Clinical Trial > N Engl J Med. 2024 Oct 17;391(15):1413-1425. doi: 10.1056/NEJMoa2403365.

Phase 3 Trial of Stereotactic Body Radiotherapy in Localized Prostate Cancer

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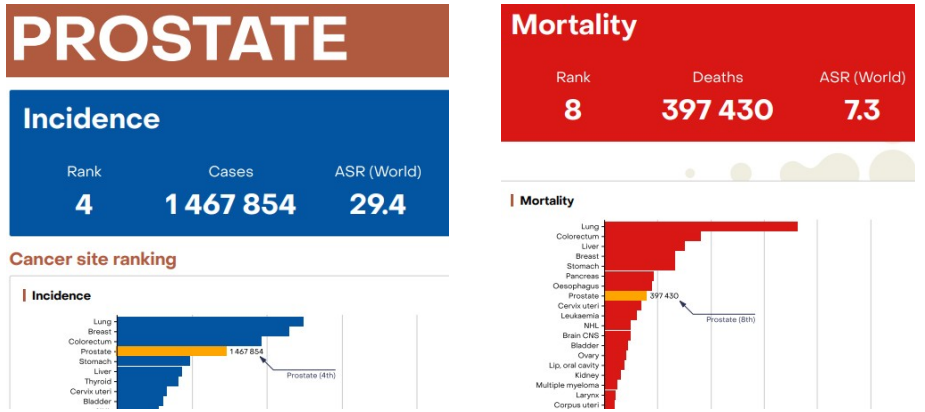
Introduction



- Prostate cancer is a global health challenge
- As per the NCDIR, prostate cancer was amongst top 10 cancers in urban cancer registries of Delhi, Bangalore, Bhopal and Mumbai in 2022
- In England in 2021, 12% & 29% of newly diagnosed prostate cancers were of low and IR respectively*
- Curative treatment options include surgery or RT
- Low α/β ratio
- Hypofractionated RT regimens are non-inferior to conventional fractionation**

*National Prostate Cancer Audit. NPCA state of the nation report. London: the Royal College of Surgeons of England, 2024

**Hypofractionated Radiation Therapy for Localized Prostate Cancer: Executive Summary of an ASTRO, ASCO and AUA Evidence-Based Guideline. J Urol. 2018

Stereotactic body radiation therapy (SBRT) in prostate cancer

- SBRT is an extreme form of hypofractionation
- Entire RT dose is delivered in 5-7 fractions
- Potential advantages include cost and patients convenience
- PACE trials evaluates the role of 5-fractions SBRT in localised ca prostate
  - PACE-A: SBRT vs radical prostatectomy
  - PACE-B: SBRT vs RT in low and IR prostate cancer not requiring ADT
  - PACE-C: SBRT vs RT in men with higher-risk disease requiring ADT
- The results of PACE-B trial, which assessed non-inferiority of SBRT to conventional or moderately hypofractionated RT will be presented

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NEJM FULL TEXT

Phase 3 Trial of Stereotactic Body Radiotherapy in Localized Prostate Cancer

PACE-B trial

- Phase 3, international, open-label, non-inferiority, RCT
- Conducted at 38 centers across the United Kingdom, Ireland, and Canada
- 2012-2018, n=874
- 1:1 randomization to SBRT or control RT (conventional or moderately hypofractionated RT)
- Randomization was done using computer-generated random permuted blocks (size of 4 and 6)
- Patients were stratified according to NCCN risk category (low vs. IR)
- This trial was approved by the respective institutional review boards

Inclusion criteria

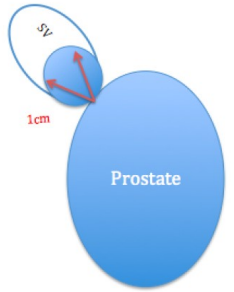
- 18 years or older
- Histologically confirmed adenoca prostate
- WHO performance status 0-2
- Life expectancy > 5 years
- T1/T2 disease on MRI
- Low risk (GS=3+3 and PSA ≤ 10 ng/ml) or
- IR (GS=3+4 and/or PSA 10.1-20 ng/ml)

Exclusion criteria

- Gleason grade 4 or higher
- Any NCCN high-risk factors
- Previous pelvic radiotherapy
- Previous treatment for ca prostate
- Prostheses in both hips

Radiotherapy planning

- Insertion of 3 or more prostatic fiducial markers was recommended
- Moderate bladder filling and bowel preparation was advised
- MRI was recommended and CT-MRI scans were fused by fiducial matching
- Clinical target volume (CTV):-
  - Low risk patients: Prostate only
  - IR patients: Prostate + proximal 1 cm of seminal vesicles



