acute toxicities between the 2 arms. Kaplan-Meier curves were used to calculate the cumulative incidence of delayed toxicities, and Cox proportional hazards regression models were used to estimate the HR of late toxicities between the 2 arms.[28] All statistical analyses were adjusted for smoking, diabetes, hypertension, and treatment technique modeled as binary variables (presence/absence). The 95% CI were computed using the profile likelihood method.[28] No adjustments were made for multiple comparisons of the coprimary endpoints. Due to changes in the statistical analysis plan and a lower-than-expected number of events, the noninferiority analysis was dropped, and no new noninferiority margin was specified for ORs and HRs. Data were recorded and logged in Excel. Matlab (R2016b) was used to compile the data and generate the figures. Statistical tests were performed with SAS (version 9.3).

We used the Kaplan-Meier product-limit method and Cox proportional hazard regressions for analyses as our objective was causal inference on treatment effects rather than risk prediction. Cumulative incidence estimates based on the Kaplan-Meier product-limit method can overestimate the probability of experiencing an outcome when death is a competing risk. However, we anticipated that the rate of death within 6 and 24 months due to treatment complications or disease progression would be minimal, and this is unlikely to influence our estimates substantively.

Results

A total of 329 patients were recruited between February 6, 2012 and March 25, 2015 (Fig. 1). One hundred sixty-four patients were randomized to the HF arm, and 165 patients were randomized to the SF arm. Nine patients never received radiation treatment (5 in the HF arm and 4 in the SF arm): 3 opted for surgery, 1 decided to be treated elsewhere, 1 decided not to be treated due to the progression of dementia, and 4 for unknown reasons. Of the patients who received treatment (n = 159 and 161 in the HF and SF arms, respectively), a total of 24 (n = 11 and 13 in the HF and SF arms, respectively) were either lost to follow-up or died (7 patients) of other causes not related to disease or complication of treatment before the 24 months follow-up. At 2 years of follow-up, 148 patients remained in each arm and were all included in the toxicity assessment. These patients were also followed as per protocol with minor variations. The median follow-up was 40.2 months, with an IQR of 33.6 to 47.7 months. The median age for the 2 groups was 73 for the HF arm and 72 for the SF arm. Most patients had T2 disease, a median PSA of slightly over 11 ng/mL, and mostly a Gleason 8 pathology. All the baseline characteristics, including GU and GI symptoms, were well balanced between the 2 arms (Table 1). By 3 years of

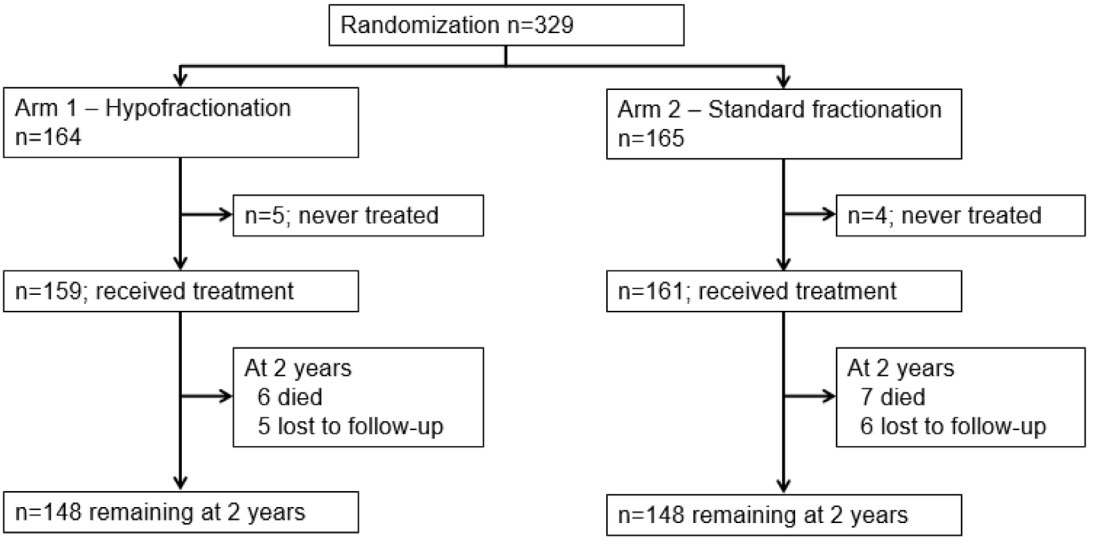

Fig. 1. Randomization and follow-up schedule.

