

NRG Oncology Clinical Protocols for Prostate Stereotactic Body Radiation: Questions and Issues

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**COMPREHENSIVE
CANCER CENTER**



Outline

- **Status of Ultra-Hypofractionated Stereotactic Ablative (Body) Radiotherapy (SBRT) for the treatment of localized prostate cancer**
 - Scientific rationale and practical benefits
 - Radiation dose and SBRT fractionation schedule
 - Tumor control and acute and late toxicity results
- **What is next?**

Phase III SBRT prostate cancer trials

 - HYPO-RT-PC
 - PACE-B
 - NRG Oncology GU005



Ultra - Hypofractionated Radiotherapy

Stereotactic Ablative

What is stereotactic ablative (body) radiotherapy for prostate cancer?

- Tumor fully encompassed
- High (>5Gy) fractional dose: 1–5 fractions = entire course, ≠ boost
- Reliable immobilization & re-positioning
- Image-guided, highly precise (high conformality) – fiducial or volumetric
- Small planning margins-2mm-5mm
- Appropriate for low- & intermediate-risk in select facilities, ideally on trial – ASTRO, ACR, NCCN

ASTRO Model Policy 2013; PL Nguyen Am J Clin Oncol 2014; JL Mohler J Natl Compr Cancer Net 2017; SC Morgan Int J Radiat Oncol Biol Phys 2018

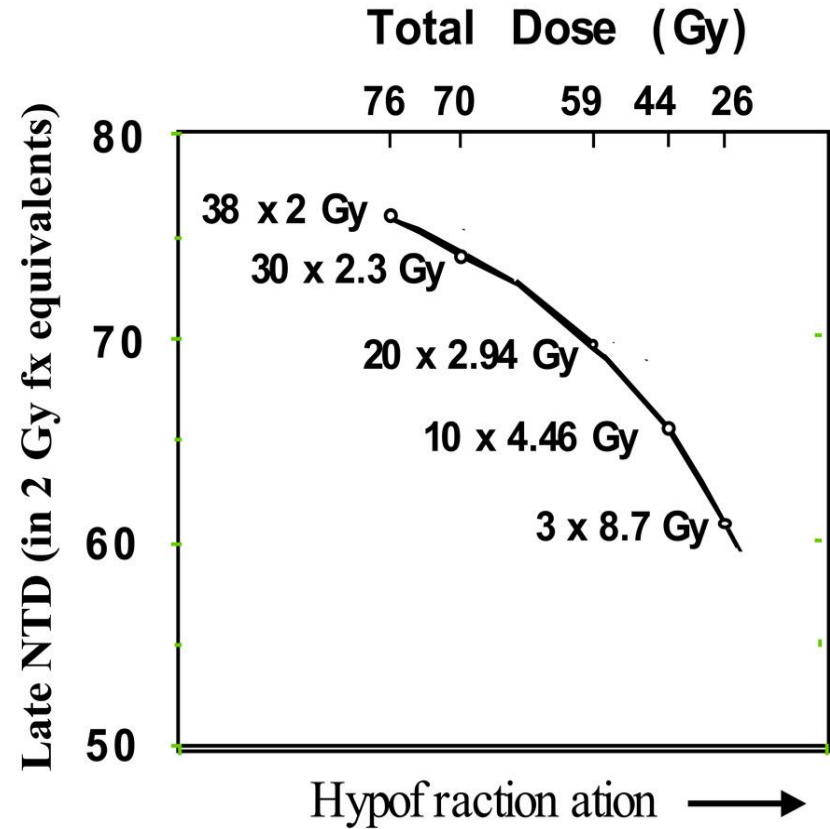
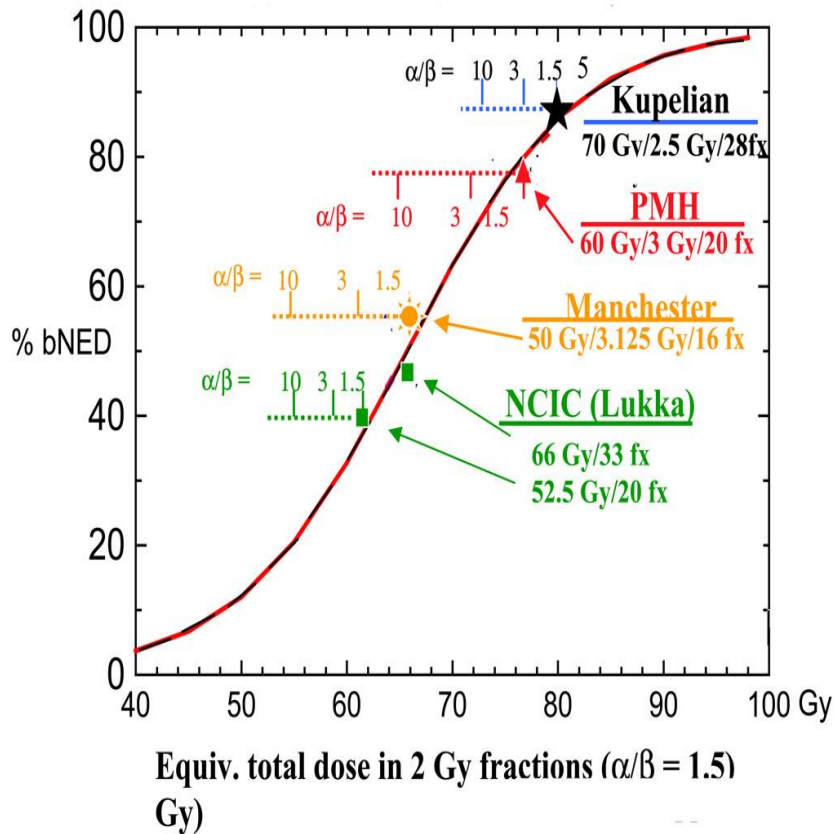
RATIONALE for SBRT

