HOMI BHABHA CANCER HOSPITAL, SANGRUR
(A Unit of TATA MEMORIAL CENTRE, Mumbai)

CANCER IS CURABLE IF DETECTED EARLY

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SBRT in Prostate cancer
Guideline and Evidences

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ACKNOWLEGEMENTS

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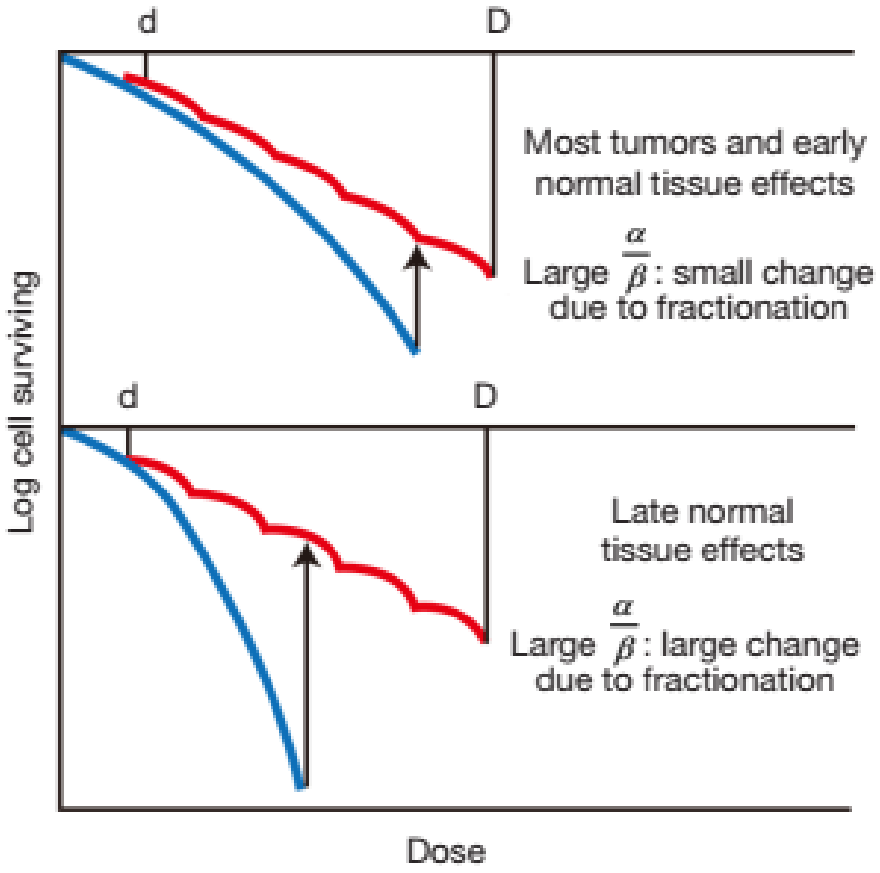
Taking Advantage of Alpha by beta for prostate Radiobiology

- Reported first by David Brenner and Eric j Hall in 1999
- Alpha by beta: Relationship between cellular proliferative status and sensitivity to changes in fractionation
- Prostatic tumours contain exceptionally low proportions of proliferating cells. Proliferation rate is described in terms of a population doubling time, the Potential Doubling Time (Tpot).
- longest Tpots of any human tumors, from 15 to more than 70 days
- Alpha by beta is 1.5 (0.8,2.2)

Brenner DJ and Hall EJ: Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys, 1999.

THREE LARGE REVIEWS

Scott Williams et al Australia 2011	Jolyon Hendry et al Manchester 2012	Dasu et al 2012 Sweden
•5063 patients from 6 institutes •Utilized long term PSA dynamics	•5969 patients from 7 institute	•11330 patients treated with conv. Fractionation •2838 patients treated with hypo fractionation
Alpha by beta was 1.55 Gy (0.46-4.52Gy)	**Alpha by beta was 1.4 Gy (0.9-2.2Gy)**	**Alpha by beta calculated 0.6 to 1.7 Gy inclusive of all risk patients**



Prostate acts like late reacting normal tissue

SBRT

- Potential to improve

1. Therapeutic window
2. Higher local control
3. Reduced toxicity
4. Better QOL
5. Shorter treatment course
6. Lower cost

SBRT

WHICH RISK GROUP ?

DOSE ?

OUTCOME ?

TOXICITY PROFILE? ACUTE AND LATE ?

TECHNICAL FEASIBILITY ?

Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline

Scott C. Morgan, Karen Hoffman, D. Andrew Loblaw, Mark K. Buyyounouski, Caroline Patton, Daniel Barocas, Soren Bentzen, Michael Chang, Jason Efstathiou, Patrick Greany, Per Halvorsen, Bridget F. Koontz, Colleen Lawton, C. Marc Leyrer, Daniel Lin, Michael Ray, and Howard Sandler

Published in JCO 2018

<u>Most elaborate guideline</u> so far published based on

1. **Retrospective series long follow up**
2. **Phase I/II studies**
3. **A few randomized trials**
4. **A guideline from ASTRO**

NCCN guideline mentions about SBRT prostate

UK SABR consortium guideline on prostate

Key questions

KQ3: Ultrahypofractionation to which risk patients ?

