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Original Article

Elective nodal ultra hypofractionated radiation for prostate cancer: Safety and efficacy from four prospective clinical trials

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ABSTRACT

Background and purpose: The role of elective nodal irradiation (ENI) in localized prostate cancer (PCa) is controversial. With increasing use of SBRT to the prostate, data is needed regarding the safety and efficacy of ENI using ultra-hypofractionated radiation (UHRT).

Materials and methods: Between 2013–2020, 4 prospective clinical trials of intermediate or high-risk PCa receiving dose-escalated RT to the prostate (via HDR brachytherapy or SBRT boost) and ENI using UHRT (25 Gy in 5 weekly fractions) were conducted. Primary endpoints included acute genitourinary and gastrointestinal toxicities (CTCAE v3.0/4.0), and secondary endpoints included late genitourinary and gastrointestinal toxicities, patient-reported quality of life (EPIC) and biochemical failure (Phoenix definition).

Results: One-hundred sixty-five patients were enrolled, of whom 98 (59%) had high-risk disease. ADT was used in 141 (85%). Median follow-up was 38 months (IQR 10–63). The worst acute genitourinary and gastrointestinal toxicities respectively were 48% and 7.5% for grade 2, and 2.7% and 0% for grade 3. Cumulative incidence of late grade 2+ genitourinary and gastrointestinal toxicities at 36 months were 58% and 11.3% and for late grade 3+ toxicities were 1% and 0%, respectively. No grade 4+ acute or late toxicities were observed. Bowel and sexual toxicity significantly worsened up to 1-year compared to baseline. Over time, urinary ($p < 0.0001$), bowel ($p = 0.0018$) and sexual ($p < 0.0001$) scores significantly improved. The 3-year biochemical recurrence-free survival was 98%.

Conclusion: ENI using UHRT is associated with low incidence of grade 3+ toxicity, while grade 1–2 acute genitourinary and gastrointestinal toxicity is common. Randomized phase 3 trials are needed.

The role of elective nodal irradiation (ENI) in patients with localized prostate cancer (PCa) is controversial. Two randomized trials, GETUG-1 and RTOG-9413, demonstrated equivalent event- or progression-free survival with the addition of ENI to non-dose-escalated radiotherapy to the primary tumor with long-term follow-up [1–4]. More recently, the POP-RT study demonstrated 5-year biochemical failure-free survival of 95% and 81% for patients receiving pelvis RT versus prostate only RT, respectively, in high-risk non-metastatic patients, the majority of whom were staged with prostate-specific membrane antigen (PSMA) positron emission tomography (PET) [5]. RTOG-0924, a phase 3 randomized trial that completed accrual in 2019, seeks to address whether the addition of ENI to prostate radiotherapy improves survival in unfavorable-intermediate and high-risk patients (clinicaltrials.gov NCT01368588).

With increasing use of stereotactic body radiotherapy (SBRT) for the management of the primary in PCa [6], more data is needed regarding the role and safety of ENI using ultra- hypofractionated radiation (UHRT). Here, we present acute and late gastrointestinal (GI) and genitourinary (GU) toxicity and patient-reported quality of life (QoL) outcomes from 4 prospective studies of pelvic UHRT.

Materials and methods

All 4 prospective phase 2 trials were approved by the Sunnybrook Research Ethics Board and registered on clinicaltrials.gov (NCT01953055, NCT04236752, NCT02911636, NCT04245670). Written informed consent was obtained by all patients.

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Table 1
Demographic information.

Variable	Number or median	Percentage or IQR
Age	71	66–78
NCCN risk group		
Favorable intermediate risk	11	6.70%
Unfavorable intermediate risk	55	33.30%
High risk	98	59.40%
Unknown	1	0.60%
Gleason score		
3 + 3	2	1.20%
3 + 4	49	29.70%
3 + 5	3	1.80%
4 + 3	42	25.50%
4 + 4	35	21.20%
4 + 5 or 5 + 5	32	19.40%
Unknown	2	1.20%
Clinical T stage		
T1a	1	0.60%
T1c	25	15.10%
T2a	40	24.20%
T2b	27	16.40%
T2c	27	16.40%
T3a	25	15.20%
T3b	12	7.30%
Unknown	8	4.80%
PSA (ng/mL)	12.2	7.0–18.0
Prostate volume (cc) (n = 60)	41	32–52
IPSS score		
0–9	103	62.40%
10–19	34	20.60%
≥20	8	4.90%
Unknown	20	12.10%
Radiotherapy treatment		
SATURN	30	18.20%
SPARE	31	18.80%
5STAR	30	18.20%
5STAR-PC	74	44.80%
ADT use		
No	24	14.60%
Yes	141	85.40%
Duration of ADT use (months)	8.2	5.0–12.2