Table 1 Demographic and baseline characteristics for all patients, and the distribution between the HF and SF arms

Characteristic		Entire cohort	HF arm	SF arm
Total		320	159 (49.7%)	161 (50.3%)
Age, y				
	Median (IQR)	72 (68-76)	73 (68-76)	72 (68-75)
T stage, n (%)				
	T1	84 (26.3%)	37 (23.3%)	47 (29.2%)
	T2	152 (47.5%)	76 (47.8%)	76 (47.2%)
	T3	81 (25.3%)	45 (28.3%)	36 (22.4%)
	T4	2 (0.6%)	1 (0.6%)	1 (0.6%)
	Unknown	1 (0.3%)	0 (0.0%)	1 (0.6%)
PSA				
	Median (IQR)	11.6 (7.0-21.0)	11.7 (5.0-9.0)	11.1 (5.0-9.0)
PSA				
	0-<5	37 (11.6%)	18 (11.3%)	19 (11.8%)
	5-<10	101 (31.6%)	47 (29.6%)	54 (33.5%)
	10-<20	95 (29.7%)	58 (36.5%)	37 (23.0%)
	20-<50	68 (21.3%)	28 (17.6%)	40 (24.8%)
Gleason				
	6	6 (1.9%)	4 (2.5%)	2 (1.2%)
	7	48 (15.0%)	25 (15.7%)	23 (14.3%)
	8	156 (48.8%)	72 (45.3%)	84 (52.2%)
	9	99 (30.9%)	53 (33.3%)	46 (28.6%)
	10	11 (3.4%)	5 (3.1%)	6 (3.7%)
Testosterone				
	Median (range)	11.6 (0.0-34.0)	11.1 (0.0-22.9)	12.0 (0.0-34.0)
	Mean (SD)	11.9 (5.3)	11.1 (4.8)	12.6 (5.6)
	Unknown	9 (2.8%)	4 (2.5%)	5 (3.1%)
IPSS				
	Median (range)	7.0 (0.0-35.0)	8.0 (0.0-35.0)	7.0 (0.0-34.0)
	Mean (SD)	8.8 (6.8)	9.2 (6.6)	8.4 (7.0)
	Unknown	6 (1.9%)	6 (3.8%)	0 (0.0%)
IIEF				
	Median (range)	12.0 (0.0-30.0)	11.0 (1.0-30.0)	12.0 (0.0-25.0)
	Mean (SD)	12.0 (7.6)	12.0 (7.7)	11.9 (7.5)
	Unknown	98 (30.6%)	48 (30.2%)	50 (31.1%)
ED				
	Yes	203 (63.4%)	100 (62.9%)	103 (64.0%)
	No	117 (36.6%)	59 (37.1%)	58 (36.0%)
Technique				
	IMRT	196 (61.3%)	95 (59.7%)	101 (62.7%)
	3D-CRT	118 (36.9%)	61 (38.4%)	57 (35.4%)
	Unknown	6 (1.9%)	3 (1.9%)	3 (1.9%)

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; ED = erectile dysfunction; HF = hypofractionated; IIEF = international index of erectile function; IMRT = intensity modulated radiation therapy; IPSS = international prostate symptom score; PSA = prostate-specific antigen; SF = standard fractionation.

follow-up, 6 patients had died in each arm of non-prostate cancer-related causes unrelated to treatment.