PTV margin for conventional radiotherapy:
PTV= CTV+ 5-9mm, except 3-7mm posteriorly

PTV margins for SBRT (36.25 Gy in 5 fractions)
PTV= CTV+ 4-5mm/ 3-5mm posteriorly

Organs at Risk (OAR)-Rectum, Bladder, Urethra, Penile bulb, Femoral head, Testis, Bowel

Radiotherapy dose
For SBRT
- 36.25 Gy/5 # /1-2 weeks to 95% of the PTV
- 40 Gy/5# to 95% of the CTV

For control RT
- 78 Gy/39 # /7.5 weeks
- 62 Gy/20 # /4 weeks was permitted after 2016 (CHHiP trial)

End points

- Primary end point was freedom from biochemical or clinical failure
- Secondary end points
  - Commencement of ADT
  - Diagnosis of metastatic disease
  - Disease-free survival
  - Overall survival
  - Clinician- and patient-assessed side effects
- The pre-specified time point of primary interest was 5 years

Follow up

- PSA level was recorded at 3, 6, 9, and 12 months after t/t and annually thereafter
- Physician assessed toxicity (CTCAE v.4.03 and RTOG) and patient-reported outcomes were assessed
  - Before t/t
  - Every 3 months until 24 months
  - Every 6 months in years 2 through 5
  - Annually to a maximum of 10 years

Patient-reported outcomes were assessed using

- 26-question Expanded Prostate Cancer Index Composite (EPIC-26) instrument
- The International Prostate Symptom Score scale (for urinary incontinence)
- The Vaizey fecal-incontinence scale
- The five-item International Index of Erectile Function (IIEF-5) Questionnaire

Statistical analysis

- Non-inferiority trial
- Sample size was calculated based on the:
  - Assumption that 85% pts in control grp will be free from biochem or clinical failure at 5 yrs
  - Non-inferiority margin - 6% points at 5 years
  - 80% power, 5% one-sided significance, and allowance for 10% loss to follow-up
- Log-rank test was used to compare primary end point in two groups
- Chi-square or Fisher's exact tests were used to compare clinician-assessed toxicity
- Cumulative incidence of toxicity was estimated and kaplan–Meier method was used for comparison
- For PROs, responses to EPIC-26 instrument were analyzed as composite scores for each domain
- All analyses are based on data as of September 11, 2023, and were conducted with the use of Stata software, version 17.0

Results: Patient characteristics

Characteristic	Stereotactic Body Radiotherapy (N=433)	Control Radiotherapy (N=441)	Total (N=874)
Age at randomization — yr			
Median (IQR)	69.8 (65.4–74.1)	69.7 (65.5–73.9)	69.8 (65.4–74.0)
Range	45.8–84.5	48.1–86.7	45.8–86.7
Race or ethnic group — no. (%)†			
Black	35 (8.1)	26 (5.9)	61 (7.0)
East Asian	4 (0.9)	3 (0.7)	7 (0.8)
Mixed heritage	2 (0.5)	2 (0.5)	4 (0.5)
Southern Asian	20 (4.6)	10 (2.3)	30 (3.4)
White	367 (84.8)	393 (89.1)	760 (87.0)
Other	5 (1.2)	7 (1.6)	12 (1.4)
Family history of prostate cancer — no. (%)			
No	312 (72.1)	326 (73.9)	638 (73.0)
Yes	89 (20.6)	88 (20.0)	177 (20.3)
Unknown	32 (7.4)	27 (6.1)	59 (6.8)
WHO performance-status score — no. (%)‡			
0	389 (89.8)	391 (88.7)	780 (89.2)
1	44 (10.2)	48 (10.9)	92 (10.5)
2	0	2 (0.5)	2 (0.2)
T stage — no. (%)§			
T1c	82 (18.9)	81 (18.4)	163 (18.6)
T2a	105 (24.2)	133 (30.2)	238 (27.2)
T2b	81 (18.7)	59 (13.4)	140 (16.0)
T2c	162 (37.4)	168 (38.1)	330 (37.8)
Unknown	3 (0.7)	0	3 (0.3)
Method of staging — no. (%)			
≥1 Staging method performed	430 (99.3)	441 (100)	871 (99.7)
Digital rectal examination	156 (36.0)	166 (37.6)	322 (36.8)
Transrectal ultrasonography	280 (64.7)	264 (59.9)	544 (62.2)
MRI of the pelvis	339 (78.3)	359 (81.4)	698 (79.9)
Gleason score — no. (%)¶			
3+3	63 (14.5)	90 (20.4)	153 (17.5)
3+4	370 (85.5)	351 (79.6)	721 (82.5)
Prostate-specific antigen level			
Median (IQR) — ng/ml	7.9 (5.5–10.9)	8.1 (6.3–11.0)	8.0 (5.9–11.0)
Range — ng/ml	0.5–20.0	0.8–20.0	0.5–20.0
Distribution — no. (%)			
<10 ng/ml	297 (68.6)	303 (68.7)	600 (68.6)
10–20 ng/ml	136 (31.4)	138 (31.3)	274 (31.4)

Table 1. (Continued.)