KQ4: Different ultrahypofractionation regimens compared with one another
Control, Quality of life, toxicity

KQ5: Different normal tissue constraints used in clinical trials

KQ6: Different treatment volumes used in clinical trials

KQ7: Moderate or ultrahypofractionation using image guided radiation therapy (IGRT)

KQ8: Moderate or ultrahypofractionation using intensity modulated radiation therapy (IMRT)

Guidance

Comments	Evidence
In men with **low-risk prostate cancer** who decline active surveillance and choose active treatment with EBRT, **ultra hypofractionation may be offered as an alternative to conventional fractionation.**	Moderate
In men with **intermediate-risk prostate** cancer receiving EBRT, ultra hypofractionation may be offered as an alternative to conventional fractionation. The task force ***strongly encourages*** that these patients be treated as part of **a clinical trial or multi-institutional registry**	Low
In men **with high-risk prostate** cancer receiving EBRT, the task force ***does not suggest*** offering **ultra hypofractionation outside of a clinical trial or multi-institutional registry** due to insufficient comparative evidence.	Low

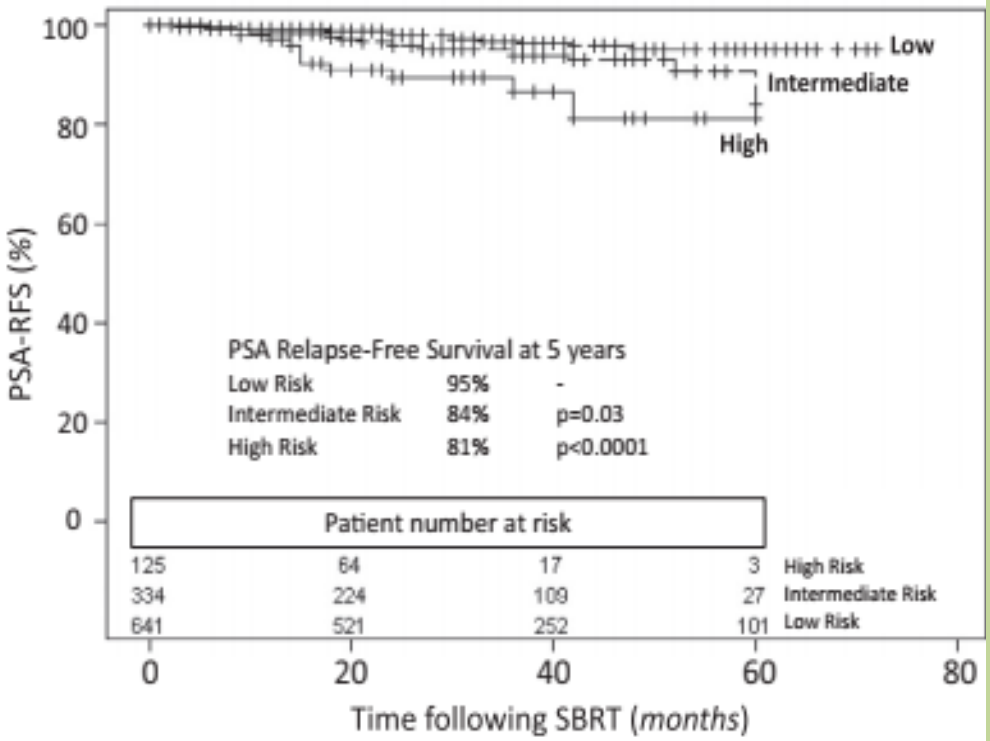
Guidance

Comments	Evidence
Ultra hypofractionated prostate EBRT of **3,500 to 3,625 cGy in 5 fractions of 700 to 725 cGy to the planning target volume may be offered to low- and intermediate-risk patients with prostate sizes less than 100 cm3**. The key dose constraints in KQ5B should be followed	Moderate
Five-fraction **prostate ultra hypofractionation at doses above 3,625 cGy to the planning target volume is not suggested outside the setting of a clinical trial or multi-institutional registry** due to risk of late toxicity	Moderate
Five-fraction prostate ultra hypofractionation **using consecutive daily treatments is not suggested** due to potential increased risk of late urinary and rectal toxicity.	Low

Evidences

KINGS ET AL 2013 POOLED ANALYSIS

Risk group	N (%)	35Gy	36.25Gy	38-40Gy	ADT use	Follow up
Low	641 (58%)	254 (40%)	319 (50%)	68(11%)	50 (8%)	36
Interm.	334 (30%)	108 (32%)	188 (56%)	38 (11%)	49(15%)	30.5
High	125 (11%)	23(18%)	82 (66%)	20 (16%)	48(38%	23



(1) Overall long term bRFS were excellent, **93% for all patients, and 95%, 84% and 81% for low-, intermediate- and high-risk patients, respectively (p < 0.001)**

(2) No differences in bRFS were observed with or without the use of ADT (p = 0.71)