Acute toxicity

The patients who underwent HF treatment had earlier onset of both the acute GI and GU toxicities (Fig. 2). Acute GI toxicities peaked early at 4 to 5 weeks and were higher at 52.2% for the HF schedule, compared with 6 to 7 weeks and 38.5% for SF schedule (the analysis of toxicity for the entire acute period covering zero to 6 months would be provided below). However, by 12 weeks, the prevalence of grade 1 or worse toxicity for both treatment arms stabilized at approximately 20% for both treatment arms. Acute GU toxicity followed a very similar temporal dynamic, with peak side effects occurring at 6 to 7 weeks at 57.9% for the HF arm, compared with 8 to 9 weeks at 50.3% for the SF schedule. The prevalence of grade 1 or worse GU toxicities took a more prolonged course to stabilize. Approximately 36% of the patients had unresolved GU toxicity of grade 1 or worse by 18 weeks in both treatment arms.

In total, 185 grade 1 or worse acute events were recorded for GI-related side effects: 102 and 83 events in the HF and SF arm, respectively (OR, 1.76; 95% CI, 1.11-2.78, P = .016; Table 2). There were fewer grade 2 or worse acute events as expected, with 59 total events: 37 and 22 events in the HF and SF arm, respectively (OR, 1.92; 95% CI, 1.06-3.47; P = .031). These results were statistically significant. There were overall more total acute GU events compared with GI side effects. Two hundred-four grade 1 or worse events were recorded: 105 and 99 events for the HF and SF arm, respectively (OR, 1.28; 95% CI, 0.8-2.04; P = .298). For grade 2 or worse, there were 102 acute events recorded: 55 and 47 events in the HF and SF arm, respectively (OR, 1.35; 95% CI, 0.84-2.17; P = .222). The differences were not statistically significant.