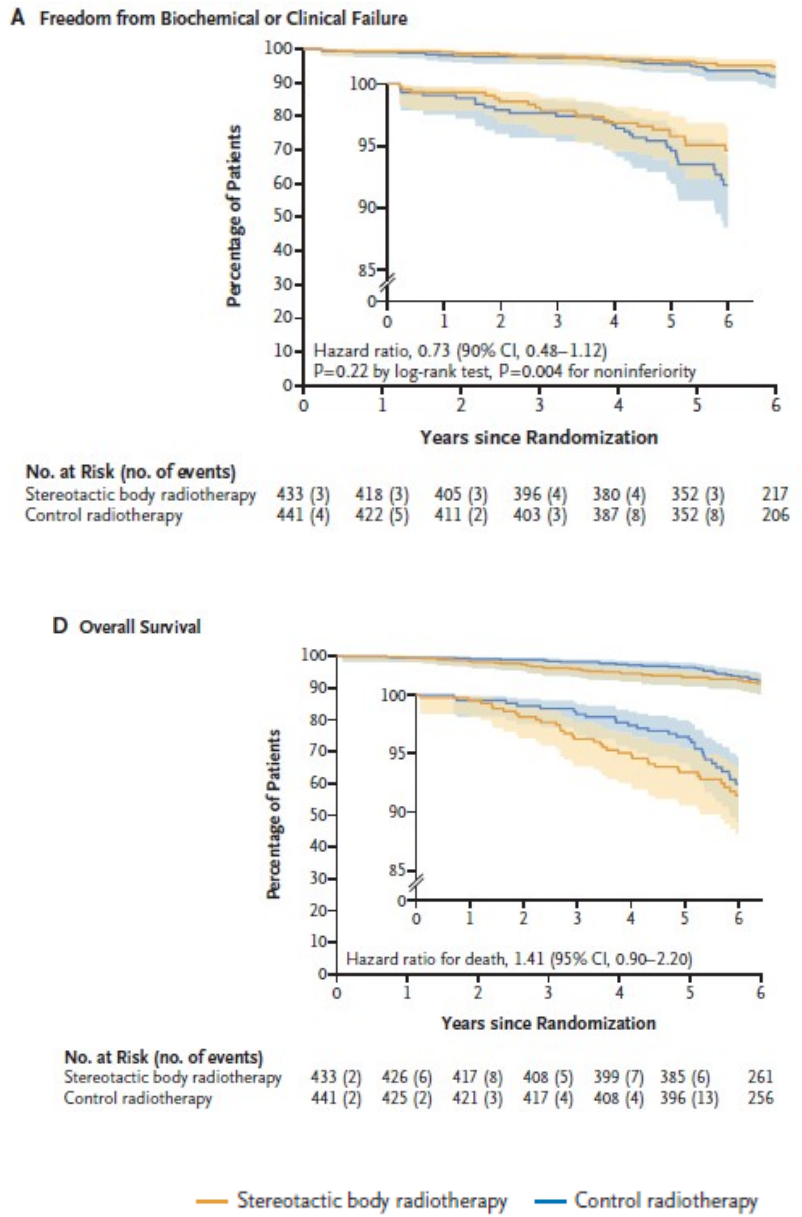
Characteristic	Stereotactic Body Radiotherapy (N=433)	Control Radiotherapy (N=441)	Total (N=874)
NCCN risk category — no. (%)			
Low	32 (7.4)	41 (9.3)	73 (8.4)
Intermediate	401 (92.6)	400 (90.7)	801 (91.6)
Favorable	86 (21.4)	106 (26.5)	192 (24.0)
Unfavorable	315 (78.6)	294 (73.5)	609 (76.0)
Prostate volume — no. (%)			
<40 ml	192 (44.3)	163 (37.0)	355 (40.6)
40 to <80 ml	198 (45.7)	223 (50.6)	421 (48.2)
≥80 ml	23 (5.3)	28 (6.3)	51 (5.8)
Unknown	20 (4.6)	27 (6.1)	47 (5.4)
Testosterone level			
No. of patients evaluated	403	407	810
Median (IQR) — μmol/liter	11.5 (9.0–15.0)	11.3 (8.7–15.0)	11.3 (8.9–15.0)
Range — μmol/liter	0.4–30.5	0.4–30.6	0.4–30.6
International Prostate Symptom Score grade — no. (%)‖			
No symptoms: score of 0	16 (3.7)	21 (4.8)	37 (4.2)
Mild symptoms: score of 1–7	202 (46.7)	197 (44.7)	399 (45.7)
Moderate symptoms: score of 8–19	136 (31.4)	141 (32.0)	277 (31.7)
Severe symptoms: score of 20–35	20 (4.6)	23 (5.2)	43 (4.9)
Unknown	59 (13.6)	59 (13.4)	118 (13.5)
Time from diagnosis to randomization — wk**			
Median (IQR)	9.9 (6.6–16.1)	11.0 (6.9–17.0)	10.1 (6.7–16.6)
Range	0.1–225.0	0.9–335.0	0.1–335.0

