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Noninferiority of Hypofractionated vs Conventional Postprostatectomy Radiotherapy for Genitourinary and Gastrointestinal Symptoms
The NRG-GU003 Phase 3 Randomized Clinical Trial

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IMPORTANCE No prior trial has compared hypofractionated postprostatectomy radiotherapy (HYPORT) to conventionally fractionated postprostatectomy (COPORT) in patients primarily treated with prostatectomy.

OBJECTIVE To determine if HYPORT is noninferior to COPORT for patient-reported genitourinary (GU) and gastrointestinal (GI) symptoms at 2 years.

DESIGN, SETTING, AND PARTICIPANTS In this phase 3 randomized clinical trial, patients with a detectable prostate-specific antigen (PSA; ≥0.1 ng/mL) postprostatectomy with pT2/3pNX/0 disease or an undetectable PSA (<0.1 ng/mL) with either pT3 disease or pT2 disease with a positive surgical margin were recruited from 93 academic, community-based, and tertiary medical sites in the US and Canada. Between June 2017 and July 2018, a total of 296 patients were randomized. Data were analyzed in December 2020, with additional analyses occurring after as needed.

INTERVENTION Patients were randomized to receive 62.5 Gy in 25 fractions (HYPORT) or 66.6 Gy in 37 fractions (COPORT).

MAIN OUTCOMES AND MEASURES The coprimary end points were the 2-year change in score from baseline for the bowel and urinary domains of the Expanded Prostate Cancer Composite Index questionnaire. Secondary objectives were to compare between arms freedom from biochemical failure, time to progression, local failure, regional failure, salvage therapy, distant metastasis, prostate cancer–specific survival, overall survival, and adverse events.

RESULTS Of the 296 patients randomized (median [range] age, 65 [44-81] years; 100% male), 144 received HYPORT and 152 received COPORT. At the end of RT, the mean GU change scores among those in the HYPORT and COPORT arms were neither clinically significant nor different in statistical significance and remained so at 6 and 12 months. The mean (SD) GI change scores for HYPORT and COPORT were both clinically significant and different in statistical significance at the end of RT (−15.52 [18.43] and −7.06 [12.78], respectively; $P < .001$). However, the clinically and statistically significant differences in HYPORT and COPORT mean GI change scores were resolved at 6 and 12 months. The 24-month differences in mean GU and GI change scores for HYPORT were noninferior to COPORT using noninferiority margins of −5 and −6, respectively, rejecting the null hypothesis of inferiority (mean [SD] GU score: HYPORT, −5.01 [15.10] and COPORT, −4.07 [14.67]; $P = .005$; mean [SD] GI score: HYPORT, −4.17 [10.97] and COPORT, −1.41 [8.32]; $P = .02$). With a median follow-up for censored patients of 2.1 years, there was no difference between HYPORT vs COPORT for biochemical failure, defined as a PSA of 0.4 ng/mL or higher and rising (2-year rate, 12% vs 8%; $P = .28$).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, HYPORT was associated with greater patient-reported GI toxic effects compared with COPORT at the completion of RT, but both groups recovered to baseline levels within 6 months. At 2 years, HYPORT was noninferior to COPORT in terms of patient-reported GU or GI toxic effects. HYPORT is a new acceptable practice standard for patients receiving postprostatectomy radiotherapy.

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Radiotherapy (RT) to the prostate fossa is a potentially curative second-line treatment after prostatectomy for prostate cancer. It has been shown to reduce recurrence when used adjuvantly for the adverse pathologic features of extraprostatic extension or a positive surgical margin.[1-3] Presently, delaying RT until the first indication of prostate-specific antigen (PSA) recurrence (ie, early salvage) is the preferred approach because it spares men RT without compromising effectiveness.[4-6]

Hypofractionation is a treatment schedule in which the daily dose of RT is larger than conventionally fractionated RT (1.8-2.0 Gy per fraction), which shortens the treatment course. The benefits of hypofractionation for patients include shorter time commitment, greater access to treatment, less expense related to travel and co-payments, and fewer absences from work and other responsibilities. The benefits of hypofractionation for physicians include increased productivity of equipment and staff, as well as increased patient capacity. The benefits of hypofractionation for payers include lower cost.