- **Biology of prostate cancer cells (alpha/beta<2.0) favors Ultra-Hypofractionation**
- **Potential to improve therapeutic window**
 - Higher local control
 - Reduced toxicity
 - Better QOL
- **Shorter treatment course**
 - Greater access for men in remote areas
- **Lower cost**



RATIONALE

Improvement of Therapeutic Ratio with Ultra-Hypofractionation (Not all Grays are the Same)



EXCLUSIVE



Lineker:
Gazza, Elton
...and the old
woman who
attacked me

FREE INSIDE
Champions League pullout



BACK OF THE NET Gary Lineker
SEE PAGES 145/15



PROSTATE CANCER CURED IN ONE WEEK

By **MARTIN BAGOT** Health & Science Editor
PROSTATE cancer patients could be cured in as little as a week with new high-dose targeted radiotherapy.
In trials, tumours were wiped out within days with treatment times slashed from the standard one to two months.
The breakthrough could save the NHS millions. It comes after Sir Rod Stewart revealed he has beaten the disease.
One patient who took part in trials said: "It was a breeze - not something I'd
TURN TO PAGES 465



HOPE New treatment revealed after Rod, left, said he has beat disease

Radiotherapy breakthrough as trials show high dosage clears tumours in days

SBRT for Prostate Cancer

Cost

- **5 fractions vs. > 40 fractions**
- **In US: SBRT \$20, 571**
vs. IMRT \$36, 837
cheaper for payor
- **In proposed CMS APM the reimbursement will be the same**



Ultra - Hypofractionated Radiotherapy

Stereotactic Selection Criteria

Largely derived from brachytherapy guidelines

- **Low-risk or intermediate-risk**
- **Prostate volume <75 cc**
- **AUA symptom index ≤ 15**
 - **No obstructive, intravesicular median lobe**
 - **If borderline, urodynamic study \pm cystoscopy**
- **Relative restrictions**
 - **Ulcerative colitis, connective tissue disorder, chronic anorectal disorder, anti-coagulants, \pm hip arthroplasty**
 - **Prior TURP, cryoablation, HIFU, radiotherapy**