*NCCN: National Comprehensive Cancer Network; PSA: prostate specific antigen; IPSS: International Prostate Symptom Score; ADT: androgen deprivation therapy.

Patient selection and treatment details

From 2013-2014, 30 patients with high-risk PCa were enrolled in SATURN. Study details were previously published [7]. Briefly, clinical target volume-1 (CTV1) encompassed pelvic lymph nodes (LNs) and seminal vesicles (SVs), with a 6 mm margin for planning target volume-1 (PTV1). CTV2 encompassed the prostate, with a 3 mm margin for PTV2. Planning doses were 25 Gy to CTV1, 23.25 Gy to PTV1, 40 Gy to CTV2 and 33.25 Gy to PTV2, in 5 weekly fractions. The protocol mandated 12–18 months of androgen deprivation therapy (ADT).

From 2014-2015, 31 patients with unfavorable-intermediate and high-risk PCa were enrolled in SPARE. Study details were described previously [8–10]. Patients were treated with high-dose-rate (HDR) brachytherapy (15 Gy) with a magnetic resonance (MR)-guided boost to the dominant intraprostatic lesion (DIL), followed two weeks later by UHRT to the prostate and pelvic LNs (25 Gy in 5 weekly fractions), and ADT for 6–18 months depending on patient's risk.

From 2016 to 2017, 30 patients with unfavorable-intermediate or high-risk PCa were enrolled in 5STAR. Study details were previously published [11]. Patients were treated with 25 Gy to the pelvic LNs and SVs and 35 Gy to the prostate with a simultaneous intraprostatic boost to an MR-detected nodule delivered in 5 weekly fractions, with 6–18 months of ADT. CTV1, CTV2 and PTV1 were created in a similar fashion to SATURN. PTV2 was created using a 2 mm expansion on CTV2 (2.5 mm superiorly-inferiorly) as a prostate-endorectal immobilization system was used [12]. Urethrogram was performed at the time of planning to identify the urethra as a dose-limiting structure. The DIL was contoured on the fused multiparametric MR and boosted up to 50 Gy so long as organs-at-risk dose limits were not exceeded.

From 2018 to 2020, 74 patients with unfavorable-intermediate and high-risk PCa were enrolled in 5STAR-PC, a multi-institutional Canadian study based on the institutional 5STAR study. All patients were treated with 25 Gy in 5 fractions to the pelvic LNs and SVs. Thirty-one patients received the 5STAR technique and 43 were treated with the SATURN technique.

In all studies, pelvic lymph nodes were contoured per the 2009 RTOG atlas [13], with a 6 mm PTV.