(3) No differences were observed as a function of total dose (p = 0.17)

(4) In cohort of long term follow up of 5 years Trend is noted for the **5-year bRFS was 93% for patients receiving a dose 35 Gy vs. 100% for those receiving P36.25 Gy**

KINGS ET AL 2013 POOLED ANALYSIS

5-year PSA relapse-free survival rates
Individual subgroup analysis

	Low risk		Interm risk		High risk	
	5yr bRFS (%)	***P***	**5yr bRFS (%)**	***P***	**5yr bRFS (%)**	***P***
ADT	96.8		97.2		82.5	
NO ADT	95.1	0.46	79.2	0.17	80.2	0.5
DOSE 35GY	95.8		72.3		NE	
DOSE 36.25GY	95	0.77	87.2	0.73	74.1	0.99
DOSE 38-40GY	94.4	0.41	96.7	0.58	NE	1

Dose change / ADT use does not have any relation (significant)

Other supportive Trials

Study	n	Dose	ADT	bRFS
Loblow et al 2017#	84 L	35 Gy in 5Fr	1%	98% (5yr)
Mcbride et al	45L	36.5-37.5Gy in 5 fr	0%	98% (3yr)
Madsen et al	40L	33.5Gy in 5 Fr	--	90% (4yr)
Bolzicco et al	41 L, 42 I, 17 H	35Gy in 5 fr	29%	3 yr 94%
Boike et al	45 (I,L)	45Gy 5Fr / 47.5Gy 5 Fr / 50Gy 5 fr	-	100%
Mantz et al 2014*	102	40Gy in 5fr over 2 weeks		100%
Zimmerman et al 2016*	80	45Gy in 9 fr		98%
Hannan et al 2016*	91 L & I	45-50 Gy in 5fr	17%	100% L 98% I
Musunuru et al 2016*	84	35Gy in 5 fr		99%

•Mostly low & intermediate risk disease
•Use of higher dose

***Prospective Trials**
#Propensity matched analysis

Note:

- Most studies **includes low and intermediate risk patients**
- Doses are variable. Most common dose **36.25 Gy in 5 fractions**
- Some prospective trials uses higher doses >40Gy in 5 Fr.
- **bRFS are comparable between studies**
- **Loblow et al 2017** : Propensity matched analysis For the conventional and ultra hypofractionation patients, a biochemical disease-free survival (bDFS) trend was seen favouring Ultra hypofractionation **prior to matching (P = 0.08)**, which achieved **significance following matching (P = 0.001).**

  At six years, bDFS was 85.9% for conventional fractionation and **100.0% for ultrahypofractionation for the matched patients (P = 0.045).**

Other studies have shown that **dose escalation** do not differ by bRFS and acute toxicity however late GI and GU toxicity >2 increase at dose level 45Gy and 50 Gy

Study	n	Dose	Toxicity
Musunuru et al 2016*	84	35Gy in 5 fr 40Gy in 5 Fr	1. ***A significant increase in late toxicity observed at the 4,000 cGy level.*** 2. Specifically, **maximum late grade 2 GI toxicity** was identified in 8% at 35 Gy compared with **20% at 40 Gy (P = 0.012)** 3. Maximum **late grade 2 GU toxicity** was seen in 5% at 35 Gy **and 13% at 40 Gy (P = 0.02)**
Hannan et al 2016*	91 L & I	45-50 Gy in 5fr	1. Incidence of **acute grade 3 GI toxicity** at 50 Gy = 1.6% **2. Late GI toxicity was identified as well at the 5,000 cGy level (6.6% grade 3 and 3.3% grade 4)** 3. No late grade 3 or 4 toxicity at the 45 Gy level, **but late grade 3 GU toxicity was identified at 47.5 Gy (6.7% grade 3) and 50 Gy (4.9% grade 3 and 1.6% grade 4).**