To our knowledge, NRG-GU003 is the first clinical trial that compares hypofractionation to conventional fractionation in patients receiving postprostatectomy RT. The primary objective of NRG-GU003 was to determine whether 62.5 Gy in 25 fractions (2.5 Gy per fraction) resulted in noninferior patient-reported gastrointestinal (GI) and genitourinary (GU) symptoms using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire compared with 66.6 Gy in 37 fractions (1.8 Gy per fraction). Secondary objectives of the trial were to compare freedom from biochemical failure (FFBF), time to progression (TTP), local failure (LF), regional failure (RF), salvage therapy (ie, institution of new unplanned anticancer treatment), distant metastasis, prostate cancer-specific survival, overall survival (OS), and adverse events (AEs).

Key Points

Question Does hypofractionated postprostatectomy radiotherapy (HYPORT) increase patient-reported genitourinary or gastrointestinal (GI) symptoms compared with conventionally fractionated postprostatectomy (COPORT)?

Findings In this randomized clinical trial of 296 patients, HYPORT was associated with greater patient-reported GI symptoms compared with COPORT at the completion of RT; however, this difference resolved within 6 months. HYPORT compared with COPORT was not associated with significantly higher patient-reported genitourinary or GI symptoms 1 or 2 years after radiotherapy.

Meaning This study found that HYPORT is noninferior to COPORT in terms of patient-reported late toxic effects and is a new acceptable practice standard.

Methods

Trial Design and Participants

Patients with a detectable PSA (≥0.1 ng/mL; to convert to micrograms per liter, multiply by 1.0) with pT2/3pNX/0 disease or an undetectable PSA (<0.1 ng/mL) with either pT3 disease or a positive surgical margin were eligible. Patients could not have pT2 disease with a negative surgical margin and PSA lower than 0.1 ng/mL, nor could patients have a postprostatectomy PSA nadir of 0.2 ng/mL or higher and Gleason score of 7 or higher (due to competing eligibility with the NRG-GU002 trial). Before study entry, evaluation included history and physical examination (including digital rectal examination) and a serum PSA test, abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI), bone scan, and EPIC questionnaire.

Participants were recruited at academic, community-based, and tertiary medical sites in the US and Canada after a central institutional review board approval. All participating centers successfully irradiated an anthropomorphic phantom from the Radiological Physics Center to ensure accurate treatment delivery capabilities. All participants provided written informed consent before registration. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Randomization

This was a multicenter phase 3 trial approved and sponsored by the National Cancer Institute (Supplement 1). Participants were stratified by the NRG Oncology Statistics and Data Management Center according to baseline EPIC score using 4 tiers based on GU and GI scores (high bowel score [>96] and high urinary score [>84], high bowel score and low urinary score [≤84], high urinary score and low bowel score [≤96], and low urinary and bowel scores) and androgen deprivation therapy (ADT) use (maximal duration ≤6 months). A permuted-block randomization treatment allocation described by Zelen[7] was used to stratify and randomize patients 1:1 to conventionally fractionated postprostatectomy (COPORT; 66.6 Gy in 37 fractions) or hypofractionated postprostatectomy radiotherapy (HYPORT; 62.5 Gy in 25 fractions).