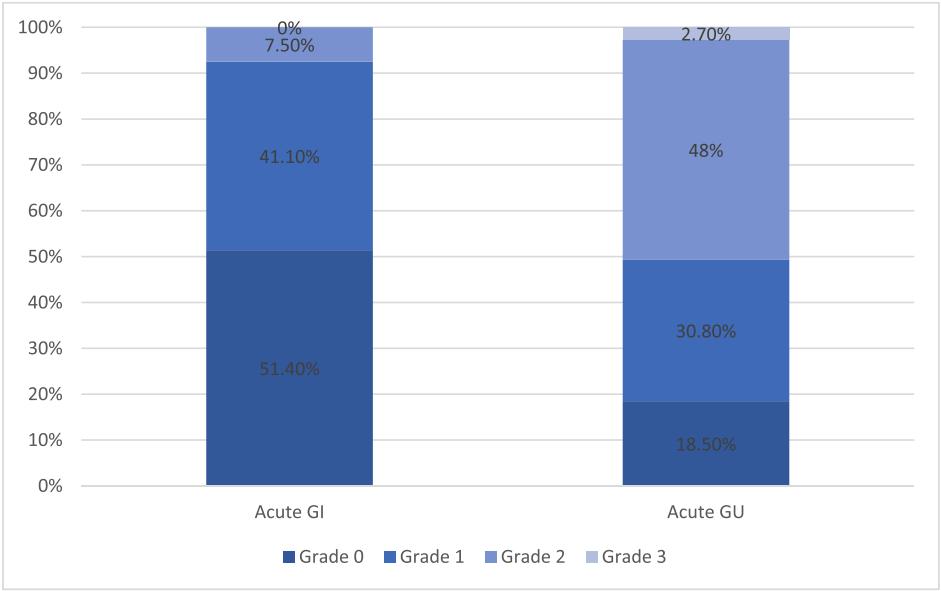

Fig. 1. Stacked bar plot for acute gastrointestinal and genitourinary toxicity.

Study endpoints and follow-up

Patients were assessed at baseline, weekly during UHRT, every 3 months for the first year following UHRT, every 6 months for years 2–5, and subsequently every year. Toxicities were collected using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (SATURN, SPARE) and 4.0 (5STAR, 5STAR-PC) up to 5 years. Patient-reported QoL was collected using the Expanded Prostate Cancer Index Composite (EPIC) up to 5 years. Primary endpoints of all trials were acute (week 2 until month 3) GU and GI toxicities.

Secondary endpoints included late (month 6 until 60) GU and GI toxicity, patient-reported QoL and biochemical failure defined per the Phoenix definition (nadir plus 2.0 ng/mL). Prostate specific antigen was measured at baseline and each follow-up visit.

Statistical analysis

Demographic and tumor characteristics were summarized using mean, standard deviation, median and range for continuous variables and proportions for categorical variables. Biochemical failure was calculated from time of first radiation treatment to failure, last follow-up or death. The cumulative incidence of grade 2+ (G2+) and grade 3+ (G3+) acute and late GU and GI toxicity, biochemical failure, metastasis-free survival, castrate-resistant prostate cancer (CRPC)-free survival and overall survival (OS) were estimated using Nelson-Aalen curves. EPIC scores over time were compared to search for significant time trends over months, and to assess for differences between baseline and at each follow-up (month 3 to month 60) using a general linear mixed model. *P*-value <0.05 was considered statistically significant. Analyses were conducted using Statistical Analysis Software (v9.4) and R (v4.0.3).

Results

165 patients were included. Baseline characteristics are outlined in Table 1. Median follow-up was 38 months (IQR 10.7–63.1). Results are reported as aggregates across all trials.

Incidence of acute toxicity is demonstrated in Fig. 1. The percentage of patients with the worst acute GU and GI toxicities were 18.5% and 51.4% for grade 0, 30.8% and 41.1% for grade 1, 48% and 7.5% for grade 2, and 2.7% and 0% for grade 3, respectively. There were no grade 4+ acute toxicities. Acute toxicities are outlined in Table 2.

Cumulative incidence of late toxicity is demonstrated in Fig. 2. The percentage of patients with the worst late GU and GI toxicities were 16.4% and 58.2% for grade 0, 41% and 31.3% for grade 1, 41.1% and 10.5% for grade 2, and 1.5% and 0% for grade 3, respectively. Prevalence of late GU and GI toxicities were 23.1% and 60.5% with grade 0, 46.3% and 35.1% with grade 1, 29.9% and 4.5% with grade 2, and 0.8% and 0% with grade 3, respectively. There were no grade 4+ late toxicities.

Urinary, bowel and sexual domain EPIC scores at baseline and follow-up are demonstrated in Fig. 3. For the urinary, bowel and sexual domains, EPIC scores significantly increased over follow-up ($p < 0.0001$, $p = 0.0018$ and $p < 0.0001$, respectively). Compared to baselined, urinary domain scores were significantly higher at month 24 ($p = 0.026$) and 60 ($p = 0.002$). Bowel domain scores were significantly lower at month 6 ($p = 0.008$) and 12 ($p = 0.020$) compared to baseline. Sexual domain scores were significantly lower at month 3, 6 and 12 compared to baseline ($p < 0.0001$, $p < 0.0001$ and $p < 0.001$, respectively).

