Hypofractionation for Prostate Radiotherapy

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RCC, Trivandrum

Why hypo fractionate?

- Hypo fractionated Radiotherapy is better for Cancers with low α/β Ratio
- The estimated α/β Ratio for Prostate Ca is 1.4-1.9 Gy
- The α/β Ratio of rectum & bladder are higher .
- Could produce better control with bigger Fractions.

- Convenient for patient
- Economical

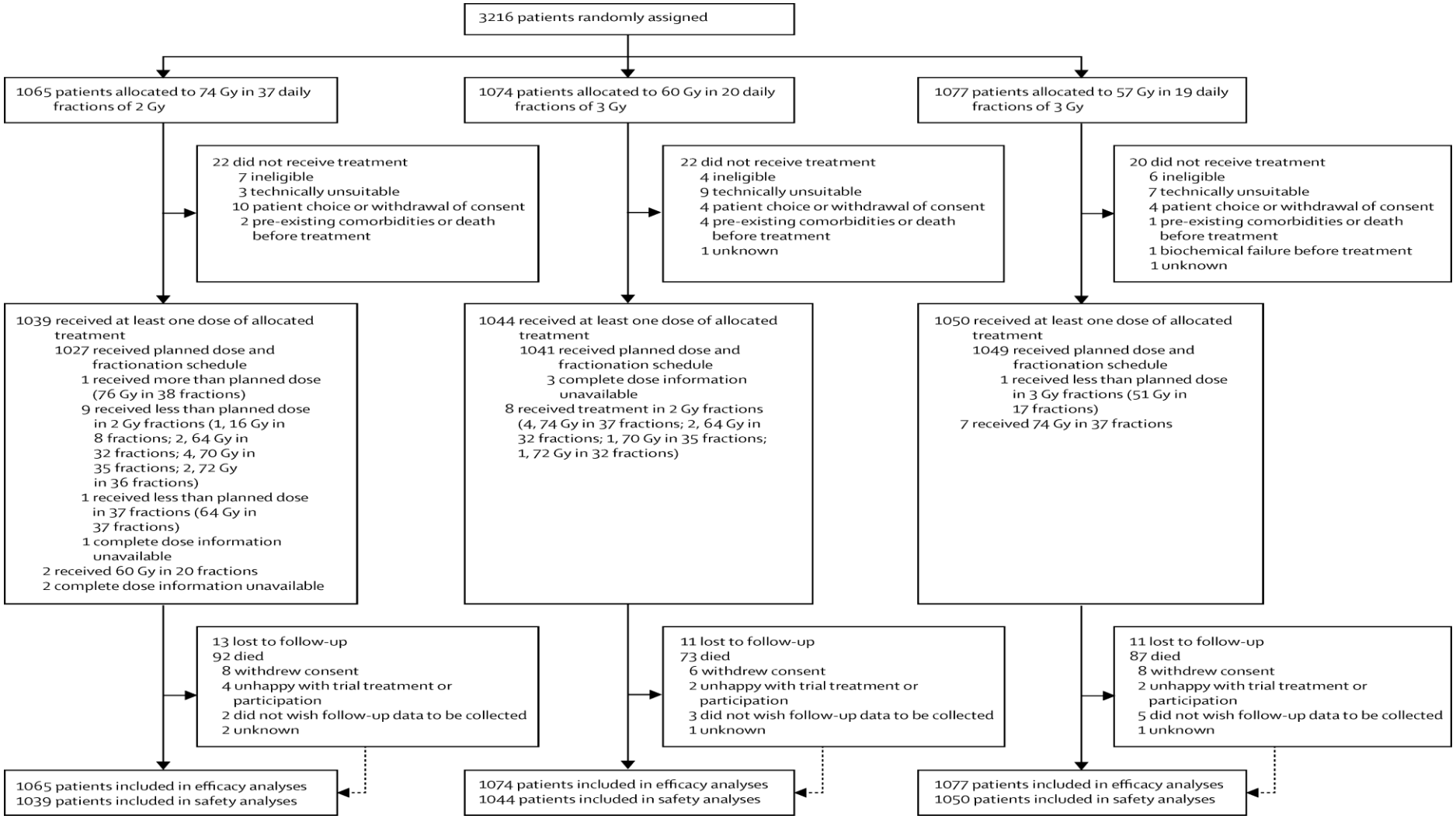
Review of Moderate hypofractionation

- CHHIP
- PROFIT
- RTOG 0415
- HYPRO
- A Pollack
- MD Anderson
- G Acrangeli

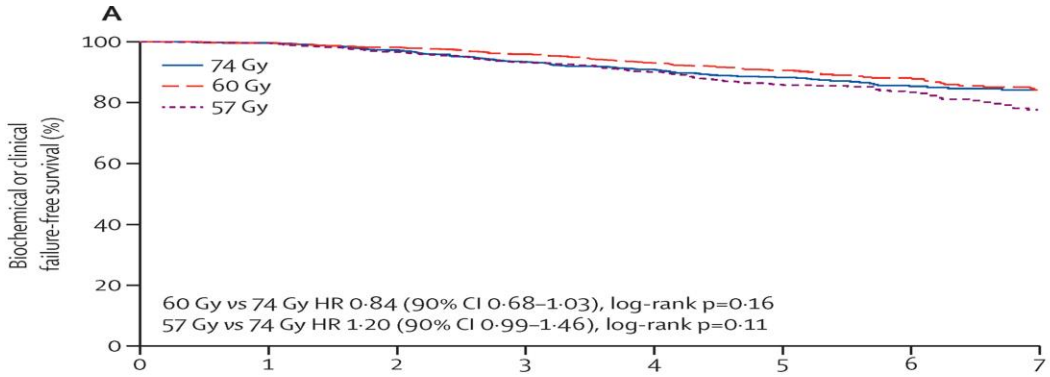
CHHIP trial

- David Dearnley, UK (PI)
- Non inferiority Trial .Largest
- From Oct 2002- Jun 2011, **3216** men .
- Low risk 15%**Intermediate Risk 73 %** ,
  High risk 12 %
- Arms were 74 Gy/37# Vs 60 Gy /20# Vs 57/19#