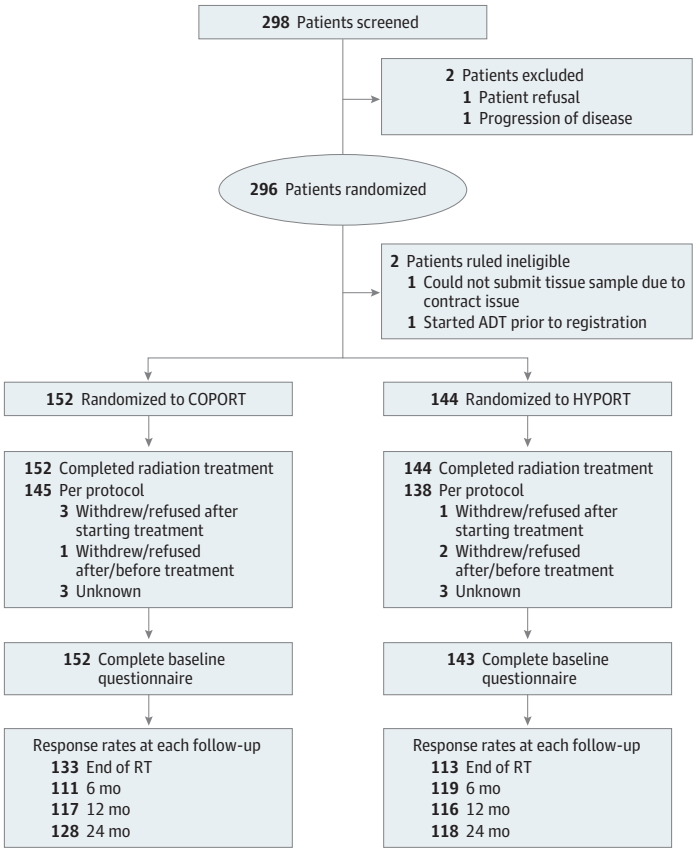
Treatment

The protocol permitted 3-dimensional conformal RT, intensity-modulated RT, volumetric modulated arc RT, MRI-guided RT, robotic RT, and helical RT. Image-guided RT was required. The clinical target volume consisted of the prostate fossa according to Radiation Therapy Oncology Group (RTOG)/NRG Oncology consensus guidelines.[8] Lymph node RT was not allowed. The clinical target volume was required to have a planning target volume margin of 0.7 to 1.0 cm surrounding them to account for setup uncertainties. For men receiving ADT, any luteinizing hormone–releasing hormone agonist/antagonist with or without an oral antiandrogen could be used.

Patient Assessment and End Points

Patients were monitored weekly during RT for AEs and tolerance to treatment. At the end of treatment, they underwent PSA level testing and AE evaluation and completed patient-reported questionnaires. Following treatment, they underwent interval history, physical examination, and PSA level testing at each visit starting 6 months from RT initiation, every 6 months for 2 years, then annually thereafter. AEs were graded

Figure 1. CONSORT Diagram



ADT indicates androgen deprivation therapy; COPORT, conventionally fractionated postprostatectomy; HYPORT, hypofractionated postprostatectomy radiotherapy; RT, radiotherapy.

using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. All data, including demographic data, were reported by site research staff.

The 50-item EPIC and EuroQol's EQ-5D-5L were used. EPIC is a patient self-administered instrument that measures urinary, bowel, sexual, and hormonal symptoms related to prostate cancer treatments, including prostatectomy, RT, and hormonal therapy.[9] Response options for each item form a Likert scale with scores transformed linearly to a 0 to 100 scale. Domain scores are also on a 0 to 100 scale, with higher scores representing better health-related quality of life. The EQ-5D-5L is a 2-part, 6-item validated utility assessment.[10-12] The first part consists of 5 items, graded on 5 levels from no problems to extreme problems, covering 5 dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The 5-item index score is transformed into a utility score between 0 (worst health state) and 1 (best health state). The sixth item is a visual analog scale scored 0 to 100 for overall health.

Biochemical failure was defined as a PSA of 0.4 ng/mL or higher and rising (ie, PSA ≥0.4 ng/mL followed by a value higher than the first by any amount) or initiation of ADT. LF was defined as the development of a new biopsy-proven mass in the prostate fossa. RF was defined as radiographic evidence (CT or MRI) of lymphadenopathy (lymph node size ≥1.0 cm in the short axis) in a patient without the diagnosis of a hematologic/lymphomatous disorder associated with adenopathy. Distant metastasis (DM) was defined as radiographic evidence of hematogenous spread (eg, bone scan, CT, MRI).

Statistical Analysis

The coprimary end points were the 2-year change in score from baseline for the bowel and urinary domains of the EPIC. The hypothesis was that the EPIC mean change score would be no worse in the HYPORT arm than it was in the COPORT arm for either type of toxic effect. Based on results from NRG/RTOG 0415,[13] which also used 2.5 Gy per fraction but for patients with an intact prostate, an EPIC bowel domain mean change score of −4.3 at 2 years was assumed for the COPORT arm with a noninferiority margin of 6 for the HYPORT arm, corresponding to a bowel domain change score of −10 in the HYPORT arm. An EPIC urinary domain score of 0.4 at 2 years was assumed for the COPORT arm, with a noninferiority margin of 5 for the HYPORT arm corresponding to a urinary domain change score of −4.6 in the HYPORT arm. The noninferiority margins were chosen based off of 0.5 × SD, as obtained in NRG/RTOG 0415 and used to denote a clinically significant magnitude.[14] The study sample size was 198 patients based on 91% power for the GU end point and 90% power for the GI end point (resulting in 82% statistical power to reject the null hypothesis for both end points) and a 1-sided $\alpha = .025$ with an overall type I error of 0.05 with a Bonferroni adjustment and 1 interim futility