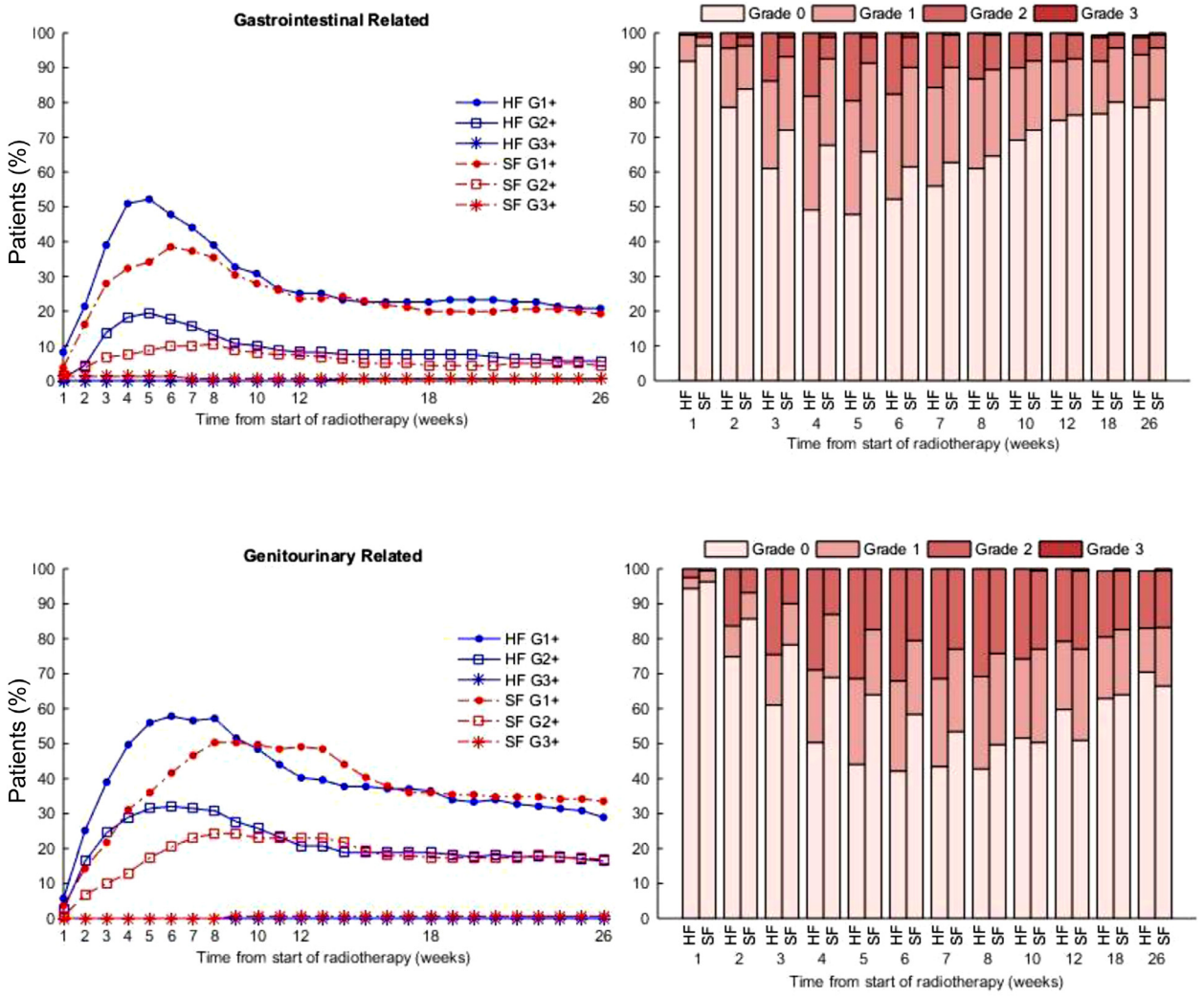

Fig. 2. Left: prevalence of gastrointestinal (top) and genitourinary (bottom) toxicity by grade categories over time from the start of radiotherapy. Right: distribution of toxicity by grade. *Abbreviations*: HF = hypofractionated; SF, = standard fractionation.

Table 2 Acute toxicity results for gastrointestinal and genitourinary related events

Acute toxicity	Total events	HF	SF	HF vs SF		*P* value
				OR	(95% Wald CI)	
Gastrointestinal related						
Grade 1 or worse	185	102	83	1.76	(1.11-2.78)	.016
Grade 2 or worse	59	37	22	1.92	(1.06-3.47)	.031
Grade 3 or worse	3	1	2			
Grade 4 or worse	0	0	0			
Genitourinary related						
Grade 1 or worse	204	105	99	1.28	(0.80-2.04)	.298
Grade 2 or worse	102	55	47	1.35	(0.84-2.17)	.222
Grade 3 or worse	1	0	1			
Grade 4 or worse	0	0	0			

Abbreviations: HF = hypofractionated; OR = odds ratio; SF = standard fractionation.

There were not enough acute GI (n = 3, 1 and 2 in HF and SF arm, respectively) or GU (n = 1, in the SF arm) related grade 3 or worse toxicity to conduct any meaningful statistical analysis, and no grade 4 side effect was reported.

Late toxicity

The cumulative incidence of delayed toxicity per grade categories arising after 6 months after the beginning of radiation for both treatment arms was recorded (Fig. 3). A rise of cumulative incidence of delayed toxicity between 6 to 12 months, followed by a slower rise between 12 to 18 months can be appreciated for both GI and GU related side effects. By 24 months, the cumulative incidence of toxicity plateaus, and no new event arose afterward. Late toxicity was most likely to arise between 6 to 12 months.

In total, there were 104 new grade 1 or worse GI events occurring 6 months after the start of radiation, 55 of which were in the HF arm, and 49 were in the SF arm (HR, 1.22; 95% CI, 0.83-1.8; P = .322; Table 3). Grade 2 or worse GI events were considerably less, with 27 total events: 15 and 12 in the HF and SF arm, respectively (HR, 1.32; 95% CI, 0.61-2.83; P = .482). There were 69 grade 1 or worse delayed GU events: 34 and 35 in the HF and SF arm (HR, 1.04; 95% CI, 0.64-1.68; P = .882). There were 14 total delayed GU grade 2 or worse events:3 in the HF and 11 in the SF schedule (HR, 0.25; 95% CI, 0.06-0.81; P = .035). There were not enough GI (n = 3, in the HF arm) or GU (n = 4, 1, and 3 in the HF and SF arm, respectively) related to grade 3 or worse toxicity to conduct any meaningful statistical analysis. No grade 4 side effect was reported.

