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Quality of life results from NRG-GU005: A Phase III Trial of SBRT vs. Hypofractionated IMRT for Localized Intermediate Risk Prostate Cancer

ASTRO Annual Meeting
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Study Rationale

- Moderately Hypofractionated IMRT (MH-IMRT) for the treatment of prostate cancer is considered standard of care since the publication of RTOG 0415 and other studies
- At the time of study design, ultrahypofractionated radiation for the treatment of prostate cancer (“SBRT”), had not been compared to MH-IMRT, and concerns existed regarding toxicity
- For intermediate risk prostate cancer, quality of life is as important as clinical outcomes
- Prior individual patient meta-analysis¹ suggested patients who underwent SBRT had ~~less fewer incidences of~~ clinically significant decline in patient reported outcomes in the bowel and urinary irritative/obstructive domains 2 years post-treatment
- ***Co-primary outcomes of Disease-Free Survival and primary patient reported outcomes will be presented tomorrow at the Plenary Session!!***

¹Johnson SB, et al. Radiother Oncol. 2016; 121: 294-298.

Study Design: NRG GU005 Randomized Phase III Trial

N=698 intermediate-risk prostate cancer patients (accrued 11/2017 to 6/2022)

S T R A T I F Y	<u>Risk Group</u>	R A N D O M I Z E	<u>Arm 1: IMRT</u>
	<u>Use of Rectal Manipulation</u>		<u>Arm 2: SBRT</u>
	<p>1. Gleason score 7(3+4) with PSA <10 ng/mL</p> <p>2. Gleason score 7(3+4) with 10 ng/mL ≤ PSA < 20 ng/mL</p> <p>3. Gleason score 6(3+3) with 10 ng/mL < PSA < 20 ng/mL</p> <p>1. No</p> <p>2. Rectal balloon</p> <p>3. SpaceOAR</p> <p>4. SpaceOAR and rectal balloon</p> <p>IMRT Standard Arm</p> <p>1) 70 Gy in 28 fractions</p> <p>2) 60 Gy in 20 fractions</p>		<p>70 Gy in 28 fractions of 2.5 Gy to the prostate or 60 Gy in 20 fractions of 3 Gy +/- proximal 1cm of seminal vesicles</p> <p>Minimal Margins: 8 mm uniform in expansion, 5 mm posteriorly</p> <p>36.25 Gy in 5 fractions of 7.25 Gy to the prostate +/- proximal 1 cm of seminal vesicles</p> <p>Minimal Margins: 5 mm superior inferior & laterally, 3 mm anterior & posterior</p>

Radiotherapy Details

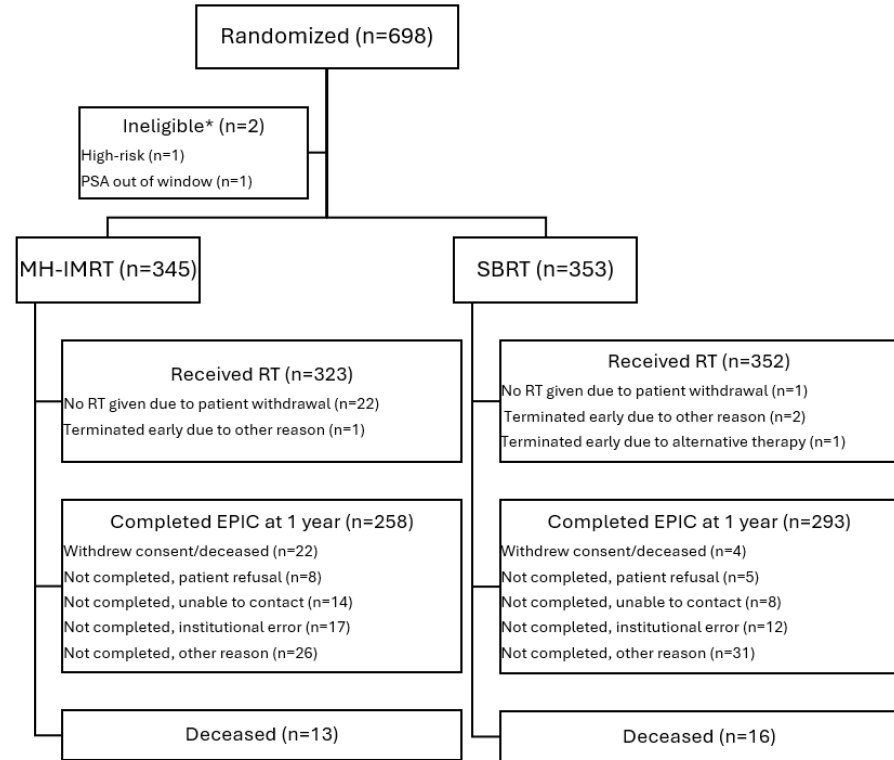
- CTV included prostate \pm 1cm of the proximal seminal vesicles at the discretion of the treating physician
- MH-IMRT included 70 Gy in 28 fractions or 60 Gy in 20 fractions
 - CTV→PTV expansion 8 mm all directions except posteriorly where 5mm allowed
- SBRT 36.25 Gy in 5 fractions, delivered 2-3 fractions per week
 - CTV→PTV expansion 5 mm all directions except posteriorly and anteriorly where 3mm allowed
 - **Maximum dose to PTV without urethral visualization was 38.78 Gy**
 - Maximum dose to 0.03cc and 50% of bladder was 39 Gy and 15 Gy, respectively
 - When maximum dose exceeded 38.78 Gy, urethral visualization and contouring was required and acceptable variation from protocol was 43.5 Gy