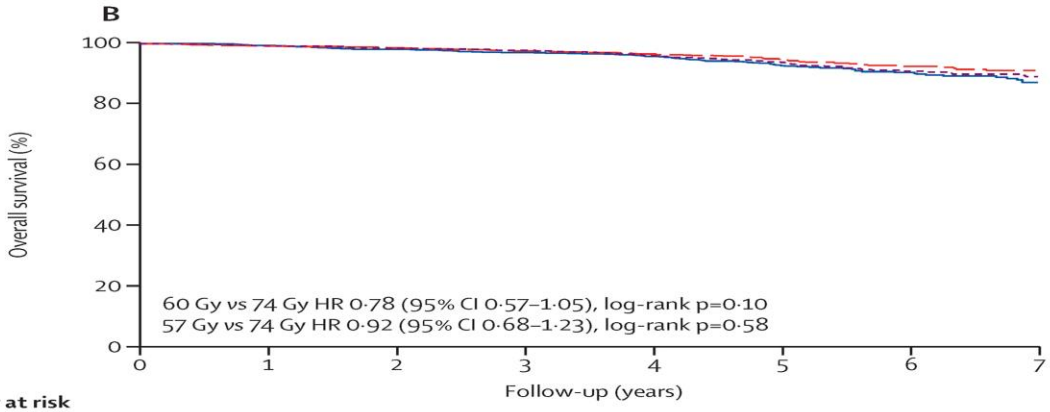
- Dearnley D, et al. Conventional versus hypo fractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol. 2016 ;17(8):1047-1060.


3216 patients randomly assigned
1065 patients allocated to 74 Gy in 37 daily fractions of 2 Gy
1074 patients allocated to 60 Gy in 20 daily fractions of 3 Gy
1077 patients allocated to 57 Gy in 19 daily fractions of 3 Gy
22 did not receive treatment
7 ineligible
3 technically unsuitable
10 patient choice or withdrawal of consent
2 pre-existing comorbidities or death before treatment
22 did not receive treatment
4 ineligible
9 technically unsuitable
4 patient choice or withdrawal of consent
4 pre-existing comorbidities or death before treatment
1 unknown
20 did not receive treatment
6 ineligible
7 technically unsuitable
4 patient choice or withdrawal of consent
1 pre-existing comorbidities or death before treatment
1 biochemical failure before treatment
1 unknown
1039 received at least one dose of allocated treatment
1027 received planned dose and fractionation schedule
1 received more than planned dose (76 Gy in 38 fractions)
9 received less than planned dose in 2 Gy fractions (1, 16 Gy in 8 fractions; 2, 64 Gy in 32 fractions; 4, 70 Gy in 35 fractions; 2, 72 Gy in 36 fractions)
1 received less than planned dose in 37 fractions (64 Gy in 37 fractions)
1 complete dose information unavailable
2 received 60 Gy in 20 fractions
2 complete dose information unavailable
1044 received at least one dose of allocated treatment
1041 received planned dose and fractionation schedule
3 complete dose information unavailable
8 received treatment in 2 Gy fractions (4, 74 Gy in 37 fractions; 2, 64 Gy in 32 fractions; 1, 70 Gy in 35 fractions; 1, 72 Gy in 32 fractions)
1050 received at least one dose of allocated treatment
1049 received planned dose and fractionation schedule
1 received less than planned dose in 3 Gy fractions (51 Gy in 17 fractions)
7 received 74 Gy in 37 fractions
13 lost to follow-up
92 died
8 withdrew consent
4 unhappy with trial treatment or participation
2 did not wish follow-up data to be collected
2 unknown
11 lost to follow-up
73 died
6 withdrew consent
2 unhappy with trial treatment or participation
3 did not wish follow-up data to be collected
1 unknown
11 lost to follow-up
87 died
8 withdrew consent
2 unhappy with trial treatment or participation
5 did not wish follow-up data to be collected
1 unknown
1065 patients included in efficacy analyses
1039 patients included in safety analyses
1074 patients included in efficacy analyses
1044 patients included in safety analyses
1077 patients included in efficacy analyses
1050 patients included in safety analyses

Outcome



Number at risk (events)								
74 Gy	1065 (4)	1037 (24)	991 (39)	926 (24)	795 (20)	495 (11)	284 (3)	167 (11*)
60 Gy	1074 (4)	1042 (15)	1011 (23)	965 (28)	816 (18)	533 (10)	280 (10)	176 (10*)
57 Gy	1077 (5)	1044 (30)	1004 (35)	944 (31)	798 (31)	492 (9)	262 (13)	151 (9*)
Number censored								
74 Gy	0	24	22	26	107	280	200	114
60 Gy	0	28	16	23	121	265	243	94
57 Gy	0	28	10	25	115	275	221	98



Number at risk (events)								
74 Gy	1065 (6)	1045 (13)	1025 (11)	996 (13)	889 (23)	585 (10)	337 (9)	201 (7*)
60 Gy	1074 (8)	1049 (6)	1035 (11)	1011 (10)	896 (14)	608 (10)	339 (4)	224 (10*)
57 Gy	1077 (7)	1053 (9)	1041 (7)	1021 (18)	910 (17)	606 (14)	336 (5)	217 (10*)
Number censored								
74 Gy	0	14	7	18	94	281	238	127
60 Gy	0	17	8	13	105	274	259	111
57 Gy	0	17	3	13	93	287	256	114

ELSEVIER

Toxicity

- Late toxicity .Similar between arms 74 Gy and 60 Gy
- Early grade ≥2 GI toxicity was more in Hypo