Discussion

In our primary safety analysis of the PCS-5 trial, we observed a higher incidence of acute and late grade 2 or worse GI and GU toxicities in the hypofractionation arm than in the standard arm. Although we dropped the prespecified noninferiority analysis due to changes in the statistical analysis plan and the lower-than-expected number of events, our results suggest that the incidence of grade 3 or worse acute and late toxicities was similarly very low in both arms, suggesting the differences are unlikely to be clinically meaningful. The 2 years' late side effects raised no concerns about the safety of the HF schedule as delivered across institutions.

The selection of HF and SF dose and schedule for the PCS-5 trial was informed by the design and results of prior phase 3 trials enrolling intermediate and high-risk patients (Fox Chase Cancer Center Study and CHHiP).[19,23,27] Each trial enrolled approximately 35% to 40% of high-risk patients and used 5 days a week fractionation and treatment schedules. Both trials completed the HF treatment in 4 to 5 weeks and demonstrated noninferiority of HF versus SF RT, with comparable toxicity outcomes between arms.[19,23,27] The HYPRO trial enrolled a substantially greater proportion of high-risk patients (75%), and it incorporated an HF schedule of 3 larger fractions per week to dose escalate (EQD2 of 90 Gy). Although the treatment duration was extended to 6.5 weeks, the dose escalation may have potentially contributed to the increased toxicity among patients receiving HF versus SF therapy.[20,22,29] Using an $\alpha\backslash\beta$ ratio of 1.5, the EQD2 of 82 Gy chosen for the PCS-5 trial was higher than that used in the CHHiP trial (EQD2 = 77 Gy and 73 Gy), lower than HYPRO (EQD2 = 90 Gy) but similar to that of the Fox Chase Cancer Center Study (EQD2 = 84 Gy).[19,20,22,23,27,29] The dose in the SF arm was similar across the trials: 74 Gy in the CHHiP trial, 78 Gy in the HYPRO trial, and 76 Gy in both PCS-5 and the Fox Chase Cancer Center studies.[19,20,22,23,27,29] All patients enrolled in the PCS-5 trial received concurrent ADT, as did the majority of patients on the CHHiP and HYPRO trials[19,20,22,27,29]; all high-risk patients in the Fox Chase Cancer Center Study received long-term ADT.[23] Pelvic lymph node (PLN) irradiation was also incorporated in the