Patient Characteristics

- No significant differences in baseline characteristics or demographics

Patient Characteristics			
Patient Characteristic	IMRT (n=345)	SBRT (n=353)	Total (n=698)
Age			
Median	68	69	68
Min - Max	42 - 83	45 - 84	42 - 84
Q1 - Q3	64 - 73	63 - 73	64 - 73
Rectal manipulation**			
None	146 (42%)	138 (39%)	284 (41%)
Rectal balloon	3 (1%)	2 (1%)	5 (1%)
SpaceOAR	188 (54.%)	198 (56%)	386 (55%)
SpaceOAR and rectal balloon	8 (2%)	15 (4%)	23 (3%)

**Stratification factor



*All randomized patients were analyzed under intent-to-treat



Statistical Plan

- Patient reported outcomes:
 - The frequency of a Minimal Clinically Important Difference (MCID) at 1 and at 2 years compared to baseline
 - Compared to group mean score, individual MCID more sensitive to treatment-related differences
 - Compares individual post-treatment quality of life to baseline
- Exploratory longitudinal analysis
 - Analysis conducted separately for each domain score using longitudinal linear modeling methods,
 - Adjusted for baseline domain score, treatment arm, stratification factors (risk group utilizing Gleason score and PSA, rectal manipulation), T-stage, age, and race.

EPIC-26 Survey

- Expanded Prostate Cancer Index Composite – 26 Questions

Domain	Minimal Clinically Important Difference (from baseline)*	1 year post treatment	2 year post treatment
Bowel	≥ 4 points	Secondary Endpoint	Primary Endpoint**
Urinary Irritative/Obstructive	≥ 5 points	Secondary Endpoint	Primary Endpoint**
Urinary Incontinence	≥ 6 points	Secondary Endpoint	Secondary Endpoint
Sexual	≥ 10 points	Secondary Endpoint	Secondary Endpoint
Hormonal	≥ 4 points	Secondary Endpoint	Secondary Endpoint

*Skolarus TA et al.; PROSTQA Consortium. Urology. 2015;85:101-5.

**Reporting at Plenary Session

Secondary Patient Reported Outcome
Endpoints:

Results

Compliance was excellent and baseline scores were similar between treatment arms

EPIC Compliance

	IMRT (n=345)	SBRT (n=353)	Total (n=698)
Patient died/withdrew prior to timepoint			
No	323 (93.6%)	349 (98.9%)	672 (96.3%)
Yes	22 (6.4%)	4 (1.1%)	26 (3.7%)
EPIC Completion - Year 1	(n=323)	(n=349)	(n=672)
Completed	258 (79.9%)	293 (84.0%)	551 (82.0%)
EPIC Completion – Year 2	(n=315)	(n=342)	(n=657)
Completed	260 (82.5%)	291 (85.1%)	551 (83.9%)

Baseline EPIC Scores

	IMRT (n=345)	SBRT (n=353)	p-value*
Bowel domain			0.69
Mean	96.3	96.0	
Q1 - Q3	95.8 - 100.0	95.8 - 100.0	
Urinary irritation domain			0.78
Mean	89.4	89.7	
Q1 - Q3	81.3 - 100.0	81.3 - 100.0	
Urinary incontinence domain			0.66
Mean	91.6	92.0	
Q1 - Q3	85.5 - 100.0	87.5 - 100.0	
Sexual domain			0.86
Mean	58.6	58.2	
Q1 - Q3	34.7 - 83.3	34.7 - 83.3	
Hormonal domain			0.093
Mean	92.0	93.5	
Q1 - Q3	90.0 - 100.0	90.0 - 100.0	

*p-values from t-test

Secondary Patient Reported Outcomes 1-year post-treatment

EPIC Meaningful Important Difference at Year 1

	IMRT (n=345)	SBRT (n=353)	p-value*
Bowel domain			0.002
≥ 4 point decline from baseline	117 (46%)	98 (33%)	
Urinary irritation domain			0.77
≥ 5 point decline from baseline	94 (37%)	105 (36%)	
Urinary incontinence domain			0.054
≥ 6 point decline from baseline	87 (34%)	80 (27%)	
Sexual domain			0.03
≥ 10 point decline from baseline	107 (44%)	94 (34%)	
Hormonal domain			0.09
≥ 4 point decline from baseline	82 (33%)	73 (26%)	