Biochemical recurrence free-survival at 3-, 4-, and 5-years is 98%, 95% and 93%, respectively. No patients had pelvic failures. The 3-year metastases-free survival, CRPC-free survival and OS were 98%, 99% and 96.3%, respectively (Fig. 4).

Discussion

ENI using UHRT resulted in low rates of grade 3+ acute and late GI and GU toxicity in the setting of 4 prospective trials, while close to half of patients experienced a grade 2 acute and late GU toxicity. Acute and late grade 2+ small-bowel toxicity appears to be minimal with symptoms such as abdominal pain and enteritis occurring at low frequency as demonstrated in Table 2, although distinguishing a small versus large bowel versus rectal-related GI toxicity can be challenging. Patient-reported bowel and sexual QoL worsened initially after treatment for one year compared to baseline, however all domains were associated with improvement over time. Initial decline in sexual function corresponds with time on ADT and anticipated testosterone recovery. Furthermore, oncologic outcomes were high across all 4 studies, although follow-up was limited.

Table 2
Descriptions of and number of patients with grade 2 and grade 3 acute and late genitourinary and gastrointestinal toxicities.

	Number of patients with grade 2 toxicity	Number of patients with grade 3 toxicity
Acute genitourinary toxicity		
Urinary retention	55	3
Urinary frequency	18	1
Urinary tract pain	10	0
Bladder spasm	7	0
Urinary incontinence	5	0
Urinary urgency	5	0
Hemorrhage GU-Urethra	3	0
Urinary tract obstruction	2	1
Cystitis- non infective	1	0
Hematuria	1	0
Obstruction- Prostate	1	1
Acute gastrointestinal toxicity		
Flatulence	4	0
Constipation	3	0
Diarrhea	3	0
Abdominal pain	1	0
Fecal incontinence	1	0
Nausea	1	0
Proctitis	1	0
Rectal hemorrhage	1	0
Late genitourinary toxicity		
Urinary retention	33	0
Bladder spasm	20	0
Urinary incontinence	13	0
Urinary frequency	11	0
Cystitis- non infective	5	0
Urinary tract obstruction	5	0
Urinary tract pain	5	0
Urinary urgency	4	0
Hemorrhage GU-Urethra	3	0
Hemorrhage GU-Urinary	3	0
Hematuria	1	1
Renal and urinary disease- other	1	0
Stricture- Urethra	1	1
Late gastrointestinal toxicity		
Constipation	8	0
Proctitis	4	0
Diarrhea	3	0
Rectal hemorrhage	3	0
Colitis	1	0
Enteritis	1	0
Fecal incontinence	1	0