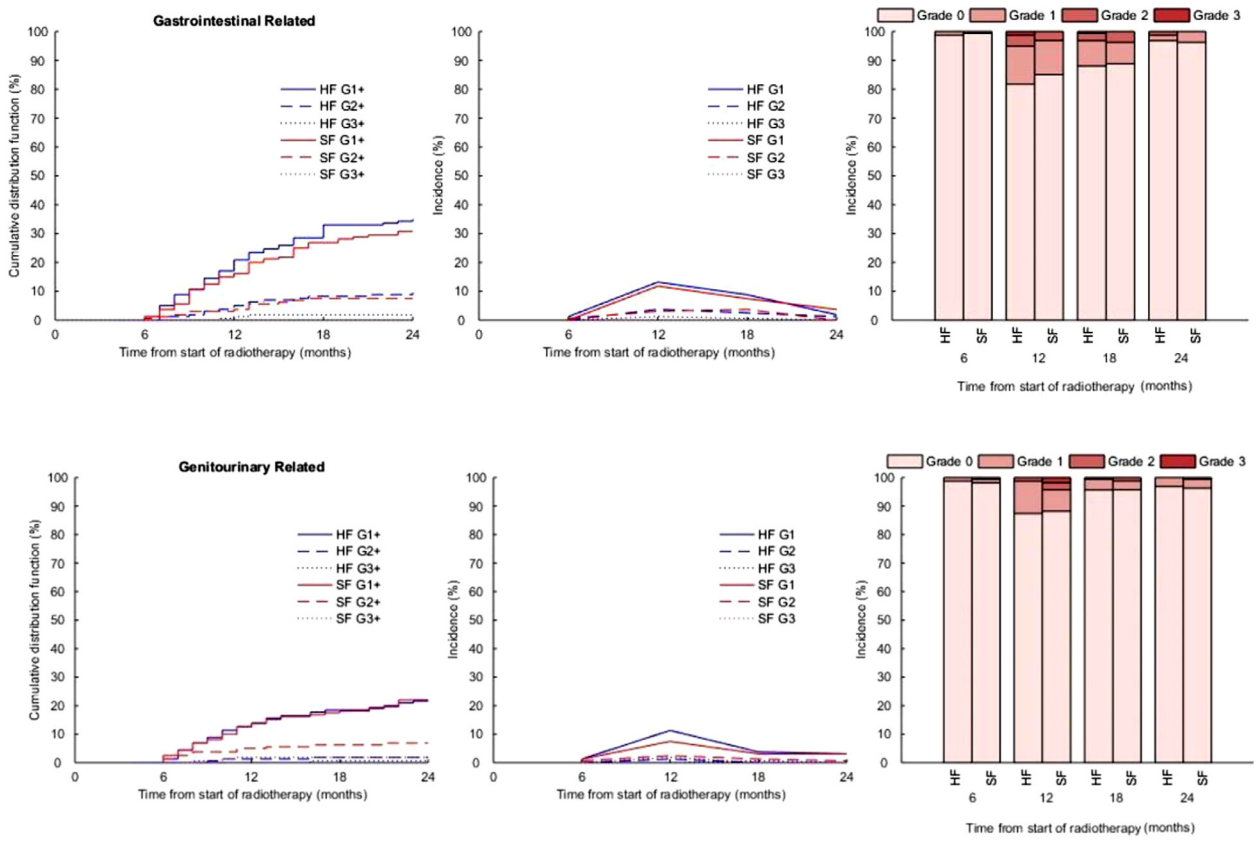

Fig. 3. Left: cumulative incidence of gastrointestinal (top) and genitourinary (bottom) toxicity by grade categories over time, beginning six months after the start of radiotherapy. Middle: same as left, but for incidence instead of cumulative incidence. Right: toxicity grade distribution over time. *Abbreviations*: HF = hypofractionated; SF, = standard fractionation.

treatment protocol for patients enrolled in the PCS-5 trial. Pelvic lymph node irradiation was not included for the National Comprehensive Cancer Network high-risk group of the CHHiP or the HYPRO trials,[19,20,22,23,27,29] whereas PLNs were treated in those with a high-risk disease in the Fox Chase Cancer Center Study.[23] The rationale for combining moderate HF RT with PLN RT is further supported by a randomized phase 2 trial by Chang et al which assessed the safety and efficacy of HF RT with simultaneous integrated boost IMRT that includes coverage of the SVs and PLNs.[30] Among enrolled patients, 40.4% had high-risk disease, and 26 received PLN irradiation. At 2 years, the cumulative

Table 3 Gastrointestinal and genitourinary related late toxicity

Late toxicity	Total events	HF	SF	HF vs SF		*P* value
				HR	(95% Wald CI)	
Gastrointestinal related						
Grade 1 or worse	104	55	49	1.22	(0.83-1.80)	.322
Grade 2 or worse	27	15	12	1.32	(0.61-2.83)	.482
Grade 3 or worse	3	3	0			
Grade 4 or worse	0					
Genitourinary related						
Grade 1 or worse	69	34	35	1.04	(0.64-1.68)	.882
Grade 2 or worse	14	3	11	0.25	(0.06-0.81)	.035
Grade 3 or worse	4	1	3			
Grade 4 or worse	0					

Abbreviation: HF = hypofractionated; HR = hazard ratio; SF = standard fractionation.

incidence of physician-reported late grade 2 or higher GU and GI toxicities were 32.6% and 18.4%, respectively, and only 10.2% of grade 2 or higher GU toxicities and 2.0% of grade 2 or higher GI toxicities remained unresolved.[30] Results were comparable to the Fox Chase Cancer Center study of moderately HF RT, which also incorporated simultaneously integrated elective nodal coverage for high-risk patients and reported similar rates of toxicity and biochemical control between conventional and HF arms.[23] Notably, even with the inclusion of PLN irradiation, no significant increase in toxicity was observed among patients receiving HF versus SF therapy on the PCS-5 trial.