Randomized study

42.7 Gy over 7 fractions
3 days per week

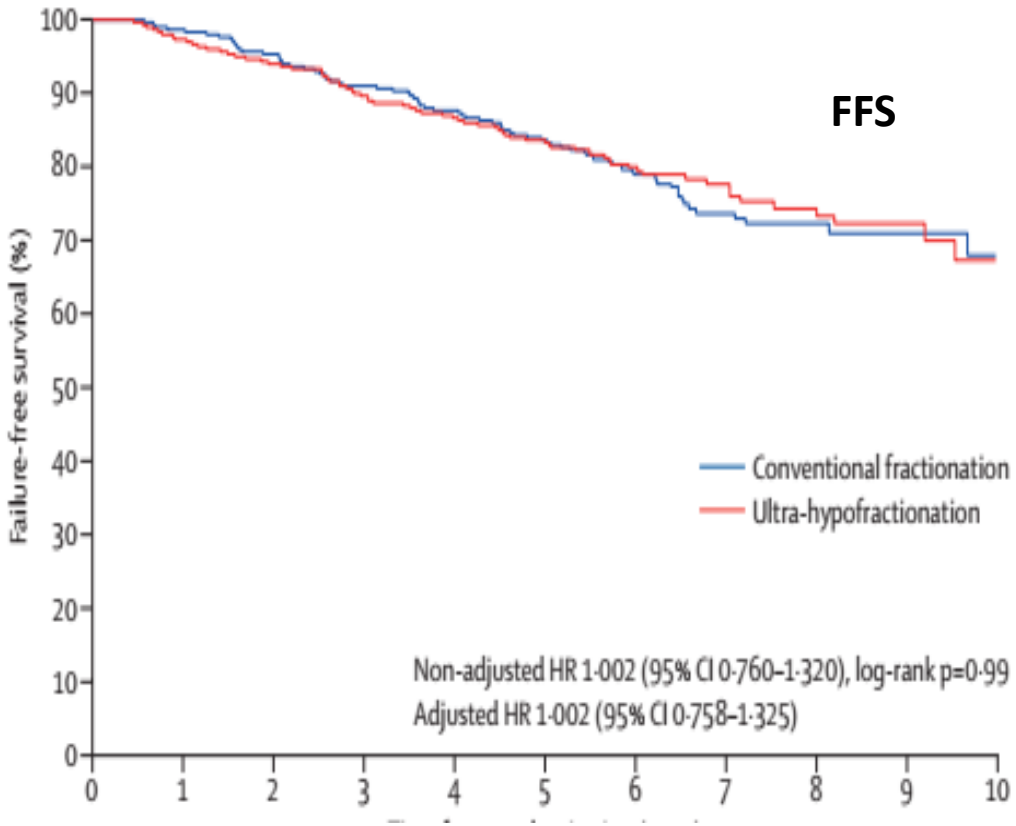
Hypo-RT-PC

78Gy in 39 fractions

Primary end point: PSA relapse, clinical failure, or both
Primary outcome: FFS
Secondary outcome: bDFS, cDFS, prostate cancer-specific survival, OS, proportion of patients achieving PSA response, time to change of treatment, QOL and toxicity

PSA, ng/mL*		
Median (IQR)	8·6 (5·7–12·0)	8·7 (6·0–12·2)
≤10 ng/mL	356 (60%)	357 (61%)
>10 ng/mL	235 (40%)	232 (39%)
Gleason score*		
5	2 (<1%)	5 (1%)
6	106 (18%)	99 (17%)
7	444 (75%)	447 (76%)
8	37 (6%)	33 (6%)
9	2 (<1%)	5 (1%)
Risk group		
Intermediate risk	527 (89%)	527 (89%)
High risk†	64 (11%)	62 (11%)
Radiotherapy technique		
3DCRT	471 (80%)	471 (80%)
VMAT/IMRT	120 (20%)	118 (20%)
Image-guided radiotherapy technique		
BeamCath	61 (10%)	61 (10%)
Fiducial markers	530 (90%)	528 (90%)

Hypo-RT-PC



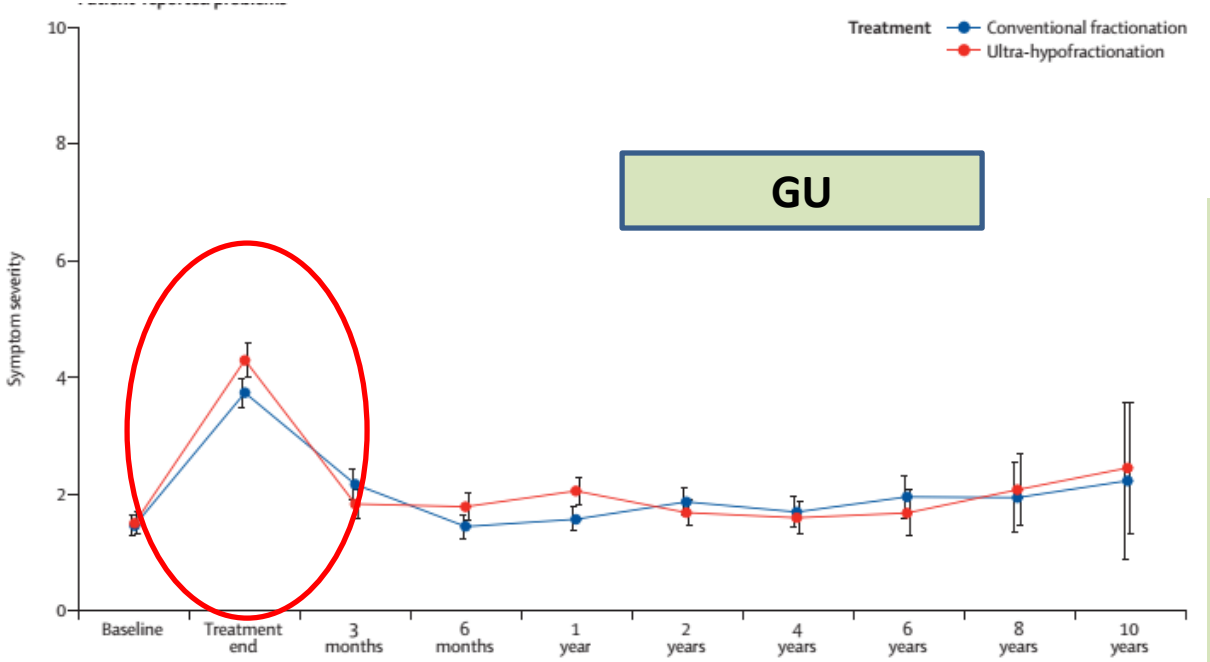
- **The 5-year failure-free survival** which was comprised of 89% intermediate-risk patients and 11% high-risk patients
- **Almost identical in the treatment groups** (84% in both groups; adjusted HR 1·002, 95% CI 0·758-1·325; log-rank p=0·99).
- **Comparable to the outcome of the moderate hypo-fractionation trials.**