Table 1. Patient and Tumor Characteristics

Characteristic	No. (%)		
	COPORT arm (n = 152)	HYPORT arm (n = 144)	Total (N = 296)
Age range, y			
≤49	3 (2.0)	3 (2.1)	6 (2.0)
50-59	27 (17.8)	31 (21.5)	58 (19.6)
60-69	75 (49.3)	83 (57.6)	158 (53.4)
≥70	47 (30.9)	27 (18.8)	74 (25.0)
Race[a]			
Asian	2 (1.3)	5 (3.5)	7 (2.4)
Black or African American	22 (14.5)	22 (15.3)	44 (14.9)
White	126 (82.9)	114 (79.2)	240 (81.1)
Unknown	2 (1.3)	3 (2.1)	5 (1.7)
Ethnicity[a]			
Hispanic or Latino	7 (4.6)	5 (3.5)	12 (4.1)
Not Hispanic or Latino	143 (94.1)	137 (95.1)	280 (94.6)
Unknown	2 (1.3)	2 (1.4)	4 (1.4)
Baseline EPIC score group[b]			
A	57 (37.5)	52 (36.1)	109 (36.8)
B	29 (19.1)	32 (22.2)	61 (20.6)
C	31 (20.4)	31 (21.5)	62 (20.9)
D	35 (23.0)	29 (20.1)	64 (21.6)
Prior ADT			
No	119 (78.3)	110 (76.4)	229 (77.4)
Yes	33 (21.7)	34 (23.6)	67 (22.6)
Baseline PSA, ng/mL			
0.0-0.5	136 (89.5)	129 (89.6)	265 (89.5)
0.6-1.0	10 (6.6)	14 (9.7)	24 (8.1)
1.1-1.5	3 (2.0)	1 (0.7)	4 (1.4)
1.6-2.0	3 (2.0)	0	3 (1.0)
Combined Gleason score			
6	16 (10.5)	7 (4.9)	23 (7.8)
7	106 (69.7)	110 (76.4)	216 (73.0)
8	14 (9.2)	15 (10.4)	29 (9.8)
9	15 (9.9)	11 (7.6)	26 (8.8)
10	1 (0.7)	1 (0.7)	2 (0.7)
T stage			
T2	77 (50.7)	60 (41.7)	137 (46.3)
T3	75 (49.3)	84 (58.3)	159 (53.7)
N stage			
NX	30 (19.7)	33 (22.9)	63 (21.3)
N0	122 (80.3)	111 (77.1)	233 (78.7)
M stage			
M0	152 (100)	144 (100)	296 (100)

Abbreviations: ADT, androgen deprivation therapy; COPORT, conventionally fractionated postprostatectomy; EPIC, Expanded Prostate Cancer Index Composite; HYPORT, hypofractionated postprostatectomy radiotherapy; PSA, prostate-specific antigen.

SI conversion factor: To convert PSA to µg/L, multiply by 1.0.

[a] Race and ethnicity were reported by the site research staff. Collection is required by the National Cancer Institute.

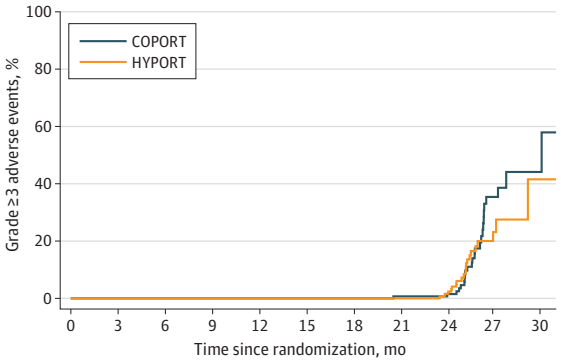
[b] EPIC score groups were defined as A, bowel score greater than 96 and urinary score greater than 84; B, bowel score greater than 96 and urinary score 84 or lower; C, bowel score 96 or lower and urinary score greater than 84; and D, bowel score 96 or lower and urinary score 84 or lower.

analysis. Adjusting for a projected 30% EPIC noncompliance rate, the required sample size was 282 patients.