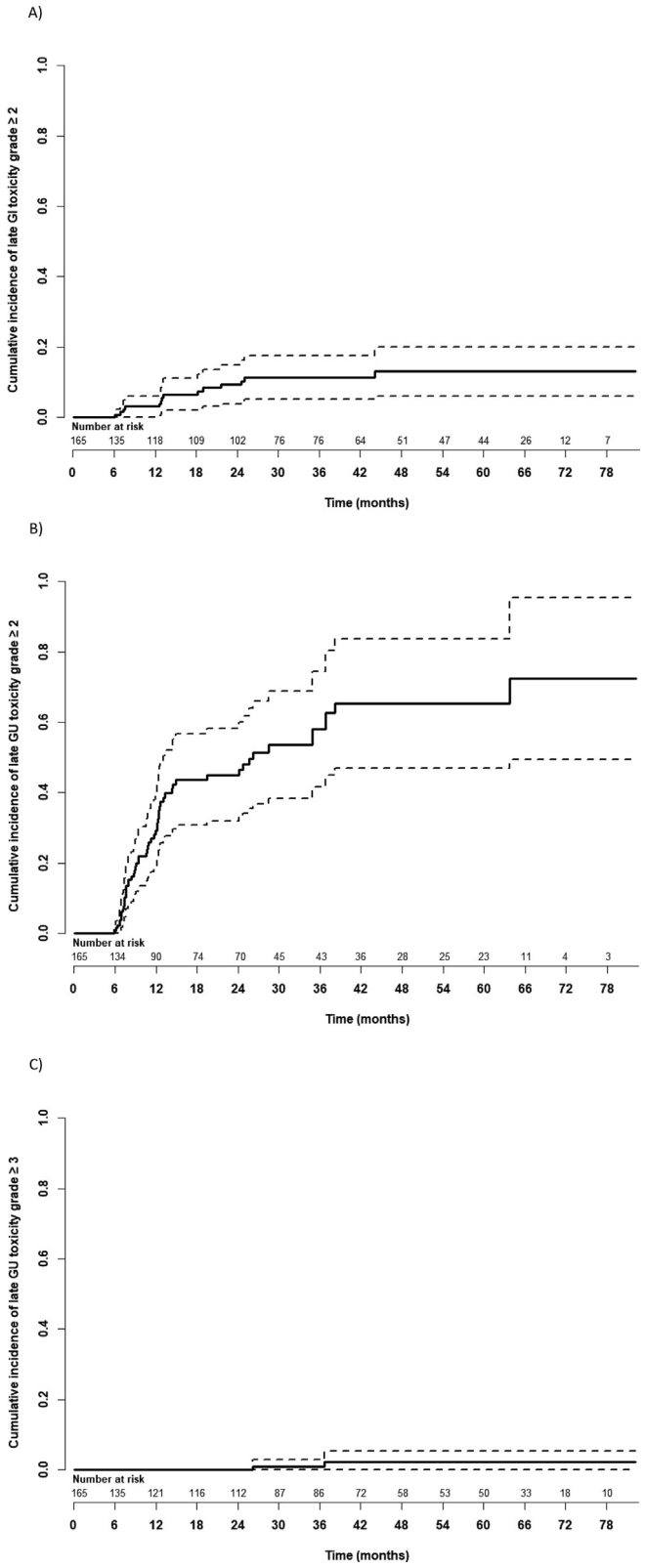

Fig. 2. Cumulative incidence of late grade ≥2 GI (A), grade ≥2 GU (B) or grade ≥3 GU (C) toxicity.