5-Year Outcomes of a Phase 1 Dose Escalation Study Using Stereotactic Body Radiosurgery for Patients with Clinically Localized Prostate Cancer



M.J. Zelefsky,¹ M.A. Kollmeier,¹ S. McBride,¹ X. Pei,¹ L. Happersett,¹ M. Lin,² and B.W. Cox³; ¹Memorial Sloan Kettering Cancer Center, New York, NY, ²Memorial Sloan Kettering Cancer Center, New York, NY, ³Department of Radiation Medicine, Northwell Health, Lake Success, NY

- **Phase I dose escalation study**
- **Low and intermediate risk prostate cancer**
- **RT doses : 32.5 , 35 , 37.5 , 40 Gy in 5 fxs**
 - **Late grade 2 GU 23%, 26%, 28%, 31%**
 - **Late grade 3 GU: only in 1 pt in 40 Gy with h/o of TURP**
 - **Late grade 2-4 GI: none**
 - **Acute grade 2 GI: 0%, 3%, 3%, 11%**
 - **Acute grade 2 GU: 18%, 23%, 8%, 17%**
 - **Acute grade 3-4 GU or GI: none**
- **5-yr PSA BCF 15%, 6%, 0%, 0%**
- **2-yr positive biopsy 48%, 19%, 18%, 8%**

SBRT doses up to 40 Gy were tolerated
Higher doses led to better bRFS



Patient Reported Outcomes in NRG Oncology RTOG 0938, Evaluating Two Ultrahypofractionated Regimens for Prostate Cancer.

Lukka HR¹, Puqh SL², Bruner DW³, Bahary JP⁴, Lawton CAF⁵, Efstathiou JA⁶, Kudchadker RJ⁷, Ponsky LE⁸, Seaward SA⁹, Daves IS¹⁰, Gopaul DD¹¹, Michalski JM¹², Delouya G⁴, Kaplan ID¹³, Horwitz EM¹⁴, Roach M 3rd¹⁵, Pinover WH¹⁶, Beyer DC¹⁷, Amanie JO¹⁸, Sandler HM¹⁹, Kachnic LA²⁰.

- **NRG Oncology RTOG 0938**
- **Randomized Phase II, non-blinded randomized study**
- **Low risk**
- **Randomized**
 - 36.25 in 5 fxs vs. 51.6 in 12 fxs
 - Primary endpoint EPIC QOL
- **Results:**
 - 1-yr EPIC GI >5 points change 30% vs 28%
 - 1-yr EPIC GU >2 points change 46% vs 42%
 - 1-yr EPIC sexual >11 points change 33% vs 31%
 - 2-yr DFS 99% v 98%



Ultra - Hypofractionated Radiotherapy

A Systematic Review and Meta-Analysis

- **Thirty-eight prospective series (22 clinical trials) with ≥ 20 pts/report ≈ 6116 patients**
- **Median f/u = 39 months (range, 12 to 115 months)**
- **Four – 9 fractions of 5.0-10.0Gy (med= 7.25 Gy) = 32.0-50.0Gy (45-50Gy dose-escalation trials)**
 - **Most common = 7.0-7.5Gy x 5 QoD**
- **CTV = prostate \pm proximal 1-2 cm SV**
- **PTV = CTV + 0.2-0.5 cm (0.2-0.3 cm post.)**
- **Organs at risk: bladder, rectum, \pm bulb, \pm urethra, \pm bowel space, \pm femoral head**
- **5-year bDFS=95.1% and less than 2% Grade III GI or GU late toxicity**