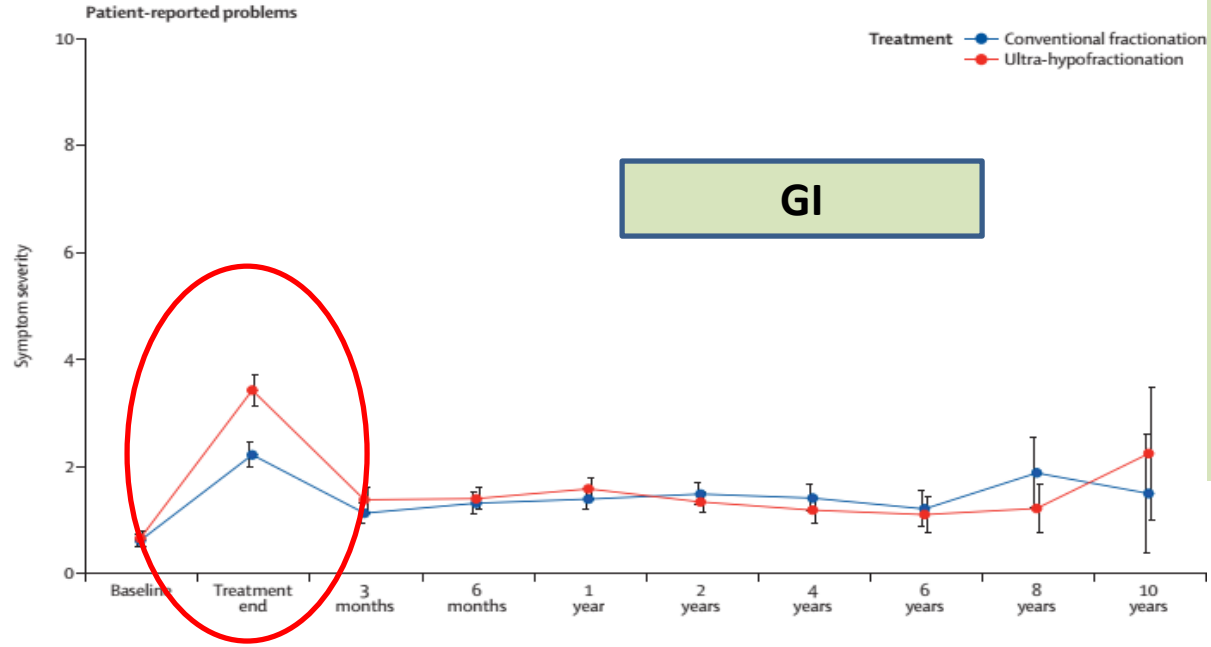
Hypo-RT-PC

OUTCOME	UHF (%)	CF (%)	*P*
GRADE2+GU	27.6	22.8	0.11
GRADE2+GI	9.4	5.3	0.23
2 YR GR 2 GU	5.4	4.6	0.59
2YR GR 2 GI	2.2	3.7	0.20
2 YR IMPOTENCE	34	34	
QOL (PRO) AT 2 YEARS	No diff		
Acute bowel QOL	**Worse <3 months**		
1 year Urinary QOL	**Worse for UHF**		
Sexual QOL	SAME		

Acute deterioration in GI and GU toxicity
With long follow up late toxicity between UHF and CF is insignificant

Hypo-RT-PC





- ***Patient-reported outcomes*** revealed **significantly higher levels of acute urinary and bowel symptoms in the UHF** group compared with the conventional fractionation group

- **No significant increases in late symptoms were found, except for increased urinary symptoms at 1-year follow-up, consistent with the physician-evaluated toxicity**

Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer

- Report on **2142 patients from 10 institution**
- **7-year OS**

  Low-risk disease was 91.4% (95% CI, 89.4%-93.0%)

  Intermediate-risk disease was 91.7% (95% CI, 89.2%-93.6%).

  Favorable intermediate-risk disease was 93.7% (95% CI, 91.0%-95.6%),

  Unfavorable intermediate-risk disease was 86.5% (95% CI, 80.6%-90.7%)
- Some patients has completed 9 year survival.