Categorical variables were compared between arms using a χ^2 test, and *t* tests were used for continuous variables. AEs were tabulated by grade, and between-arm differences in the time to first grade 3 AE were estimated using cumulative incidence and tested using the Gray test. EPIC domain change scores were calculated as baseline score subtracted from follow-up score. The between-arm difference of the 24-month EPIC bowel and urinary domain change scores were tested against the noninferiority margins of −6 and −5, respectively, using a *t* test. A mixed-effects repeated-measures model using restricted maximum-likelihood estimation incorporating all follow-up time points was conducted for each EPIC domain score, adjusting for baseline score, treatment arm, and pretreatment characteristics. A *t* test comparing the means between arms at 2 years was conducted within the context of the model that assumes data are missing at random.

For secondary time-to-event analyses, OS was measured from the date of randomization to the date of death from any cause. TTP was measured from the date of randomization to the date of the first occurrence of biochemical failure, LF, RF, DM, initiation of new unplanned anticancer treatment, or prostate cancer–specific survival. Patients not experiencing an event were censored at their last known follow-up time. TTP treated death not due to prostate cancer without failure as a competing risk and was estimated using cumulative incidence and compared between arms using the Gray test.[15] OS and FFBF were esti-

Figure 2. Time to First Occurrence of Grade 3 or Higher Adverse Events



No. of patients

COPORT	149	146	146	146	145	144	143	142	131	22	4
HYPORT	142	139	139	139	139	139	137	132	119	25	3

COPORT indicates conventionally fractionated postprostatectomy; HYPORT, hypofractionated postprostatectomy radiotherapy.

mated by the Kaplan-Meier method[16] and compared between arms with the log-rank test.[17] Statistical tests for between-arm differences were conducted only if at least 10 events were reported. All analyses were conducted on an intent-to-treat basis using SAS, version 9.4 (SAS Institute). All statistical tests used a 2-sided significance level of .05 except the primary end point, which used a 1-sided significance level of .025.

Results

Between June 2017 and reaching the target accrual in July 2018, a total of 296 patients were randomized from 93 institutions: 152 to COPORT and 144 to HYPORT (**Figure 1** and **Table 1**). The RT plans for all patients were centrally reviewed. RT target volumes were defined per protocol or with an acceptable variation in 142 patients (93%; 95% CI, 89%-97%) for COPORT and 131 (91%; 95% CI, 86%-96%) for HYPORT. Organs at risk were defined per protocol or with an acceptable variation in 147 patients (97%; 95% CI, 94%-100%) for COPORT and 140 (97%; 95% CI, 95%-100%) for HYPORT. Tumor dose-volume coverage was per protocol or with an acceptable variation in 143 patients (94%; 95% CI, 90%-98%) for COPORT and 135 (94%; 95% CI, 90%-98%) for HYPORT. Organs at risk dose-volume avoidance was per protocol or with an acceptable variation in 144 patients (95%; 95% CI, 92%-99%) for COPORT and 139 (97%; 95% CI, 94%-99%) for HYPORT.

There was no difference between arms in terms of grade 3 or higher AEs regardless of treatment attribution or related to treatment. In the COPORT arm, 25 patients (17%; 95% CI, 15%-19%) reported grade 3 AEs, and no grade 4 or 5 AEs were reported, regardless of attribution to treatment. In the HYPORT arm, 18 patients (13%; 95% CI, 12%-17%) reported grade 3 AEs, 2 (1%; 95% CI, 0%-3%) reported grade 4 AEs, and no grade 5 AEs were reported, regardless of attribution to treatment. Nine patients (6%; 95% CI, 2%-10%) in the COPORT arm and 13 (9%; 95% CI, 4%-14%) in the HYPORT arm reported grade 3 AEs related to treatment. No grade 4 or 5 AEs related to treatment were reported in either arm. There was no difference in the time to grade 3 or higher AEs between arms (hazard ratio [HR], 0.81; 95% CI, 0.45-1.46; $P = .52$; **Figure 2**). There were 6 patients (5%; 95% CI, 1%-9%) receiving HYPORT who experienced grade 3 cystitis (eTable 1 in Supplement 2). Only 1 of these 6 patients, however, reported urinary function overall as a big problem in the EPIC questionnaire at the time of the AE. The remaining 5 patients reported urinary function overall as a very small or small problem in the EPIC questionnaire at the time of the AE.