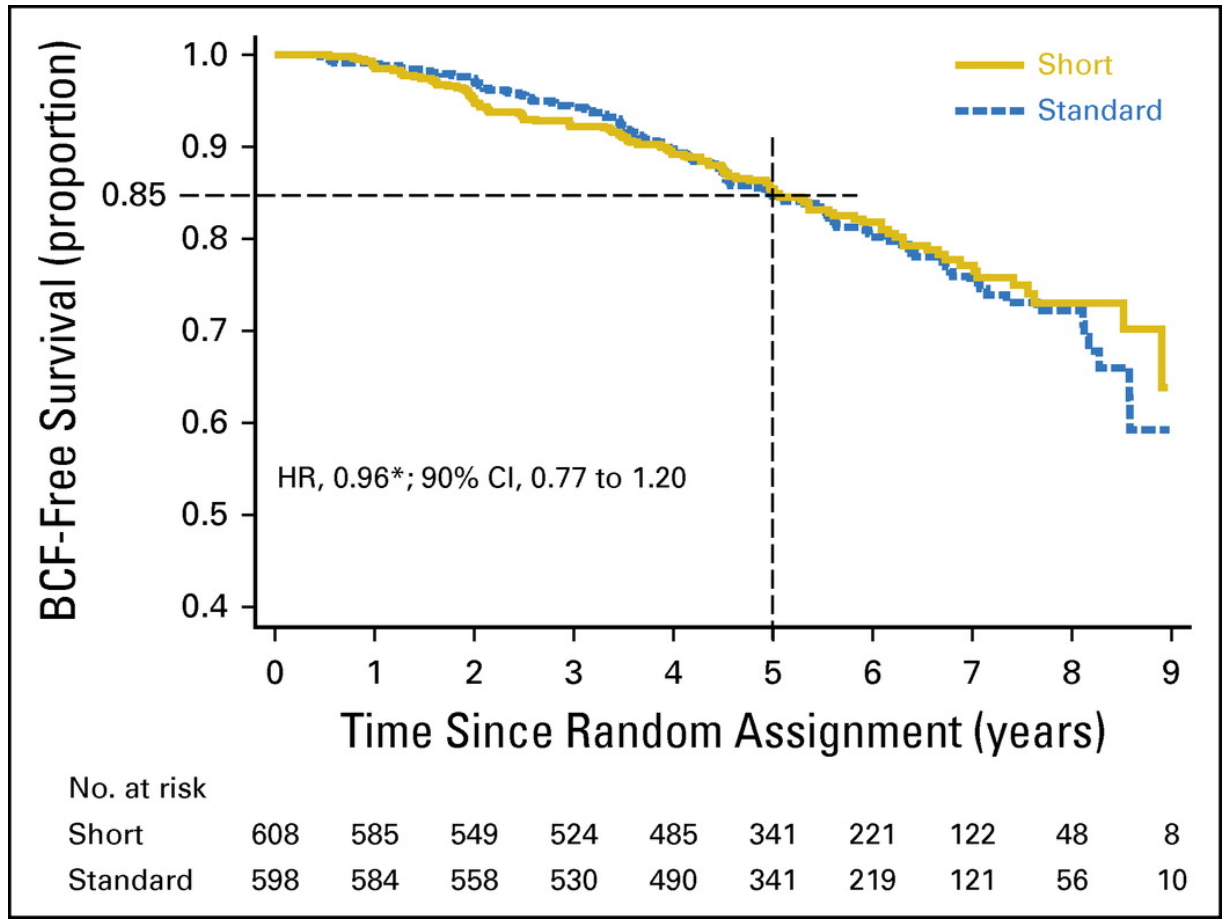
PROFIT trial

- Charles Catton . PMH, Canada
- Non inferiority Trial
- May 2006- Nov 2011,
- 1,206 patients at 27 centers

(14 in Canada, 12 in Australia, and one in France)

Intermediate risk :

- 28296582Catton CN, et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. J Clin Oncol. 2017 Jun 10;35(17):1884-1890.


BCF-Free Survival (proportion)
1.0
0.9
0.85
0.8
0.7
0.6
0.5
0.4
Short
Standard
HR, 0.96*; 90% CI, 0.77 to 1.20
0
1
2
3
4
5
6
7
8
9
Time Since Random Assignment (years)
No. at risk
Short 608 585 549 524 485 341 221 122 48 8
Standard 598 584 558 530 490 341 219 121 56 10

Toxicity

- Lower late GI toxicity compared to conventional arm.7.4% Vs 11% (p =0.006)

RTOG 0415

- All low risk
- Non inferiority Trial
- No: 1115 Men
- Arms . 73.8Gy/41# Vs 70 Gy/28#
- 5 year DFS 85.3% and 86.3%
- **Late grade 2&3 GI/GU toxicity higher**

- Lee WR et al . Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. J Clin Oncol. 2016 ;34(20):2325-32.