Biochemical failure and OS

Median FU -74 months (IQR, 64.8 to 86.3)		
	SBRT (n=433)	Control arm (n=441)
Biochem/clinical failure (n)	26	36 (p-NS)
5-year incidence of freedom from biochemical/clinical failure	95.8% (95% CI, 93.3 to 97.4)	94.6% (p-NS) (95% CI, 91.9 to 96.4)
ADT commencement (n)	10	19 (HR- 0.55)

- Total 79 patients died
  - SBRT: n=46 (2 due to ca prostate)
  - Control arm: n=33 (2 due to ca prostate)
  - HR-1.41

- SBRT was non-inferior to control radiotherapy
- HR for biochemical or clinical failure =0.73
- A post hoc test for superiority was not significant

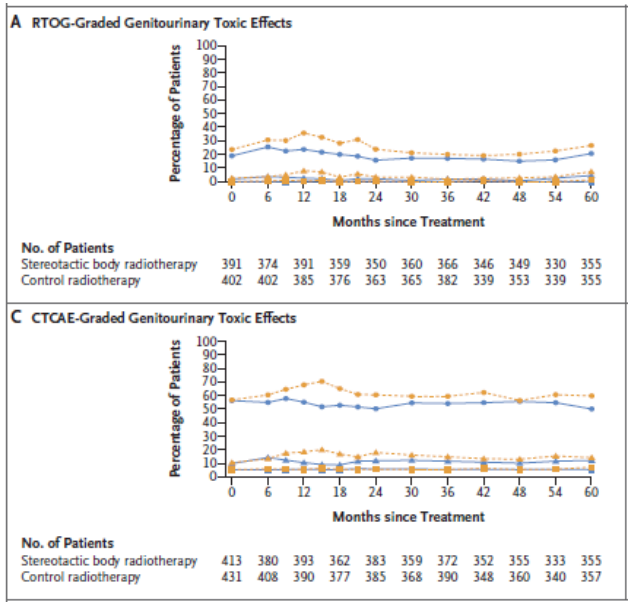


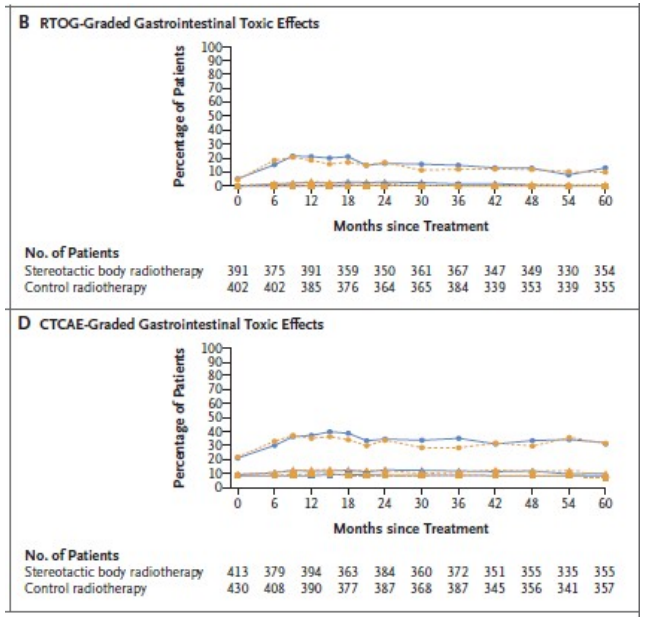
Toxicity at 5 years

Grade ≥2 GU toxicity	SBRT arm	Control arm	P value
RTOG	26 of 355 (7.3%)	16 of 355 (4.5%)	0.11
CTCAE	31 of 355 (8.7%)	24 of 357 (6.7%)	0.32