The safety results of our trial, conducted in exclusively high-risk patients, align with other trials conducted in intermediate-risk or mixed intermediate and high-risk populations[19,23,25,27] showing that HF RT is as well-tolerated as SF regimens. This is in contrast to the results of the HYPRO trial, which did not demonstrate the noninferiority of the safety of the HF regimen compared with SF in a predominately high-risk patient population.[20,22,29] For the HYPRO trial, it was hypothesized that patients with predisposing factors (eg, high risk, advanced age, bladder symptoms before treatment) might be less tolerant of HF, similar to results seen with high-dose-rate brachytherapy.[31] Therefore, enrollment of a high percentage of patients with baseline bladder symptoms equivalent to grade 2 or higher toxicity may have further heightened the rates of acute toxicity in HYPRO.[22]

Peaks in both acute GI and GU toxicity of the PCS-5 trial followed patterns observed in prior trials of HF RT for localized prostate cancer. Acute GI toxicity peaked earlier (4-5 weeks) in the HF group compared with the control group (6-7 weeks) in the PCS-5 trial. Similar patterns were observed in the HF arms of the predominately intermediate-risk CHHiP trial and the predominately high-risk HYPRO trial.[22,27] In the CHHiP trial, GI toxicity peaked at 4 to 5 weeks for both HF arms.[27] In the HYPRO trial, acute toxicity was only measured at 4 weeks, 6 weeks, and 3 months, with the highest reported GI toxicity on the HF arm occurring at 4 and 6 weeks.[22] There was also an earlier peak in GU toxicity for the HF arm of the PCS-5 trial (5-6 weeks) compared with the SF arm (8-9 weeks), with similar peak timing of GU toxicity for both the CHHiP (4-5 weeks) and HYPRO (4 and 6 weeks) trials.[22,27] Similar to CHHiP and HYPRO trials, the acute GI and GU toxicities of the PCS-5 significantly improved 2 weeks after completion of RT in both arms.

Peak rates of GI toxicity were more elevated in the HF arm compared with the SF arm of the PCS-5 for both grade 1 (52.2% vs 38.5%, respectively) and grade 2 or higher toxicity (20% vs 10%, respectively), and rates of grade 3 or higher toxicity were negligible. Similar toxicity grade distribution was seen in the CHHiP trial, with the highest rates of grade 1 toxicity, followed by lower levels of grade 2 and negligible levels of grade 3 or higher toxicity.[27] In the HYPRO trial at 4 and 6 weeks, grade 1 and 2 GI toxicity occurred at comparable rates, with negligible rates of grade 3 and no grade 4 toxicity. However, the peak rate of grade 2 or higher GI toxicity was approximately 31%, with the highest rate observed at the 6-week assessment.[22]

Peak rates of GU toxicity were slightly higher in the HF arm compared with the SF arm of the PCS-5 trial for both grade 1 (60% vs 55%, respectively) and grade 2 or higher toxicity (30% vs 25%, respectively) and rates of grade 3 toxicity were negligible. Again, toxicity rates of the HF arms in the CHHiP trial followed a similar pattern, but with higher overall toxicity rates (grade 1, 80%-90% and grade 2, 35%-40%) and very low rates of grade 3 toxicity or higher (<5%).[27] In the HYPRO trial at 4 and 6 weeks, grade 1 and 2 GU toxicity showed similar grade distribution, and there were somewhat higher rates of grade 3 (10%-15%) and very low rates of grade 4 (<1%) toxicity. Their peak rate of grade 2 or higher GU toxicity was approximately 31%, with the highest rate observed at the 4-week assessment.[22]