		Cumulative Incidence Estimate (95% CI)		
Toxic Event	Crude Incidence, No. (%)[b]	5 y	7 y	10 y
Grade 2				
Acute GU	153 (9.0)	NA	NA	NA
Acute GI	56 (3.3)	NA	NA	NA
Late GU	163 (9.6)	11.2 (9.7-12.8)	12.3 (10.8-14.0)	13.4 (11.6-15.4)
Late GI	67 (3.9)	4.5 (3.6-5.6)	4.5 (3.6-5.6)	4.5 (3.6-5.6)
Grade ≥3				
Acute GU	13 (0.6)	NA	NA	NA
Acute GI	2 (0.09)	NA	NA	NA
Late GU	46 (2.1)	1.8 (1.3-2.5)	2.4 (1.8-3.2)	3.2 (2.2-4.6)
Late GI	7 (0.3)	0.4 (0.2-0.8)	0.4 (0.2-0.8)	0.4 (0.2-0.8)

Kishan et al 2019

Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies

- **Thirty-eight unique prospective series** were identified **comprising 6116 patients**
- **92% :low risk , 78%-intermediate risk**, and ***38%-high risk***
- 5- and 7-year bRFS rates were 95.3% and 93.7% respectively.
- **Estimated late grade 3 genitourinary and gastrointestinal toxicity rates were 2.0% (95% CI, 1.4%- 2.8%) and 1.1% (95% CI, 0.6%-2.0%), respectively.**
- **By 2 years post-SBRT, *Expanded Prostate Cancer Index Composite urinary and bowel domain scores returned to baseline.***
- **Increasing dose of SBRT was associated with improved biochemical control (P = .018) but worse late grade 3 GU toxicity (P = .014).**

Jackson et al, IJROBP, 2019

Ongoing studies

Pace trial

PACE A
Potential surgical candidates are randomised between radical prostatectomy and SBRT (36.25 Gy in 5 fractions).

Slow Accrual

PACE B
Randomisation is between standard radiotherapy (78Gy in 39 fractions or 62Gy in 20 fractions) and SBRT (36.35Gy in 5 fractions).

Primary outcome: freedom from biochemical or clinical failure.
Co- primary outcomes: Acute toxicity , gastrointestinal or genitourinary toxic effects score up to 12 weeks after radiotherapy