Grade ≥2 GI toxicity	SBRT arm	Control arm	P value
RTOG	3 of 354 (0.8%)	1 of 355 (0.3%)	0.37
CTCAE	9 of 355 (2.5%)	6 of 357 (1.7%)	0.43
RTOG late effect	10.7%	10.2%	0.94 (HR-1.03)

Grade ≥2 erectile dysfunction	SBRT arm	Control arm	P value
CTCAE	78 of 296 pts (26.4%)	86 of 296 pts (29.1%)	0.46

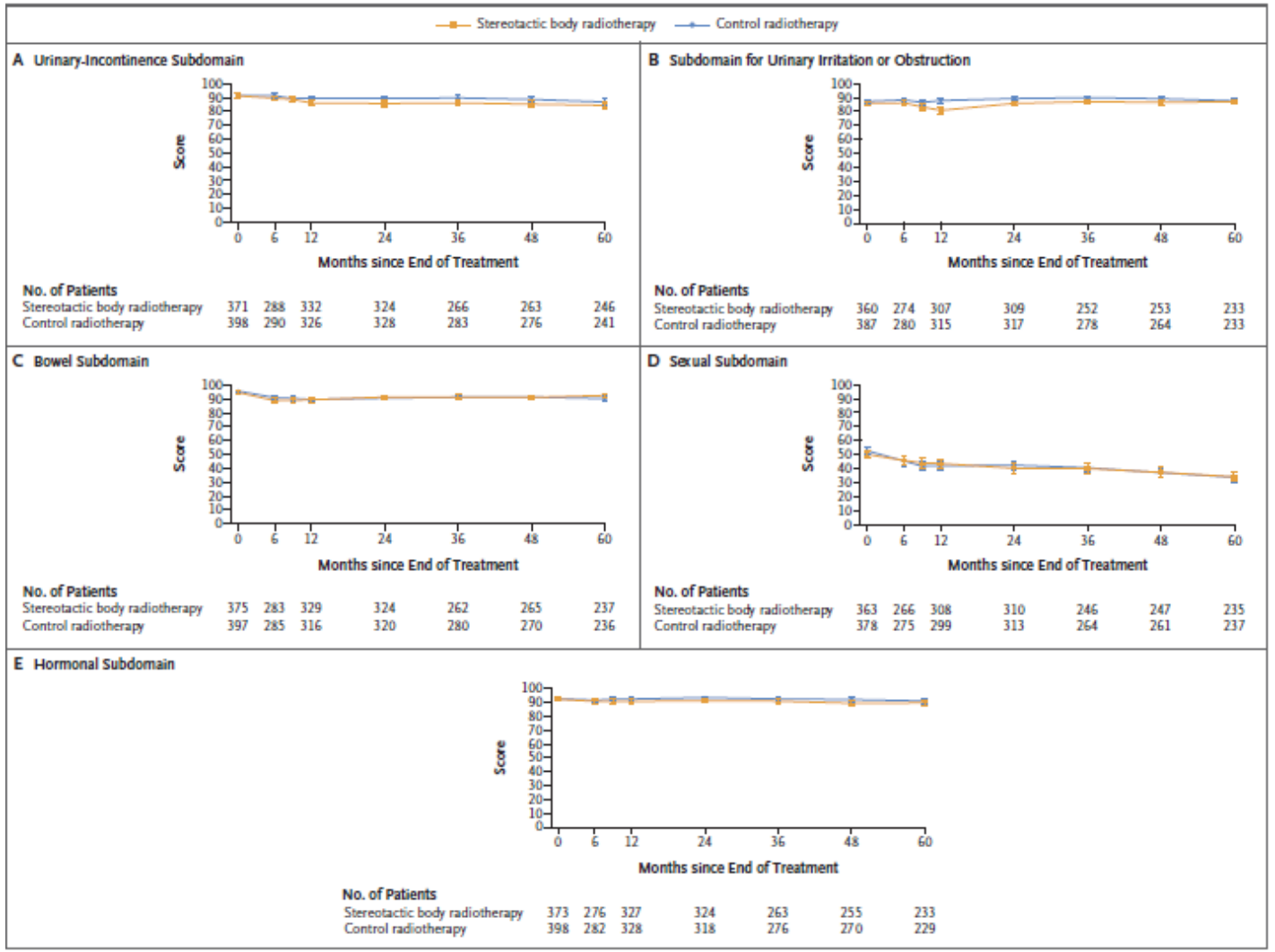




Stereotactic body radiotherapy: grade ≥1
Control radiotherapy: grade ≥1
Stereotactic body radiotherapy: grade ≥2
Control radiotherapy: grade ≥2
Stereotactic body radiotherapy: grade ≥3
Control radiotherapy: grade ≥3