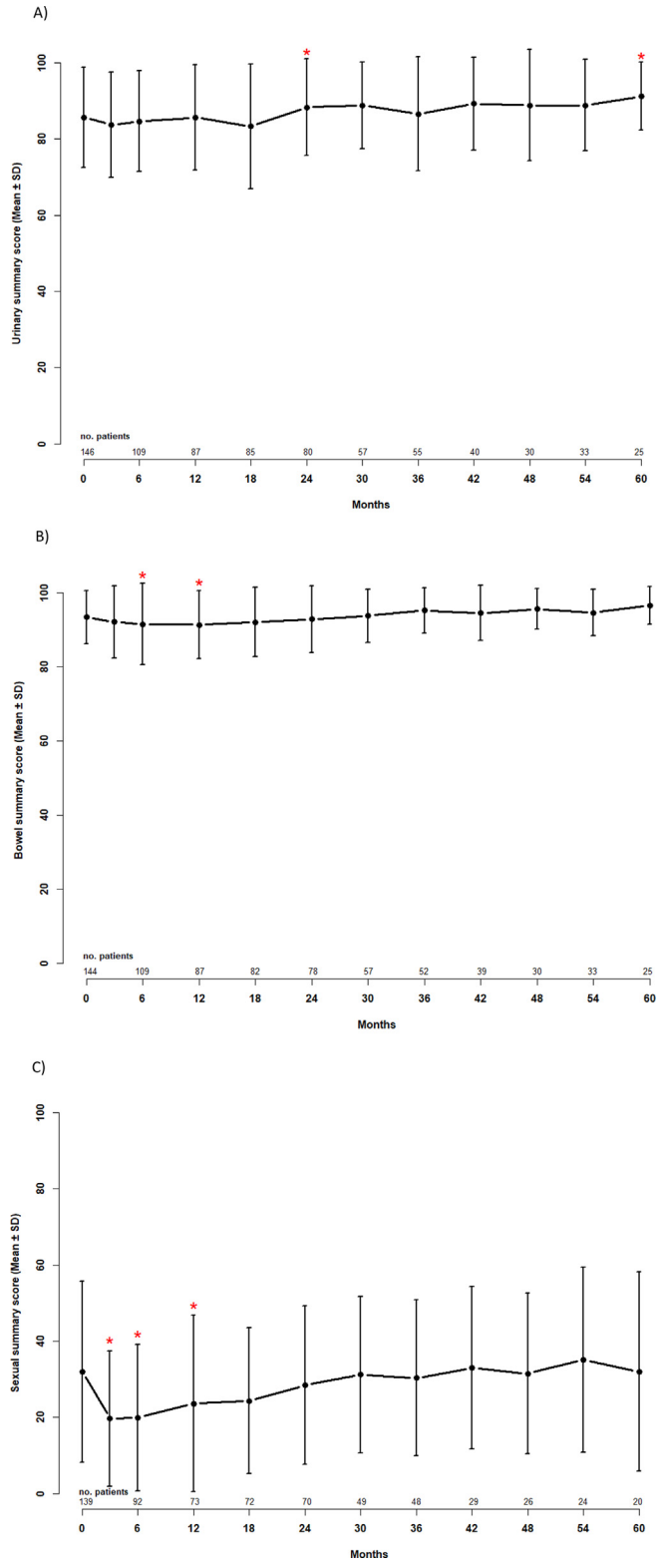

Fig. 3. Patient-reported quality of life Expanded Prostate Cancer Index Composite (EPIC) up to mean and standard deviation scores at baseline and over time for urinary (A), bowel (B), and sexual (C) domains.

To our knowledge, this study represents the largest prospective series of patients receiving ENI using UHRT. Murthy et al reported on 68 prospective patients with high-risk and node-positive disease treated with prostate and pelvic UHRT with similar rates of late toxicity and oncologic outcomes, albeit with shorter median follow-up of 18 months [14]. Recently, the SHARP pooled consortium of 344 patients with high-risk PCa treated with prostate SBRT, including 66 treated with ENI, demonstrated high efficacy and