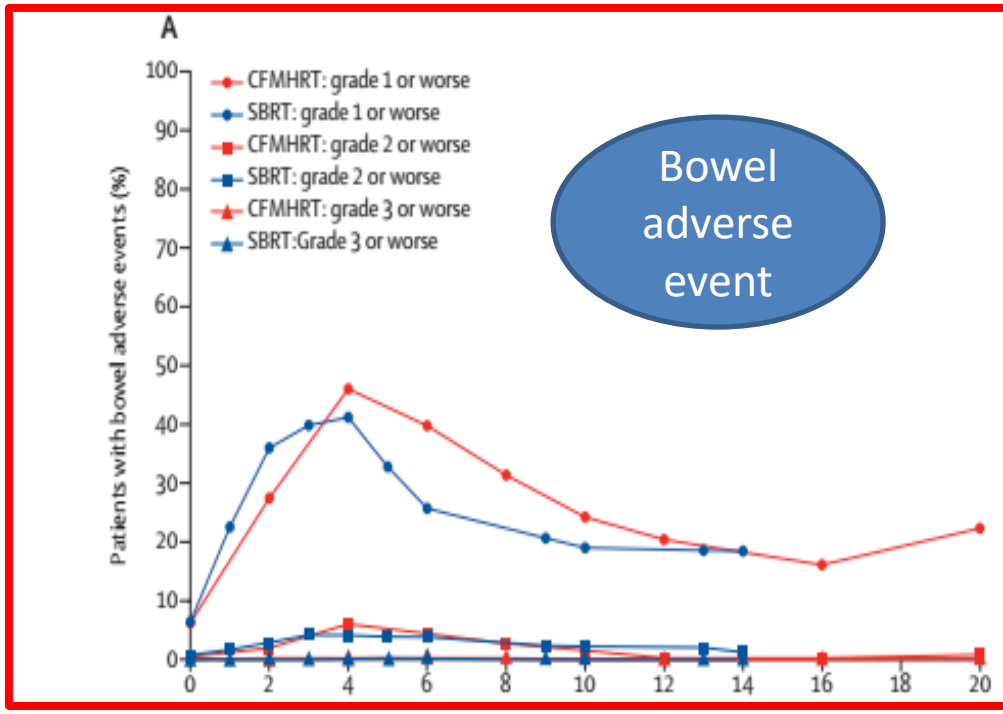
Toxicity data reported

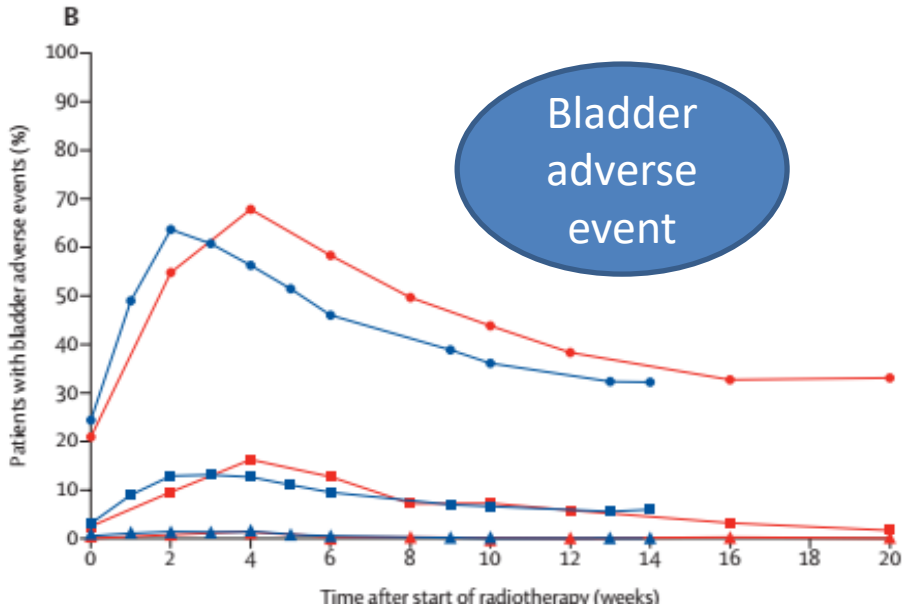
GI	MF	UF
GR 1	264 (61%)	219(53%)
GR 2	49(11%)	42(10%)
GR 3	4(1%)	1(<1%)
GR 4	0	0
GU		
GR 1	254(59%)	236(57%)
GR 2	111(26%)	86(21%)
GR 3	6(1%)	8(2%)
GR 4	1(<1%)	2(<1%)

Further data is awaited

1. Used IGRT: however preliminary data does not show any toxicity difference in Cyberknife vs LINAC.

2. Comparator arm was moderately fractionated)in HYPO RT PC





NRG –GU005	HEAT
70.2 Gy in 26 fractions VS. 36.25 Gy in 5 fractions to PTV	SBRT (5 fractions of 7.25 Gy) vs. hypo fractionated IMRT (28 fractions of 2.5 Gy)
Primary outcome : Two-year failure rates (biochemical or clinical failure, or positive biopsy)	**Primary outcome :** Toxicity DFS
Secondary outcome: Acute toxicity QOL Efficacy Cost efficacy Late toxicicty	**Secondary outcome:** OS QOL Biochemical Failure Local failure

These studies are about SBRT in low and intermediate risk prostate
However there are other trials in node positive and high risk prostate

PRIME TRIAL (Vedang Murthy et al; TMH Mumbai)

- **Adenocarcinoma prostate localised to prostate and pelvic nodes : first trial**

A. **High-risk/very high-risk** (High risk clinical stage T3a or Gleason score 8/Gleason grade group 4 or Gleason score 9 to 10/Gleason grade group 5, prostate-specific antigen (PSA) >20ng/mL

B. **Very high risk prostate cancer**, that is, T3b/T4 or primary Gleason pattern 5/Gleason grade group 5 or >4 cores, Gleason score 8 to 10/Gleason grade group 4 or 5)

Prostate 68Gy in 25 Fr
Pelvis 50Gy in 25 Fr
On the basis of nodal response to ADT 62.5Gy in 25 Fr

SBRT prostate 36.25Gy in 5Fr
Pelvis 25 Gy in 5 Fr
On the basis of nodal response to ADT 30-35Gy in 25 Fr

Primary outcome : 4yr bRFS
Secondary outcome: Acute and late toxicity ascertaining to OS and prostate cancer specific survival
QOL
Out of pocket expenditure in two arms

High risk and node positive ca prostate

Initial data from TMH (prostate and gross node dose was 35-37.5 Gy in 5 alternate day fractions. Node-positive patients received 25 Gy to pelvic nodal regions until the common iliac nodes)

- No acute grade ≥ 3 GU or GI toxicity was noted.
- **Acute grade 2 GU and GI toxicity were 12% and 3%, respectively**.
- **Late grade 3 GU and GI toxicity was 3% and 0%, respectively**.
- There was no increase in acute or late gastrointestinal toxicity with prophylactic pelvic nodal radiotherapy.
- Prior transurethral resection of prostate (n = 11) did not increase toxicity.
- At a median follow-up of 18 months, 97% patients were alive and 94% were biochemically controlled.

- Another Propensity score matched analysis between **TURP and Non -TURP patient** showed **some modest increase in GU toxicities however it remains low with SBRT in post-TURP patients**. SBRT can be safely performed in carefully selected post-TURP prostate cancer patients.