EPIC-26 Subdomain Scores

At 5-years	SBRT arm	Control arm	p
Median urinary-incontinence score	96.9	100	0.45
Median score for urinary irritation or obstruction	93.8	93.8	-
Bowel subdomain score	100	95.8	0.10



- Patients reported stable urinary and bowel symptoms from 2 to 5 yrs, with little difference b/w groups
- Sexual subdomain scores declined from 2 to 5 yrs, with no significant difference b/w groups at 5 years (P = 0.87)

Discussion

- PACE-B trial showed non-inferiority of 5-# SBRT c/w moderately fractionated RT
- Incidence of freedom from biochem/clinical failure was 96% with SBRT & 95% with control RT, achieved without ADT and exceeded the expectations of the trial design
- Acute toxicity data of PACE B was published in 2019 and showed comparable toxicities at 2 yrs
- Better outcomes compared to previous studies such as CHHiP, HYPO-RT-PC may reflect advancements in RT planning and delivery techniques

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

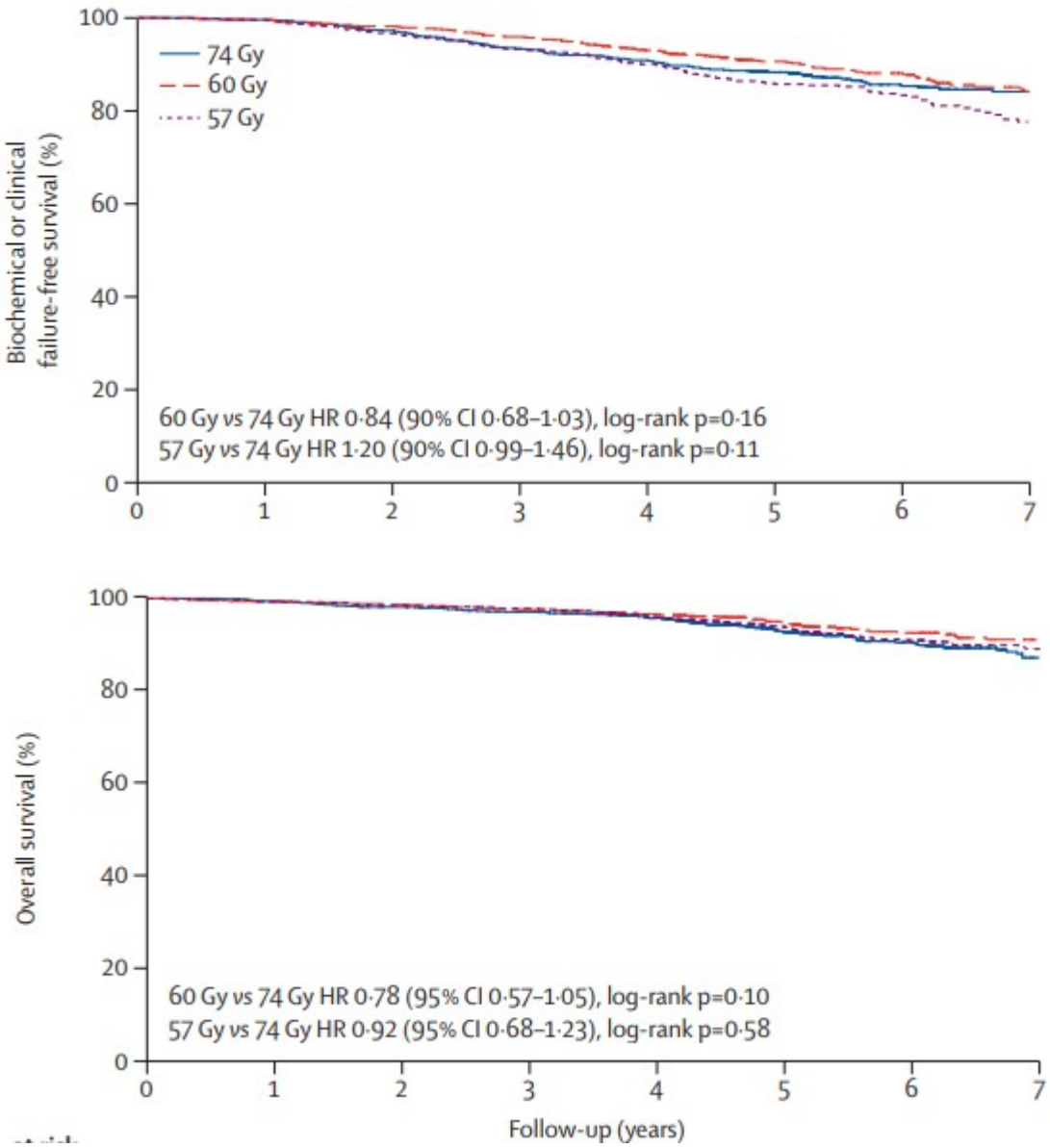
Findings Between Aug 7, 2012, and Jan 4, 2018, we randomly assigned 874 men to conventionally fractionated or moderately hypofractionated radiotherapy (n=441) or stereotactic body radiotherapy (n=433). 432 (98%) of 441 patients allocated to conventionally fractionated or moderately hypofractionated radiotherapy and 415 (96%) of 433 patients allocated to stereotactic body radiotherapy received at least one fraction of allocated treatment. Worst acute RTOG gastrointestinal toxic effect proportions were as follows: grade 2 or more severe toxic events in 53 (12%) of 432 patients in the conventionally fractionated or moderately hypofractionated radiotherapy group versus 43 (10%) of 415 patients in the stereotactic body radiotherapy group (difference –1·9 percentage points, 95% CI –6·2 to 2·4; p=0·38). Worst acute RTOG genitourinary toxicity proportions were as follows: grade 2 or worse toxicity in 118 (27%) of 432 patients in the conventionally fractionated or moderately hypofractionated radiotherapy group versus 96 (23%) of 415 patients in the stereotactic body radiotherapy group (difference –4·2 percentage points, 95% CI –10·0 to 1·7; p=0·16). No treatment-related deaths occurred.