In the PCS-5 trial, rates of cumulative grade 1 or higher GI toxicity of 30% to 35% at 2 years after the start of RT were comparable across treatment arms. Similarly, the cumulative incidence of grade 2 or higher GI toxicity was 8% to 10% across arms of the PCS-5 trial; and negligible grade 3 toxicity was observed. The HF arms of the CHHiP trial showed similar rates of grade 1 or higher GI toxicity compared with the PCS-5 trial, with rates of 25% to 30%, along with low rates of grade 2 or higher toxicity of 5% to 10% and negligible grade 3 toxicity.[27] In contrast to the PCS-5 and CHHiP trials, the rate of late grade 2 or higher GI toxicity at 2 years on the HF arm of the HYPRO trial was somewhat higher, at approximately 18%.[27,29]

There were also comparable rates of cumulative grade 1 or higher GU toxicity of 20% to 25% at 2 years after the start of RT across treatment arms in the PCS-5 trial. However, an unexpected result was the lower rates of late grade 2 or higher GU toxicity with HF (4.3%) versus SF (15.9%; $P = .035$). Although statistically significant, these very few grade 2 or greater late GU toxicity events do not appear clinically significant. Moreover, the HF arms of the CHHiP trial showed similar to grade 1 or higher GU toxicity compared with the PCS-5 trial, with rates of 10% to 20%, along with low rates of grade 2 or higher toxicity of 5% to 10% and <5% grade 3 or higher toxicity.[27] The rate of late grade 2 or higher GU toxicity at 2 years on the HF arm of the HYPRO trial was substantially higher, at approximately 35%, compared with that reported for either the PCS-5 or CHHiP trials.[27,29]

In exploring possible explanations for lower grade 2 or higher GU toxicity among patients receiving the HF regimen compared with the SF schedule in the PCS-5 trial, the individual files of these patients were thoroughly reviewed. The baseline patient characteristics were well-balanced, and all analyses were controlled for hypertension, diabetes, smoking, and treatment technique. No patient or treatment-specific factors that could have contributed to the higher grade 2 GU toxicities were identified among patients treated with SF RT. One possibility is that the bladder may be less fraction-sensitive but more cumulative dose sensitive than the rectum, resulting in higher toxicity with SF via the greater cumulative dose compared with HF therapy. This,

combined with the reduced length of therapy (ie, 5 weeks for HF vs 7.5 weeks for SF), may have conferred some protective effect for bladder over bowel tissues.[19,25] This apparent effect in bladder rather than bowel tissues in the PCS-5 trial could have been influenced by a lower biologically effective dose for normal tissues (α/β ratio of 3-5 Gy) compared with the prostate (1.5 Gy) with HF therapy, based on the linear quadratic model prediction.[13-17,25]

In addition to the potential radiobiological advantage of HF versus SF therapy, there are significant convenience and cost benefits for the patient, which may lead to general benefits for the health system.[32] From a patient-centered care perspective, considering 2 treatments with similar efficacy and safety, moderate HF (ie, fewer treatments) may reduce costs of transportation and travel and minimize time lost from work compared with an SF regimen. For providers, HF may increase efficiency and significantly reduce costs while maintaining or improving the quality of patient care.[32]

Data from prior trials of mixed-risk prostate cancer populations have demonstrated both noninferiority of efficacy and adequate safety of moderate HF RT. Our data are the first to demonstrate an acceptable safety profile for HF RT among patients with localized, exclusively high-risk disease who are treated with the contemporary standard of PLN irradiation and long-term ADT. Peak timing and resolution of acute GI and GU toxicity and rates of acute and cumulative toxicity on the HF arm of PCS-5 showed no clinically meaningful differences compared with the SF arm, and no long-term safety signals were identified. These data demonstrate safety outcomes and support the continued use of HF RT for high-risk prostate cancer therapy.

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