Jackson, et al, Int J Radiation Oncology Biol Phys, 104 (4), 778-789, 2019



Phase II SBRT Trials for Localized CAP

Author (Pub Year)	N	Med F/u (Yrs)	RT Dose (Gy)	BED (Gy) $\alpha/\beta=2$	*5 year bDFS 2 year bDFS	Early G3 Toxicities		Late G3 Toxicities		Erectile Dysfunction
						GU	GI	GU	GI	
Mantz (2014)	102	>5	40 / 5	200	100%*	2%	0%	NR	0%	NR
Hannan (2016)	91	4.5	45-50/ 5	247-300	99%*	0%	2%	5%	7%	26%
Musunuru (2016)	84	6.2	35 / 5	157	97%*	1%	0%	0%	1%	43%
Zimmerman (2016)	80	6.9	45 / 9	157	96%*	NR	NR	4%	13%	NR
Lukka (2018)	121	3.8	36.25 / 5	167	99.2%	1%	1%	1%	1%	NR
	125	3.8	51.6 / 12	162.5	97.2%	0%	2%	1%	1%	NR
Meier (2018)	309	5	40 / 5	200	97.1%*	0%	0%	0%	0%	NR
Jackson (2019)	6116	3.25	35-50/5-9	150-300	95.3%*	0%	0%	2 %	1.1%	3 year reduction

Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial

Prof Anders Widmark, MD   • Adalsteinn Gunnlaugsson, MD • Lars Beckman, MD •

Camilla Thellenberg-Karlsson, MD • Prof Morten Hoyer, MD • Magnus Lagerlund, MD • et al. [Show all authors](#)

Published: June 18, 2019 • DOI: [https://doi.org/10.1016/S0140-6736\(19\)31131-6](https://doi.org/10.1016/S0140-6736(19)31131-6) •



- **Phase III, Non-inferiority trial**
- **1200 pts, int risk (89%) (T1c-T3a, PSA <20, with one or two of the following risk factors: T3a or Gleason 7 or PSA >10), high risk (11%)**
- **No ADT allowed**
- **Randomize:**
 - **78 Gy in 39 fxs (2Gy)**
 - **42.7 Gy in 7 fxs (6.1Gy) q3d**
 - **Used fiducials, 7mm PTV margin, V90% <15% for rectum, 80% 3D, 20% VMAT**
- **Results:**
 - **Median follow up 5 years**
 - **Weak evidence (p=.057) of grade 2+ GU toxicity higher in ultra-hypofx 95%) at end of RT.**
 - **1 yr post-RT, 4% increased grade 2+ GU toxicity in ultra-hypofx (p=0.0037)**
 - **5-yr FFS 84% in both arms**
 - **5-yr late grade 2+ GU 5%; 5-yr late grade 2+ GI 1% vs 4%, p=0.14**

Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial



Douglas H Brand, Alison C Tree*, Peter Ostler, Hans van der Voet, Andrew Loblaw, William Chu, Daniel Ford, Shaun Tolan, Suneil Jain, Alexander Martin, John Staffurth, Philip Camilleri, Kiran Kancharla, John Frew, Andrew Chan, Ian S Dayes, Daniel Henderson, Stephanie Brown, Clare Cruickshank, Stephanie Burnett, Aileen Duffton, Clare Griffin, Victoria Hinder, Kirsty Morrison, Olivia Naismith, Emma Hall, Nicholas van As, on behalf of the PACE Trial Investigators*



- **Multicenter, phase 3, open-label, randomized, trial to assess non-inferiority of SBRT compared w/conventionally fractionated or mod hypofx RT for biochemical or clinical failure**
- **874 men randomized to conventionally fractionated (78 Gy/39 fx) or moderately hypofractionated (62 Gy/20 fx) [n=441] or SBRT (36.25 Gy/5 fx) [n=433]**
- **Low and intermediate risk (T1-T2, Gleason \leq 3-4, PSA \leq 20 mg/ml, not willing or suitable for prostatectomy**
- **No ADT allowed**
- **Grade \geq 2 GI toxicity: 12% in conventional vs. 10% in SBRT (p=.038)**
- **Grade \geq 2 GU toxicity: 27% in conventional vs 23% in SBRT (p=.16)**
- **Suggests no difference in acute toxicity. Ongoing studies for late toxicity**