Interpretation Previous evidence (from the HYPO-RT-PC trial) suggested higher patient-reported toxicity with ultrahypofractionation. By contrast, our results suggest that substantially shortening treatment courses with stereotactic body radiotherapy does not increase either gastrointestinal or genitourinary acute toxicity.

Lancet Oncol 2019; 20: 1531–43

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

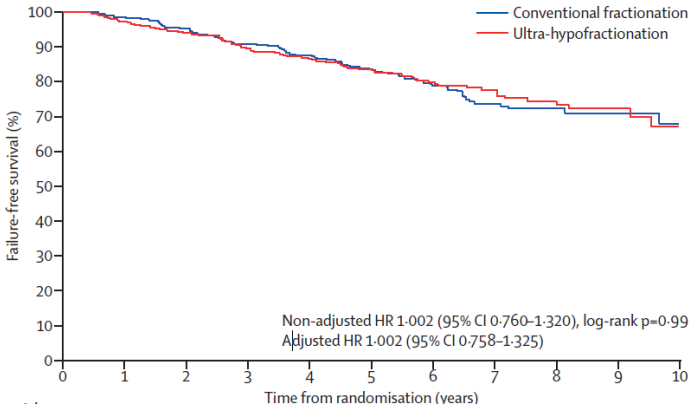
- T1b-T3aN0M0
- **74 Gy/37#** vs **60 Gy/20#** vs **57 Gy/20#**
- Median FU-62.4 months
- 5-yrs biochemical/clinical failure free survival
  - 88.3% in 74 Gy c/w
  - 90.6% in 60Gy and
  - 85.9% in 57 Gy
- 60 Gy was non-inferior to 74 Gy
- Non-inferiority of 57 Gy could not be claimed
- Long-term side-effects were similar in the groups

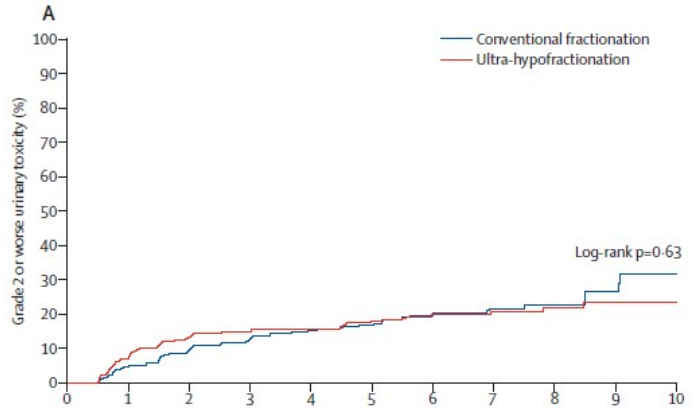


Lancet Oncol 2016; 17: 1047–60

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

- IM and HR prostate cancer with WHO PS 0-2
- Ultra-hypofractionation (42·7 Gy in 7#, 3 days a week)
- Conventional RT (78·0 Gy in 39 #, 5 days a week)
- No ADT was allowed
- Median FU 5 years
- 5-yr failure-free survival-84% in each group (HR-1)
- Non-significant increase in early GU side-effects with SBRT
- Late toxicity was similar
- Results support ultra-hypofractionated RT for prostate cancer