RTOG 0415

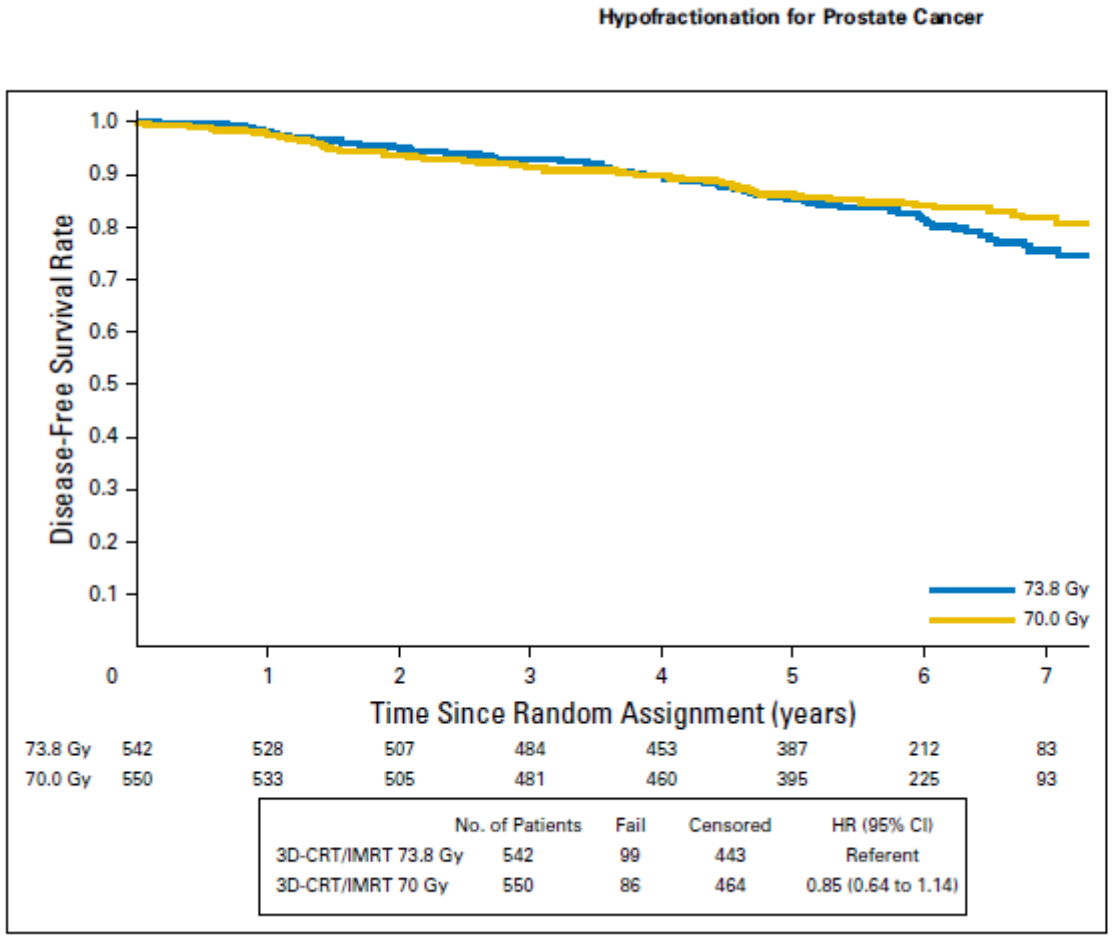
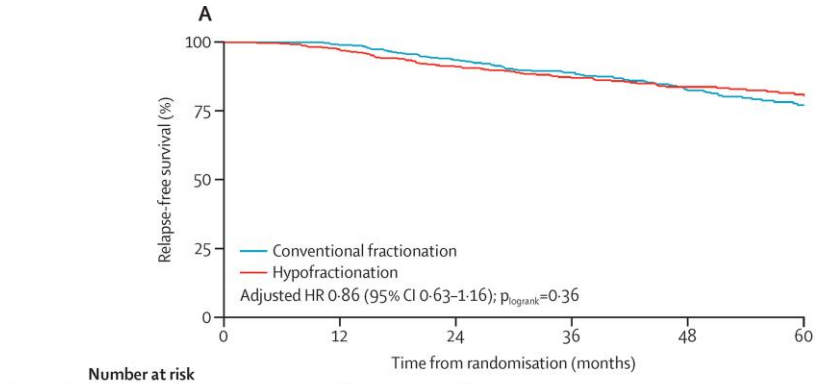


Fig 2. Estimates of disease-free survival (DFS) according to treatment assignment. The hazard ratio (HR) comparing DFS between the two arms (hypofractionated radiotherapy/conventional radiotherapy) is 0.85 (95% CI, 0.64 to 1.14). The prespecified noninferiority criterion was met (null hypothesis HR > 1.52 rejected; $P < .001$). 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

HYPRO

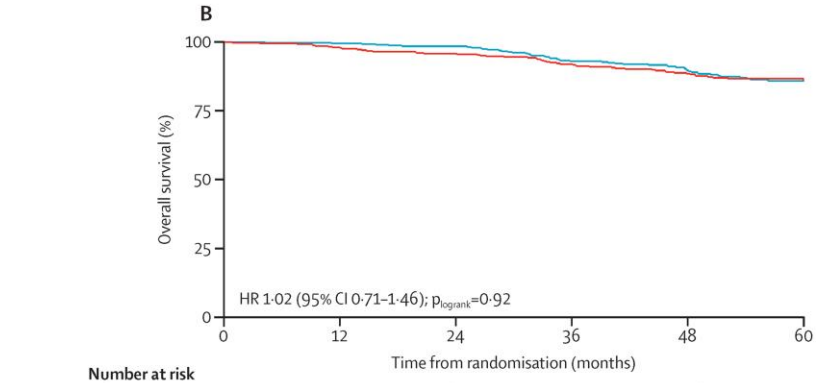
- Rotterdam
- Randomised Superiority trial
- 820 men from 2007-2010.
- Intermediate and high risk patients
- 64.6 Gy/19#/3 # per week Vs 78 Gy/ 39#/5# per week
- 5 year RFS for Hypo was 80.5% and conventional 77.1%
- 7 year RFS .71.7% and 67.6% (IJROBP 2020)
- Hypo Not superior

- Incrocci L et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2016 ;17(8):1061-1069.



Number at risk						
Conventional fractionation	397	386	356	314	247	127
Hypofractionation	407	384	350	309	254	142

Number censored						
Conventional fractionation	0	7	9	25	46	108
Hypofractionation	0	11	11	26	44	105



Number at risk						
Conventional fractionation	397	391	382	354	306	177
Hypofractionation	407	396	384	360	311	185

Number censored						
Conventional fractionation	0	4	5	7	36	118
Hypofractionation	0	2	4	9	36	119

Toxicity

- Cumulative grade 3 or worse late GU toxicity was significantly higher for Hypofractionated arm (19% Vs 12.9%. P =0.021)

Allan Pollack

- Fox chase
- 76 Gy/38#/7.5 weeks Vs 70.2 Gy/ 26#/5 weeks
- 307 patients (Intermediate risk - 36% and High risk- 64%)
- 5 year biochemical free survival 85 and 81%

- Late GU toxicity more for Hypo if IPSS is higher than 12.