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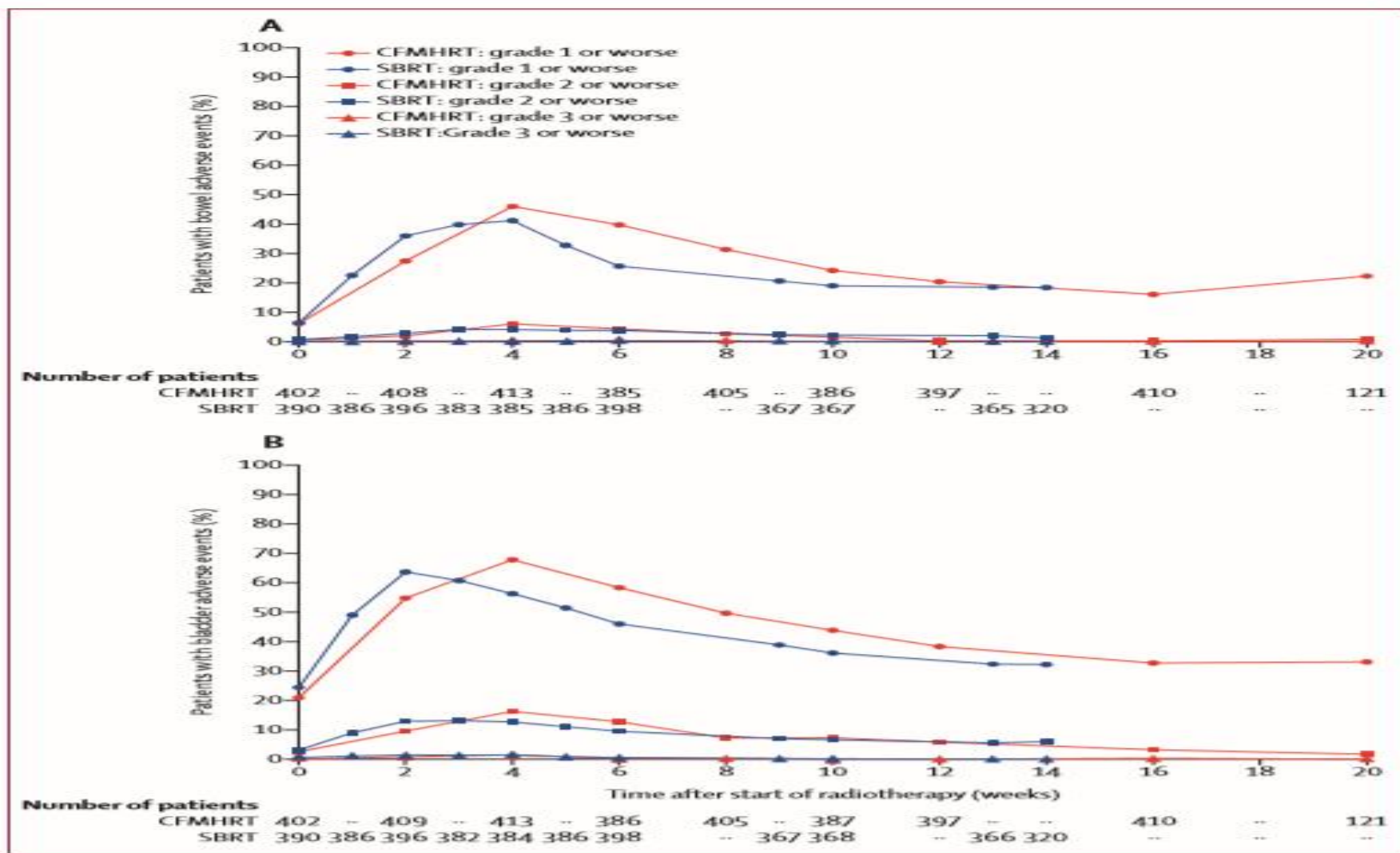


Figure 2: Acute Radiation Therapy Oncology Group toxicity for gastrointestinal (A) and genitourinary (B) systems