Compliance with EPIC was 100% at baseline, 83% (95% CI, 79%-87%) at the end of RT, 78% (95% CI, 73%-83%) at 6 months, 79% (95% CI, 74%-84%) at 12 months, and 83% (95% CI, 79%-87%) at 24 months (eTable 2 in Supplement 2). At the end of RT, patients in the HYPORT arm experienced statistically significant lower bowel change scores vs those in the COPORT arm (mean [SD], −15.52 [18.43] vs −7.06 [12.78]; $P < .001$). There were also statistically significant differences in both bowel subscale scores (eTable 3 in Supplement 2). This difference resolved, as there were not statistically significant differences between arms at 6 or 12 months (eTable 3 in Supplement 2). The between-arm difference in EPIC bowel and urinary domain change from baseline to 2 years was −2.76 (95% CI, −5.19 to −0.32) and −0.94 (95% CI, −4.68 to 2.80), respectively. Both bowel and urinary domain ranges did not reach the noninferiority margins of −6 and −5, respectively (**Table 2**). Urinary domain scores were similar between arms at baseline (**Figure 3**A), and there were no statistically significant differences in change from baseline to end of RT, 6 months, or 1 year. Similarly for the bowel domain, there was not a statistically significant difference between arms at baseline (Figure 3B). For the primary end point at 2 years, there were no observed between-arm differences, rejecting the null hypothesis of inferiority, and the mean (SD) change score for patients in the HYPORT arm vs those in the COPORT arm was less than −5 for the urinary domain (−5.01 [15.10] vs −4.07 [14.67], respectively; $P = .02$) and less than −6 for the bowel domain (−4.17 [10.97] vs −1.41 [8.32], respectively; $P = .005$).

The longitudinal model for the EPIC urinary domain showed no statistically significant difference for treatment arm or treatment × time interaction, indicating no overall treatment difference or difference across time. It did show that the baseline urinary domain score was associated with score in follow-up (mean [SE] difference, 0.69 [0.04]; $P < .001$) and a higher score for 6 months compared with end of RT (mean [SE] difference, 5.30 [1.29]; $P < .001$; eTable 4 in Supplement 2). The bowel domain score had statistically significant treatment arm differences in favor of the COPORT arm, time point differences in favor of the later time points, and time × treatment arm interactions in favor of HYPORT at the later time points (eTable 4 in Supplement 2). Higher baseline bowel scores were associated with higher scores in follow-up (estimate [SE], 0.59 [0.06]; $P = .60$).

Median (range) follow-up for all censored patients was 2.1 (0.0-3.0) years. Five deaths were reported (2 in the COPORT arm and 3 in the HYPORT arm), 4 patients experienced LF (3 in the COPORT arm and 1 in the HYPORT arm), and 5 patients experienced DM (2 in the COPORT arm and 3 in the HYPORT arm). There was no difference between arms for FFBF (HR,