- Pollack A et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. J Clin Oncol. 2013 ;31(31):3860-8.

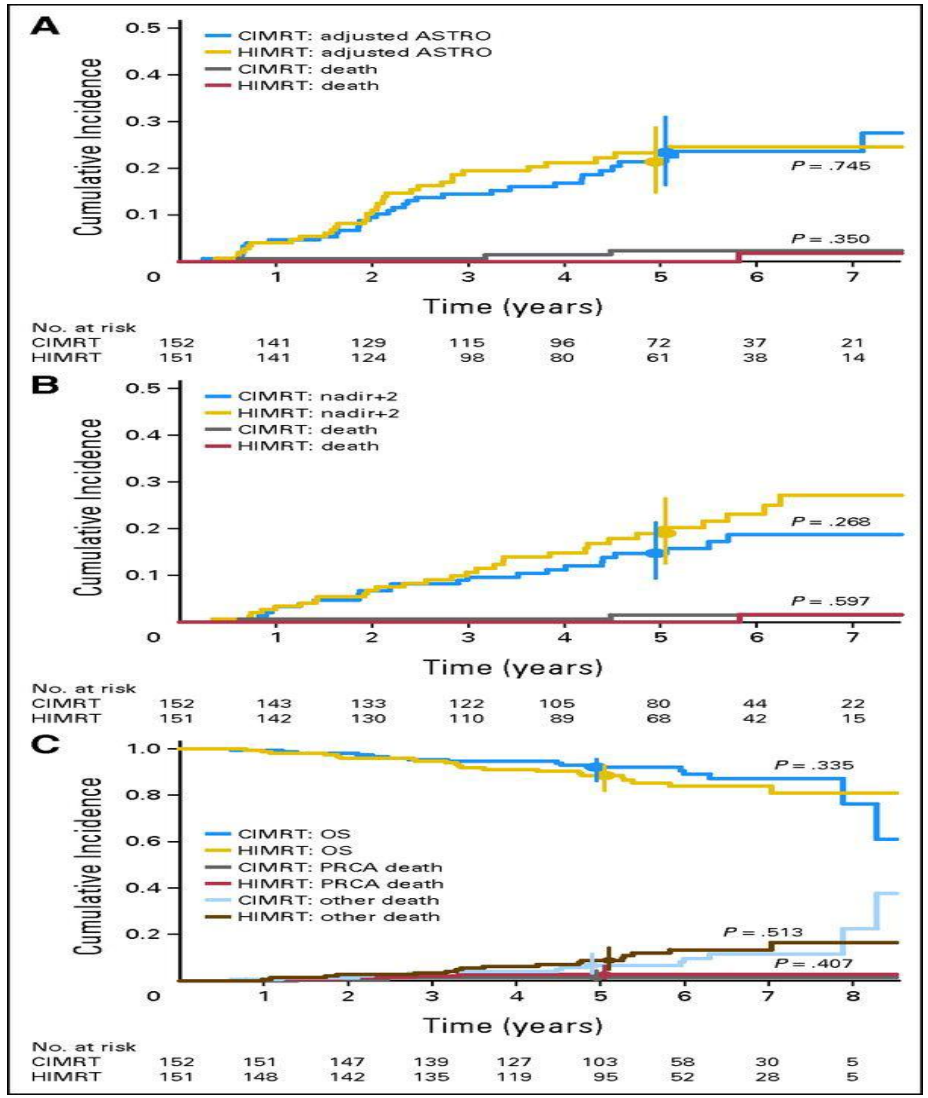


Fig 2. Incidence of biochemical or clinical disease failure (BCDF) using (A) protocol-adjusted ASTRO (American Society for Radiation Oncology) and (B) nadir plus 2 criteria for biochemical failure and (C) overall survival (OS) and incidence of prostate cancer death (PRCA) and death resulting from other causes. P values compare treatment arms using Gray's test for cumulative incidence of BCDF and PRCA; log-rank test was used for OS. The 5-year rates for BCDF using the protocol-adjusted ASTRO definition of biochemical failure were 21.4 (95% CI, 14.8 to 28.7) and 23.3 (95% CI, 16.4 to 31.0) for conventional fractionated intensity-modulated radiotherapy (CIMRT) and hypofractionated intensity-modulated radiotherapy (HIMRT), respectively. The 5-year rates for BCDF using the nadir plus 2 definition of biochemical failure were 14.8 (95% CI, 9.3 to 21.4) and 19.0 (95% CI, 12.6 to 26.5) for CIMRT and HIMRT, respectively. Vertical bars depict 95% CIs.