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NRG-GU005

**Phase III IGRT and SBRT vs IGRT and
Ultra-Hypofractionated IMRT for
Localized Intermediate Risk Prostate
Cancer**

NRG Oncology GU005

Schema

S T R A T I F Y	<p style="text-align: center;"><u>Risk Group</u></p> <ol style="list-style-type: none">1. Gleason score 7(3+4) with PSA <10 ng/mL2. Gleason score 7(3+4) with 10 ng/mL <= PSA < 20 ng/mL3. Gleason score 6(3+3) with 10 ng/mL < PSA < 20 ng/mL	R A N D O M I Z E	<p style="text-align: center;"><u>Arm 1: IMRT</u></p> <p>70 Gy in 28 fractions of 2.5 Gy to the prostate +/- proximal 1cm of seminal vesicles</p> <p style="text-align: center;">Minimal Margins: 8 mm uniform in expansion, 5 mm posteriorly</p>
	<p style="text-align: center;"><u>Use of Rectal Manipulation</u></p> <ol style="list-style-type: none">1. No2. Rectal balloon3. SpaceOAR4. SpaceOAR and rectal balloon		<p style="text-align: center;"><u>Arm 2: SBRT</u></p> <p>36.25 Gy in 5 fractions of 7.25 Gy to the prostate +/- proximal 1 cm of seminal vesicles</p> <p style="text-align: center;">Minimal Margins: 5 mm superior inferior & laterally, 3 mm anterior & posterior</p>

NRG-GU005

PRIMARY OBJECTIVE

- **To determine if SBRT is superior to Ultra-Hypofractionated IMRT in terms of minimal important decline (MID) in urinary irritation/obstructive and bowel HRQOL as measured by EPIC-26 at 24 months post completion of therapy**
- **To determine if SBRT (5 fractions of 7.25 Gy) is superior to Ultra-Hypofractionated IMRT (28 fractions of 2.5 Gy) as measured by Disease Free Survival (DFS)**

SBRT for Prostate: Radiation Dose Constraints

Organ At Risk	PACE B	NRG GU005
Rectum	V18.1 Gy < 50% V29 Gy < 20% V36 Gy < 1 cc	V18.12 Gy < 50% V29 Gy < 20% V32.63 Gy < 10% V34.4 Gy < 3 cc
Bladder	V18.1 Gy < 40% V37 Gy < 10cc (optimal V37 Gy < 5cc)	V18.12 < 10% V38.06 Gy < 0.03 cc
Urethra	V42 Gy < 50%	V38.78 Gy < 0.03 cc
Femoral head	V41.5 Gy < 5%	V19.9 Gy < 10cc V15.6 Gy < 1 cc
Penile bulb	V29.5 Gy < 50%	V19.9 Gy < 3 cc
Bowel	V18.1 Gy < 5 cc	

Phase III SBRT Trials for Localized CAP

Trial	N	Eligibility	RT Dose (Gy)	BED $\alpha/\beta=2$ (Gy)	Primary Endpoint	Secondary Endpoint
PACE B	874	T1c-T2c, GS \leq 3+4, PSA \leq 20	78 in 39 Fx	156	BF and PFS	OS, PCSS, CRO-acute
		MRI Staged No ADT	36.25 in 5 Fx	167		CRO-late PROs ADT
NRG GU 005	622	GS 6 and PSA 10-20 or GS 7(3+4) and PSA <20 IPSS < 15	70 in 28 Fx	157	24 mo HRQOL DFS	12 mo HRQOL BF, LF, OS
		Charlson score \leq3 if \leq 60 and \leq4 if >60	36.25 in 5 Fx	167		MRI Biopsy

Ultra - Hypofractionated Radiotherapy SBRT

Conclusions & Guidelines

American Society for Radiation Oncology

American Society of Clinical Oncology
and American Urological Association

- **Standard = 36.25 - 38.0Gy in five fractions for selected patients, planned with specified dose constraints, trial enrollment highly preferred**
- **Gantry or robotic arm (Cyberknife™) LINAC**
 - **Protons = ↓ “integral” dose = ALARA standard**
- **Guidelines based on Phase II test results**
 - **Phase III randomized controlled testing is ongoing**



Grazie.....