*p-values from two-sided chi-square test

← Favors SBRT

← Favors SBRT

Secondary Patient Reported Outcomes 2 years post-treatment

EPIC Meaningful Important Difference at Year 2

	IMRT (n=345)	SBRT (n=353)	p-value*
Bowel domain ≥ 4 point decline from baseline			
Urinary irritation domain ≥ 5 point decline from baseline			
Urinary incontinence domain ≥ 6 point decline from baseline	90 (35%)	75 (26%)	0.02
Sexual domain ≥ 10 point decline from baseline	102 (41%)	116 (43%)	0.67
Hormonal domain ≥ 4 point decline from baseline	82 (32%)	84 (30%)	0.65

*p-values from two-sided chi-square test

Primary Endpoint:
reporting at Plenary
Session

← Favors SBRT

Longitudinal Model: Urinary Incontinence

Longitudinal Model of EPIC: Urinary Incontinence Domain

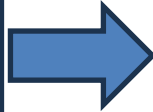
Parameter	Referent	Estimate	95% CI	p-value
Intercept		40.6424	(33.5837, 47.7010)	<0.0001
Baseline EPIC Urinary Incontinence		0.5173	(0.4426, 0.5919)	<0.0001
Treatment arm	IMRT	2.9076	(0.8473, 4.9678)	0.0058
Timepoint	Year 1	-0.4488	(-1.8894, 0.9917)	0.54
Risk group - Gleason 7 and 10 \geq PSA < 20	Gleason 7 and PSA < 10	-0.6780	(-3.2004, 1.8444)	0.60
Risk group - Gleason 6 and 10 < PSA < 20	Gleason 7 and PSA < 10	3.8745	(-0.7280, 8.4770)	0.099
Rectal manipulation	Rectal balloon and/or SpaceOAR	-0.7668	(-2.8509, 1.3173)	0.47
Ethnicity	Not Hispanic or Latino	-1.0062	(-5.3911, 3.3787)	0.65

Longitudinal analysis of the urinary incontinence domain showed significant treatment effect **in favor of SBRT** (least square mean difference=2.91, 95% confidence interval: 0.85-4.97, p=0.0058)

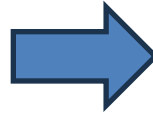
No treatment effect seen for sexual and hormonal domains. Baseline function significantly associated with higher subsequent domain scores. Longitudinal analysis of bowel and urinary irritative/obstructive domains reported later at plenary session

Investigator Reported Toxicity – Attributed to Treatment

More treatment-related grade 3 genitourinary adverse events occurred in the MH-IMRT arm as compared to the SBRT arm



More patients on the MH-IMRT arm as compared to the SBRT reported toxicity (of any grade) for rectal hemorrhage and fatigue



Protocol-Specified Adverse Event Analyses*			
	IMRT (n=323)	SBRT (n=352)	p-value**
Treatment-related GU† toxicity Grade ≥3	8 (2.5%)	2 (0.6%)	0.04
Treatment-related GI toxicity Grade ≥3	7 (2.2%)	3 (0.9%)	NS
Hematuria Grade ≥3	4 (1.2%)	2 (0.6%)	NS
Rectal hemorrhage Grade ≥3 Any Grade**	5 (1.5%) 56 (17.3%)	2 (0.6%) 37 (10.5%)	NS 0.01
Fatigue Any Grade**	164 (50.8%)	138 (39.2%)	0.0025

*23 patients received no study treatment and are not included in adverse event tables


** p-values from Chi-square test

***No grade 3 fatigue reported

† Corresponds to the CTCAE v5 Renal and Urinary Disorders SOC



Summary of Key Findings

- Significantly fewer SBRT patients compared to MH-IMRT patients experienced MCID in **sexual and bowel** health-related quality of life at 1 year, and **urinary incontinence** at 2 years post-treatment
 - Longitudinal analysis also favored SBRT over MH-IMRT in terms of patient reported urinary incontinence-related quality of life
 - SBRT very safe for the treatment of intermediate risk prostate cancer and associated with low rates of investigator reported toxicity
- 

Context: Comparison to PACE-B

2 year MCID frequency

Domain	PACE-B ¹ CRT	PACE-B ¹ SBRT	P	NRG GU005 MH-IMRT	NRG GU005 SBRT	P
Urinary incontinence*	23%	32%	0.011	35%	26%	0.02
Bowel*	34%	24%	0.0076	Primary Endpoint: reporting at Plenary Session		

- Urinary incontinence related quality of life outcomes are the opposite of PACE-B
- Is there more GU toxicity with SBRT or less?
 - Perhaps it depends on urethral dose² (or, as a surrogate for urethral dose, intraprostatic dose maximum?)
 - PACE-B Dmax <48 Gy for gantry based SBRT, but up to 48-55.7 Gy depending urethra contoured;
 - NRG GU005 <38.78 Gy to Urethra per protocol – variation up to 43.5 acceptable

*Slightly different definitions used: PACE-B ≥ 8 vs. NRG GU005 ≥ 6 for urinary incontinence, PACE-B ≥ 5 for bowel vs. NRG GU005 ≥ 4 for bowel

¹van As et al. NEJM. 2024; 391: 1413-1425.

²Repka et al. Frontiers in Radiation Oncology. 2016

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1975-2024

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