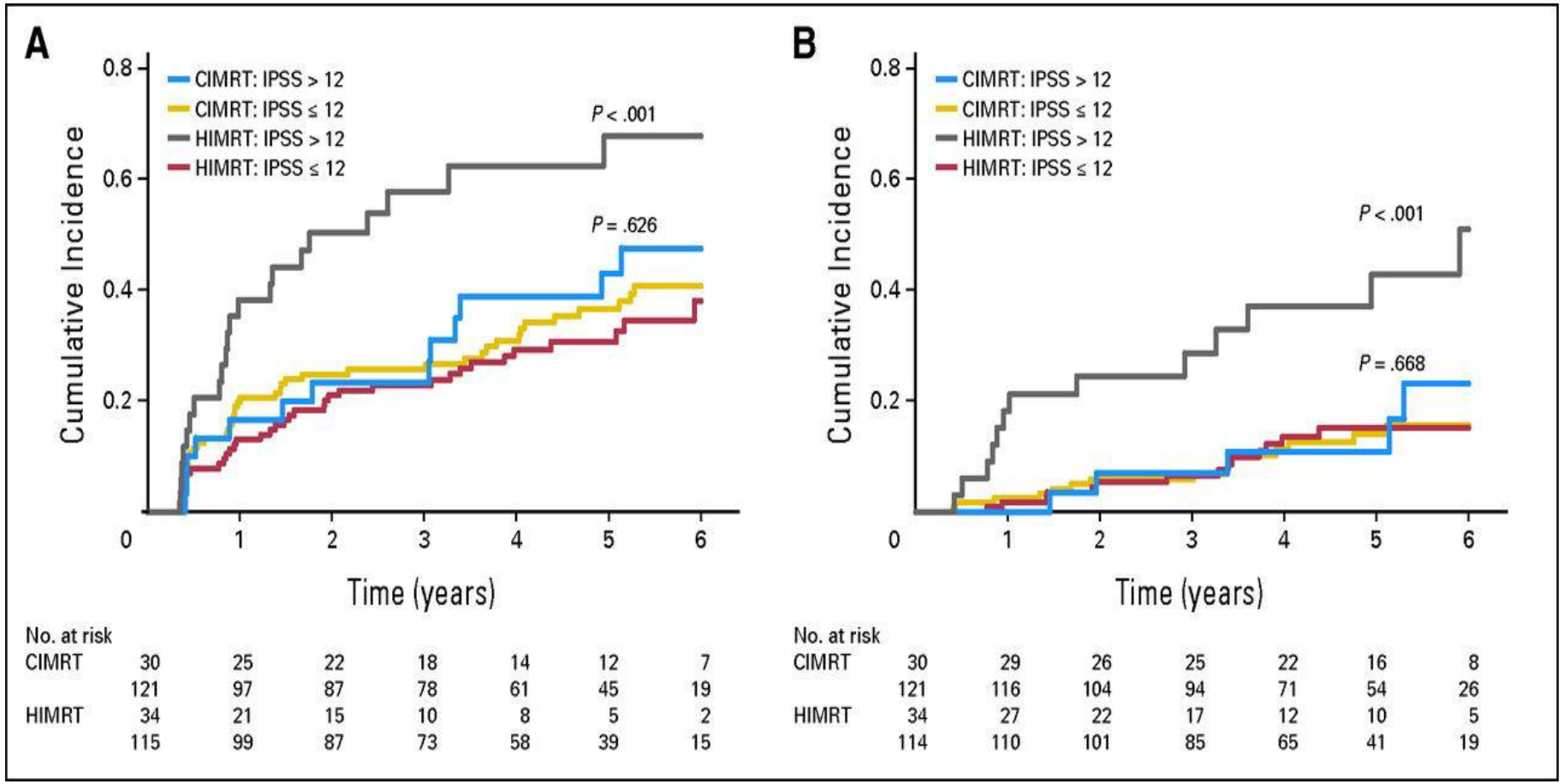


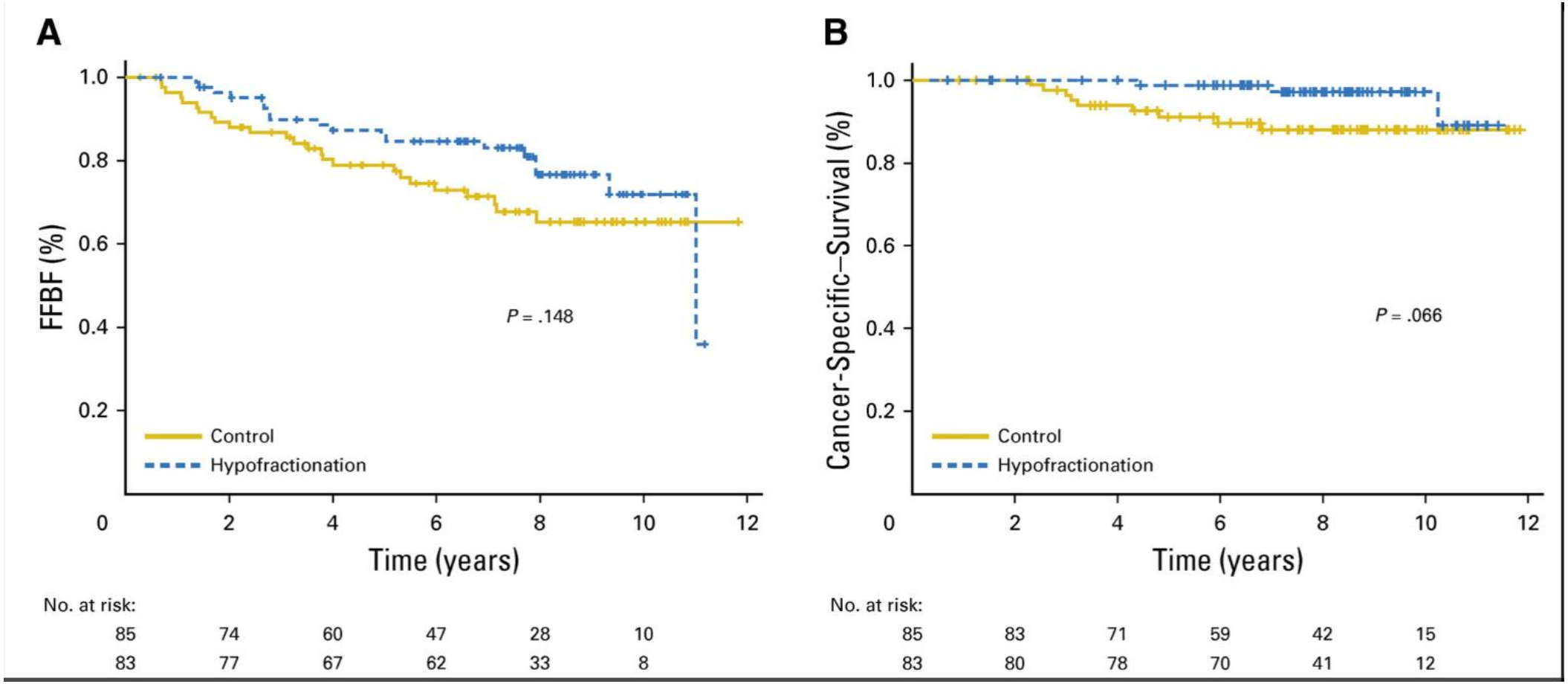
Fig 4. Cumulative incidence of late grade ≥ 2 genitourinary (GU) toxicity subdivided by treatment arm (conventional fractionated intensity-modulated radiotherapy [CIMRT] v hypofractionated intensity-modulated radiotherapy [HIMRT]) and International Prostate Symptom Score (IPSS) at a cut point of 12. Results using (A) original protocol definition of GU toxicity and (B) amended criteria are shown. P value determined using Gray's test.