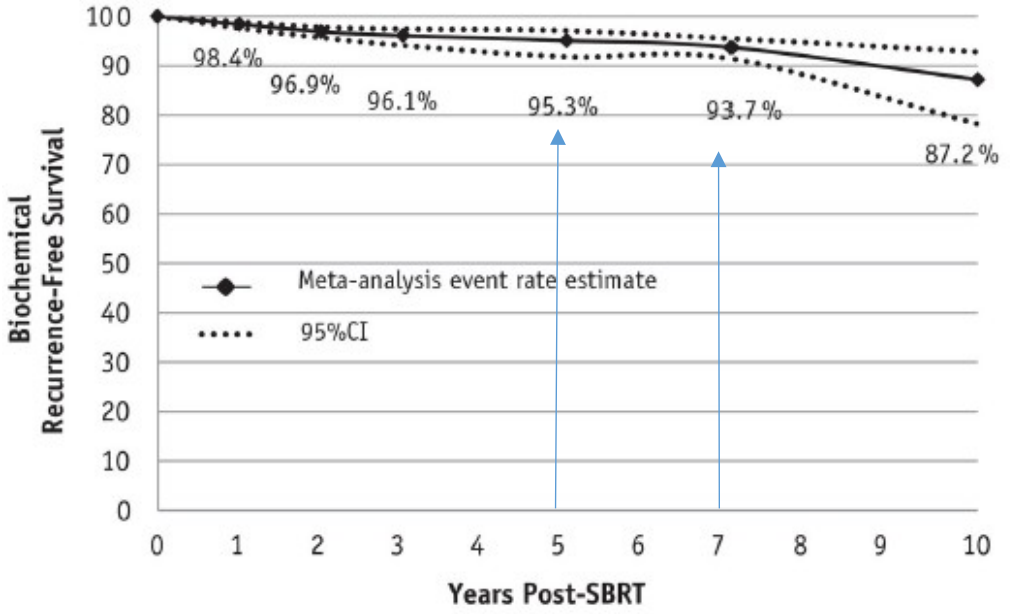


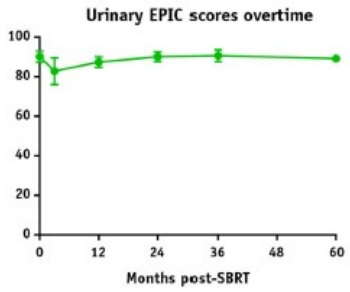
- Better outcome in PACE B can be due to the inclusion of deaths not from ca prostate as events in the HYPO-RT-PC trial

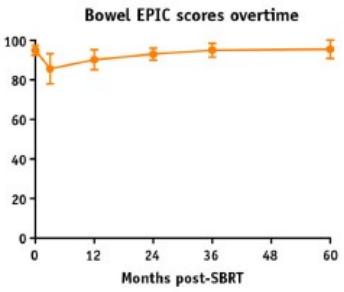
Lancet 2019; 394: 385–95

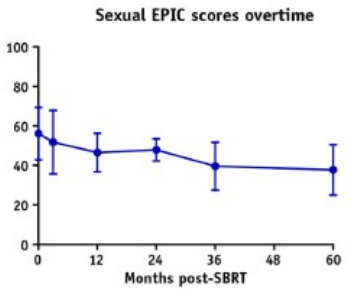
Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies

- 38 prospective series, 6116 patients
- Most common dose/# - 7.25 Gy (range,5-10 Gy)
- Median fraction number - 5 (range, 4-9)
- Median FU- 39 months (range, 12-115 months)
- Overall, 5- and 7-year bRFS rates were 95.3% and 93.7% respectively
- Estimated late grade ≥3 GU & GI toxicity- 2% and 1.1% respectively
- EPIC urinary and bowel scores returned to baseline by 2-yrs post SBRT
- Higher SBRT dose - better bRFS (p- .018), worse late grade ≥3 GU toxicity (p- .014)









Int J Radiat Oncol Biol Phys. 2019 Jul 15;104(4):778-789

- Strengths of the PACE-B trial
  - Large sample size
  - Multicenter recruitment across three countries
  - Quality-assured radiation delivery a well-defined and homogeneous population
- Limitation-
  - Only 5-years toxicity data
  - What proportion of the patients in this trial would now receive active surveillance remains unclear

Conclusion

- SBRT is a robust and viable alternative to moderately fractionated RT for low and IM risk ca prostate, offering equivalent efficacy
- Shorter treatment time, patient convenience, resource utilization
- May slightly increase the risk of acute GI/GU toxicities
- Late toxicities similar to conventional RT
- Careful patient selection is important

Thank you