Early Results of Extreme Hypofractionation Using Stereotactic Body Radiation Therapy for High-risk, Very High-risk and Node-positive Prostate Cancer. Vedang Murthy et al 2018
Safety of Prostate Stereotactic Body Radiation Therapy after Transurethral Resection of Prostate (TURP): A Propensity Score Matched Pair Analysis Vedang murthy 2019

SHORT TRIAL

- **Phase I/II study**
- **Any Gleason score, T1-4 prostate with PSA <60ng/ml**
- **35Gy in 5 Fr to primary and 25Gy in 5 Fr to pelvis**
- **Out of 30 patients, 20 patients are in high risk**
- **Urinary symptom score showed a clinically meaningful worsening from a mean of 20/100 at baseline to 34/100 at the end of treatment (P < 0.001), but reduced to 24/100 at 6 months (P = 0.08).**
- **With a median follow-up of 41.5 months, two patients each reported grade 2 late urinary and rectal toxicity.**
- **The 3- and 4-year biochemical control rates were 96.7 and 87.9%, respectively.**

I Mallick et al 2020

TECHNIQUES

- Selecting a case
- Segmentation
- Treatment technique
- *Image guidance*

<u>Selecting cases</u>

1. **Low or intermediate risk case**
2. **Prostate volume <100 CC however large prostate is not per se an absolute contraindication**
3. **No prior irradiation / inflammatory bowel disease**
4. **Large TURP defects : SBRT not practiced**
5. **Obstructive urinary features e.g.: IPSS >20**

Simulation

1. **Bladder :** Bladder protocol to reduce bowel toxicity but has inherent reproducibility issue (usual practice).
2. Empty bladder is more reproducible.

- **Rectal contour** : Empty rectum is the norm. Liberal use of laxative is practiced along with low motility low gas forming diet.

- Other interventions :

I. **Rectal balloons**: Rectal balloons **increase the high dose irradiated area** along with **superior part which may get higher dose**

II. **Rectal hydro gel spacer**: It may be used to facilitate **more distance between prostate and rectum**

- **<u>Simulation :</u>**

1. CT simulation with 2.5 mm cuts
2. Planning MRI T2W : co registered with prostate

Segmentation

- **MRI fusion assisted segmentation**

➢ Extra prostatic spread , SV invasion are better appreciated
➢ Better OAR delineation – urethra, penile bulb
➢ Over estimation of prostate can be prevented

- **CTV** : **Low risk : Prostate**

  Intermediate risk : prostate and proximal SV

  High risk : poorly representated (Prostate and node)

- ***PTV :*** **Most common 5 mm isotropic margin with 3 mm posterior in rectal interface.**
- **Nodes : Nodal contour up to L5-S1**

Planning parameters:

Goals:

1. *Prescription dose should cover a minimum of 95% of the PTV.*

2. Minimum dose within the PTV (*0.03 cc in size) must be ≥95% of the prescribed dose.*

3. **For IMRT,** the maximum dose within the PTV is 7% above the prescribed dose (a point of 0.03 cc).

4. **For Cyber knife,** the max dose allowed within the PTV is 20% above the prescribed dose (a point of 0.03cc)

5. *The prescription doses must not occur outside of the PTV.* **Any *hotspots should be manipulated to avoid the prostate-rectal and prostate-bladder interfaces* as defined by the CTV.**

6. ***Acceptable Variation**:* Cases in which this small volume of at *least 0.03cc* receives a minimum dose that is <95% but *>93%* or a *maximum dose* that is >107% and *<110%* of the prescribed dose.

ASTRO guideline

Normal tissue constraints (At least two dose-volume constraint points for rectum and bladder should be used for moderately or ultra-hypofractionated EBRT: **one at the high-dose end (near the total dose prescribed) and one in the mid-dose range (near the midpoint of the total dose).**

Organ EQD2 α/β 3		V14 (16.2 Gy)	V17.5 (22.8 Gy)	V28 (48.2 Gy)	V31.5 (58.6 Gy)	V35 (70 Gy)
Bladder	N+	<40%	<27%	<20%	–	<3%
	N-	<35%	<20%	<10%	–	<3%
Rectum	N+	<50%	<40%	<15%	<8%	<3%
	N-	<40%	<30%	<15%	<8%	<3%
Femoral heads		<5%				
Bowel (cc)				80 cc		

*Prime Study Protocol

*Murthy V, *et al*. *BMJ Open* 2020

- **IGRT is advisable (ASTRO)**
- Studies have used different techniques and machines
- (**Outcome is not different among 3D / CYBERKNIFE/ IGRT)**

- **Yu Wen Li et al 2014** compared treatment plans between non-isocentric plans in **cyberknife vs. Isocentric Rapidarc** : differences are evident attributable to different machines.

<u>Rapid arc compared to Cyber knife showed</u>

1. **Better dose conformity,**
2. **Better adjacent**
3. **Organ sparing**
4. **Better dose fall off profile as it has FFF**
5. **Less MU**
6. **Less time**

Prostate localization & motion management

- **Intra fraction and inter fraction motion**

- Happens due to rectal distension and variable bladder filling, cystitis feature, long treatment time

- **Image guidance:**

1. **Gold fiducials** : Intra prostatic gold fiducials helpful in image matching by 2D (e.g.: **Exactrac, EPID**) and 3D (e.g.: **CBCT , Helical tomo MV imaging**) method.
2. **Magnetic transponders** : **Real-time tracking by Calypso beacon transponders**
3. **Trans abdominal ultrasound system**: To confirm the prostate position along other OAR position.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Thank you