G Acrangeli ,Madison

- Hypo fractionated RT 62 Gy /20 # /5 weeks Vs 80 Gy/40#/8 weeks
- 168 patients (High risk 76% and L/I risk 24%)
- 10 yr FFBF was 72% and 65% (P=0.148).
- 10 yr Pca SS was 95% and 88% (P=0.066)
- Toxicity were similar long term

- Arcangeli G et al.. Moderate Hypofractionation in High-Risk, Organ-Confined Prostate Cancer: Final Results of a Phase III Randomized Trial. J Clin Oncol. 2017 ;35(17):1891-1897.

G Acrangeli , Madison



KE Hoffman ,MD Anderson

- 75.6 Gy/108 gy / 8.4 weeks Vs 72 Gy/2.4 Gy/30 # (equivalent to 85 Gy if α/β ratio of 1.5)
- 206 patients . (LR 28%, IR 72% HR 1%)
- 8 yr Biochemical failure was 12.7% (95% CI, 6.8% to 23.0%) for Hypo and 18% (95% CI, 10.5% to 29.8%) for Conventional (P=0.033).
- Late Gi and GU toxicity similar

- Hoffman KE et al. Randomized Trial of Hypofractionated, Dose-Escalated, Intensity-Modulated Radiation Therapy (IMRT) Versus Conventionally Fractionated IMRT for Localized Prostate Cancer. J Clin Oncol. 2018 ;36(29):2943-2949.