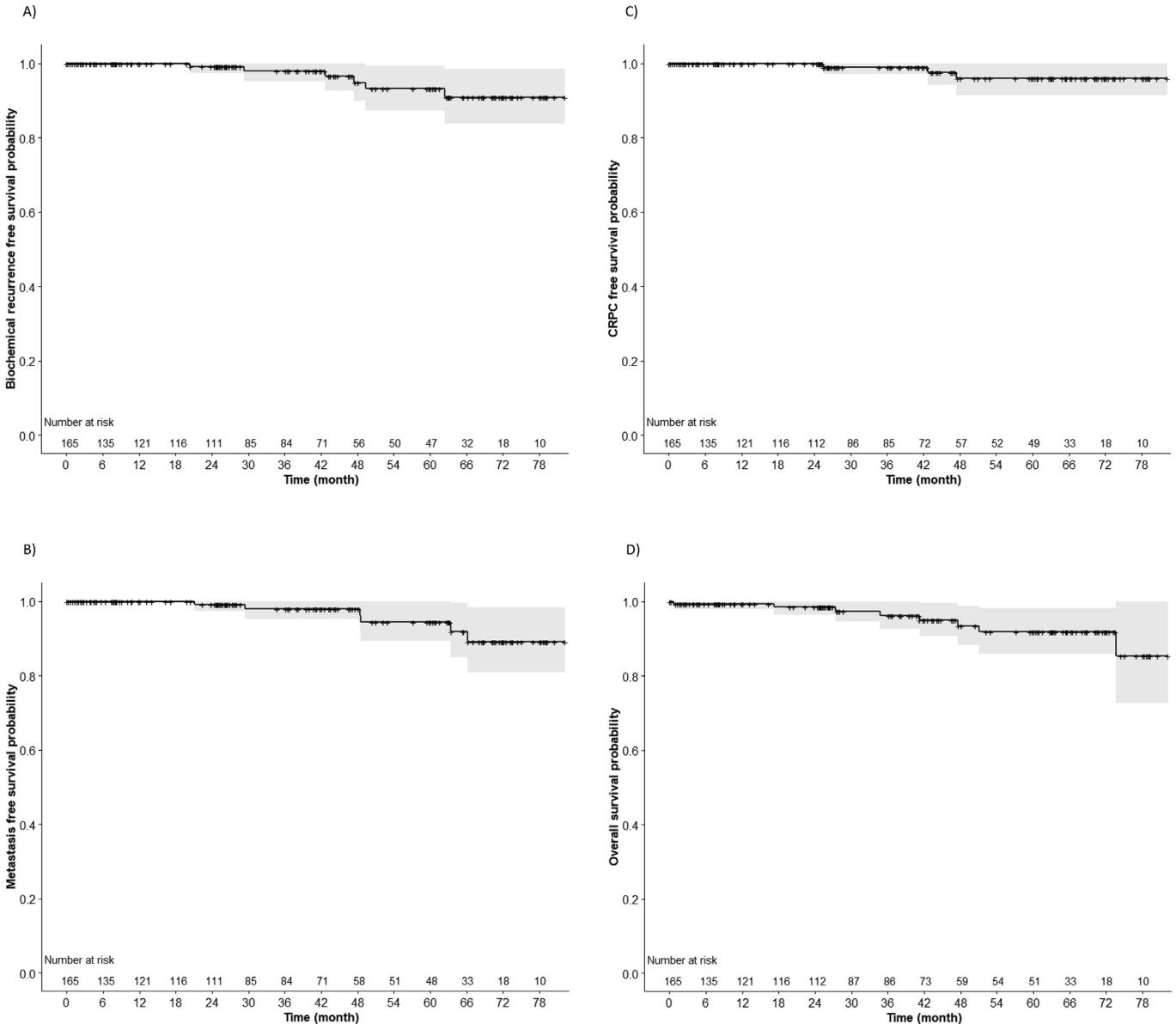

Fig. 4. Biochemical recurrence-free survival (A), metastasis-free survival (B), castrate-resistant prostate cancer-free survival (C), and overall survival (D).

safety [15]. The PRIME trial (clinicaltrials.gov NCT03561961), comparing moderate- versus extreme-hypofractionation to the prostate and pelvis for high-risk and/or node-positive PCa is an ongoing randomized study with an aim to accrue 434 patients. The HOPE trial (clinicaltrials.gov NCT04197141) and the SHARP trial (clinicaltrials.gov NCT04861415) are ongoing studies planning to accrue 58 and 55 patients, respectively, both randomizing patients to conventionally fractionated RT or UHRT following an HDR brachytherapy boost.

There are a number of limitations to this analysis. First, this cohort was developed from 4 separate prospective trials where different treatment protocols were employed, including use of different PTV margins which may account for differences in toxicity [16], which cannot be accounted for in this combined analysis. Second, these were single-arm studies without a comparator arm that omitted pelvic UHRT, and therefore the toxicity from the ENI portion of treatment alone cannot be determined, although comparison can be made to prostate-only SBRT series for high-risk patients [17]. Furthermore, these studies did not include a comparator arm that treated the pelvis with conventionally fractionated or moderately-hypofractionated RT to assess the effects from the fractionation scheme. Ongoing trials comparing fractionation schemes such as PRIME, HOPE and SHARP described above will be important.

In summary, ENI using UHRT was associated with low rates of grade 3+ acute and late GU and GI toxicities, with favorable oncologic outcomes. Randomized phase-3 trials of ENI using conventionally-fractionated and UHRT techniques to guide clinical practice are ongoing and much anticipated.

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Ride For Dad (SATURN), Prostate Cancer Canada (SPARE), Prostate Cure Foundation (5STAR, 5STAR-PC).

Conflict of Interest Statement

Loblaw: Honoraria/Travel - AbbVie, Astellas, Bayer, Janssen, Sanofi, TerSera; Advisory Boards/Consulting: AbbVie, Astellas, Jans-

sen, Sanofi, TerSera; Patents: Endorectal immobilization device (GU-Lok).

Cheung: Research grants- AbbVie; Honoraria: TerSera.

All other authors declare no conflicts.

Data sharing statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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