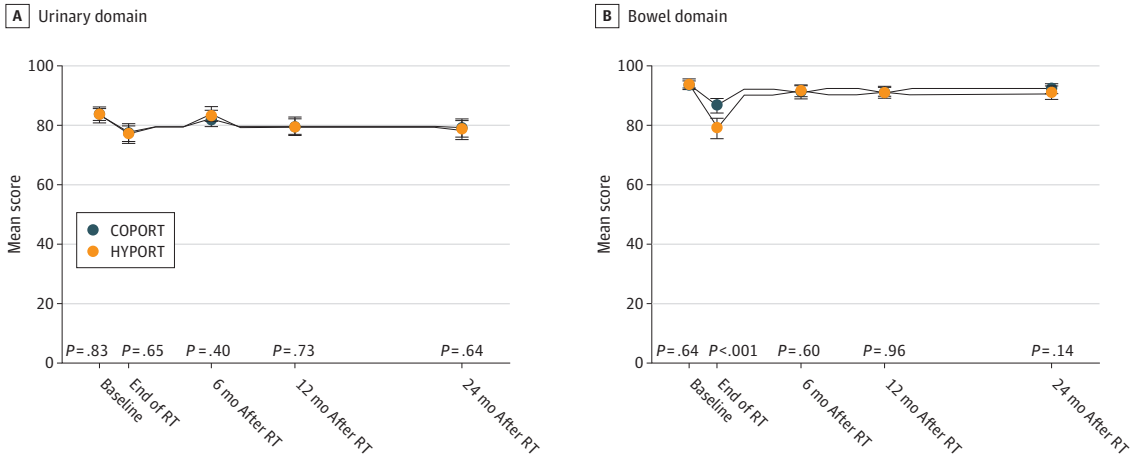
Table 2. Between-Arm Differences in Expanded Prostate Cancer Index Composite Domains

24-mo Change score	COPORT arm (n = 128)	HYPORT arm (n = 118)	*P* value[a]
Urinary domain			
Mean (SD)	−4.07 (14.67)	−5.01 (15.10)	.002
Median (range) [IQR]	−2.08 (−66.00 to 46.50) [−11.08 to 2.08]	−3.50 (−63.82 to 31.33) [−9.75 to 4.17]	
Bowel domain			
Mean (SD)	−1.41 (8.32)	−4.17 (10.97)	.02
Median (range) [IQR]	0.00 (−33.93 to 25.00) [−5.36 to 1.79]	−1.79 (−41.07 to 35.71) [−8.93 to 1.79]	

Abbreviations: COPORT, conventionally fractionated postprostatectomy; HYPORT, hypofractionated postprostatectomy radiotherapy.

[a] *P* value from 1-sided *t* test with pooled variances for tests of H_O: $\mu_{HYPORT} - \mu_{COPORT} > -5$ for urinary and H_O: $\mu_{HYPORT} - \mu_{COPORT} > -6$ for bowel.

Figure 3. Expanded Prostate Cancer Index Composite Domain Scores Across Time



Error bars indicate SD. COPORT indicates conventionally fractionated postprostatectomy; HYPORT, hypofractionated postprostatectomy radiotherapy; RT, radiotherapy.

1.48; 95% CI, 0.73-3.02; *P* = .28; eFigure 1 in Supplement 2). Similarly, there were no between-arm differences for TTP (HR, 0.98; 95% CI, 0.54-1.78; *P* = .96; eFigure 2 in Supplement 2). Of the 21 patients who had further salvage treatment after radiation therapy, 13 were in the COPORT arm and 8 in the HYPORT arm, and there was not a statistically significant difference between arms (HR, 0.69; 95% CI, 0.28-1.67; *P* = .41).

Discussion

This trial showed that patient-reported GU and GI symptoms at 2 years from the completion of RT were not significantly greater when hypofractionation was used compared with conventional fractionation. It was not surprising to observe low-grade acute GI adverse effects on the completion of either COPORT or HYPORT. This is typical of prostate RT, and it is well established that the rectum is the dose-limiting organ at risk. The important observation to note is that GU and GI function in both arms recovered to pretreatment levels. The GI change scores at 6 months (compared with baseline) for COPORT and HYPORT were neither clinically significant nor different in statistical significance.

Postprostatectomy RT is a well-established, potentially curative practice standard.[18] Recent studies have indicated that early detection and treatment of biochemical recurrence based on a measurable and rising PSA level is the preferred indication for postprostatectomy RT for patients with Gleason score 6 or 7 prostate cancer.[4-6] This approach reduces the burden of prostate cancer by prescribing treatment to only patients who benefit without compromising treatment success compared with adjuvant therapy. It is estimated that 5-year FFBF rates for men receiving RT for a PSA of 0.5 ng/mL or lower is approximately 70%.[4,5,19] However, postprostatectomy RT has been poorly utilized, with between 5% and 15% of patients receiving it when indicated.[20-22] Hypofractionation lowers barriers to treatment for patients and increases access to treatment.

The effectiveness of postprostatectomy RT can be improved with the addition of ADT and further still with pelvic lymph node RT. The 5-year FFBF rate from the NRG Oncology/RTOG 0534 SPPORT trial for men receiving prostate fossa RT with the addition of ADT was 83% and with the addition of both ADT and pelvic lymph node RT was 89% compared with 71% for prostate fossa RT alone.[23] There was no difference between the 3 approaches in late grade 3 or higher GU or GI events. The present study permitted the use of ADT but not lymph node RT. HYPORT easily allows for the incorporation of simultaneous treatment of the pelvic lymph node region. A radiation dose of 45 Gy or 50 Gy are well-accepted standards, and more than 25 fractions equates to conventional fractions sizes of 1.8 Gy or 2.0 Gy per fraction. Assuming appropriate strati-

fication and adherence to the rectal dose constraints, having incorporated the pelvic lymph nodes would unlikely alter the results and conclusions of this study.

Regarding adoption of HYPORT, the rapid accrual and completion of this trial is also an indicator of the enthusiasm for the adoption of HYPORT. Rogers describes 5 elements that are important for adoption: (1) relative advantage, (2) compatibility, (3) complexity, (4) trialability, and (5) observability to health care professionals.[24] As described herein, the relative advantages of hypofractionation include improved productivity of equipment and staff and improved capacity for all patients. HYPORT is compatible with physicians' existing values of reducing the burden of prostate cancer for patients and increasing access to potentially curative treatment. HYPORT is no more complex than COPORT, as demonstrated by the successful conduction of this study and low treatment planning variation rate. Adhering to the technical guidance provided herein will allow physicians to trial and observe with expectations provided by these results. As for future trialability and observability, one would not expect a reversal of the superimposable toxic effects and cancer control outcomes based on a wealth of existing literature. For example, a meta-analysis of 29 randomized trials (n = 18 069) with a median follow-up of 6 years demonstrated no evidence of an increase in the relative risk of any grade of GU or GI toxic effects following RT with follow-up beyond 3 years.[25] Additionally, 3 randomized trials (n = 5514) have demonstrated noninferiority of hypofractionation for intact prostate cancer.[26-28]

Limitations

The primary end point is based on patient-reported questionnaires, and incomplete reporting of data may underreport toxic effects. In this study, there was 83% compliance at 2 years with the bowel and urinary domains of EPIC. Longer follow-up could demonstrate a difference in cancer control if one exists, although the small sample size of the trial limits the statistical power for this analysis. Additionally, the magnitude of GI toxic effects may not be directly applicable when the pelvic lymph nodes are incorporated.

Conclusions

In this phase 3 randomized clinical trial, HYPORT was associated with greater patient-reported GI toxic effects compared with COPORT at the completion of RT, but both groups recovered to baseline levels within 6 months. At 2 years, HYPORT was noninferior to COPORT in terms of patient-reported GU or GI toxic effects. HYPORT is a new acceptable practice standard for patients receiving postprostatectomy RT.

ARTICLE INFORMATION

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Correction: This article was corrected on April 18, 2024, to fix an error in the y-axis of Figure 2.

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Data Sharing Statement: See Supplement 3.

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Invited Commentary

Hypofractionation for Postprostatectomy Radiotherapy

Julia R. Murray, PhD

Hypofractionation for prostate radiotherapy is well established, with international guidelines supporting the use of moderately hypofractionated radiotherapy for patients who choose external beam radiotherapy for treatment of prostate cancer.[1]

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Hypofractionated radiotherapy enables better convenience for patients and cost benefits and, in comparison with conventional fractionation, has similar cancer-related outcomes and late gastrointestinal (GI) and genitourinary (GU) adverse effects.[2] Long-term data regarding the effect on quality of life with moderate hypofractionation shows similar prevalence of overall bowel, urinary, and sexual problems compared with conventional fractionation. Additionally, patient-reported outcomes for bowel and urinary problems showed little change between 6 months and 5 years.[3]

The first trial results for moderate hypofractionated prostate radiotherapy were reported more than a decade ago, with technological advancements for postprostatectomy radiotherapy being more gradual. The timing for postprostatectomy radiotherapy has been investigated, with a meta-analysis including 3 randomized trials (RADICALS, GETUG-AFU 17, and RAVES) showing that early salvage radiotherapy is currently the preferable management strategy.[4] Within the