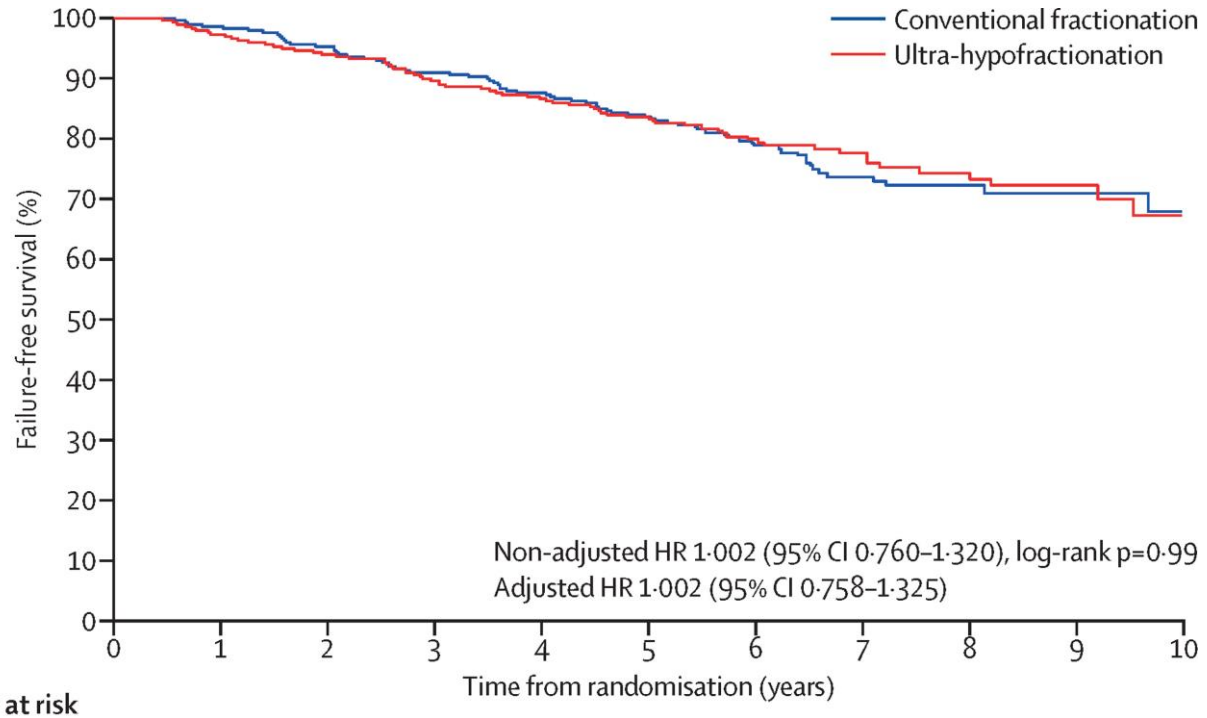
Extreme hypofractionation

- SBRT
- Usually 6-10 Gy Dose per fraction
- Delivered daily /3 per week/weekly

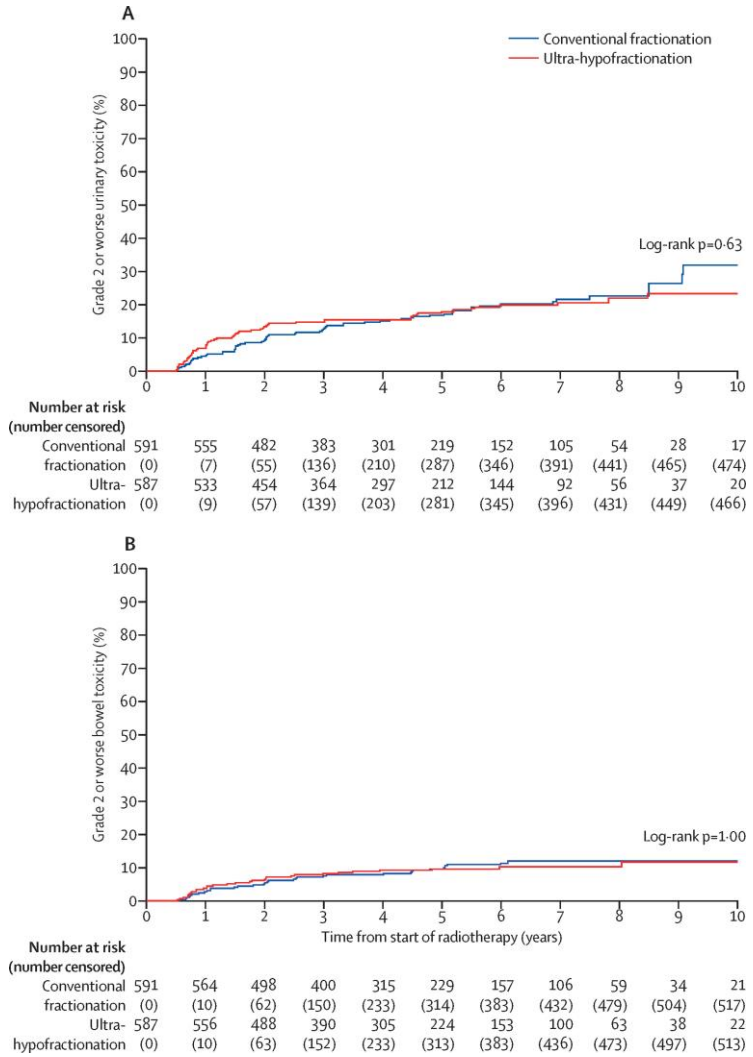
HYPO-RT-PC . Widmark

- 42.7 gy /7# /3 days per week versus 78Gy /39# conventional
- 1200 patients (Intermediate 89% & high risk 11%)
- Failure free at 5 years 84% in both arms
- Toxicity: higher acute toxicity ,not Late Toxicity

- Widmark A et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet. 2019 ;394(10196):385-395.



Number at risk (number censored)											
Conventional fractionation	591 (0)	580 (4)	540 (24)	433 (108)	332 (196)	242 (273)	171 (332)	108 (386)	67 (425)	37 (454)	23 (467)
Ultra-hypofractionation	589 (0)	569 (4)	527 (27)	408 (125)	325 (196)	242 (269)	160 (342)	113 (385)	71 (423)	38 (454)	20 (470)



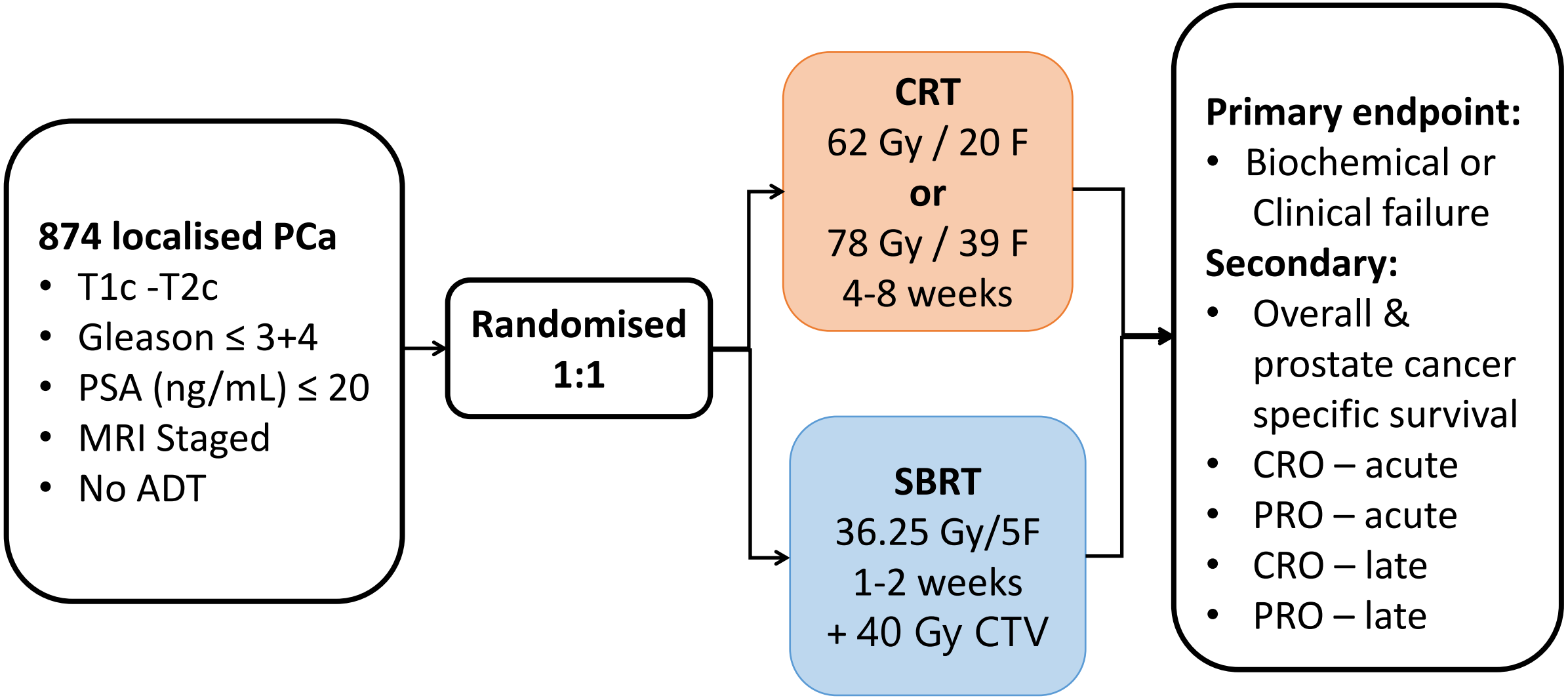
5-year outcomes from PACE-B:

An international phase III randomized controlled trial comparing stereotactic body radiotherapy (SBRT) vs conventionally fractionated or moderately hypofractionated external beam radiotherapy for localised prostate cancer

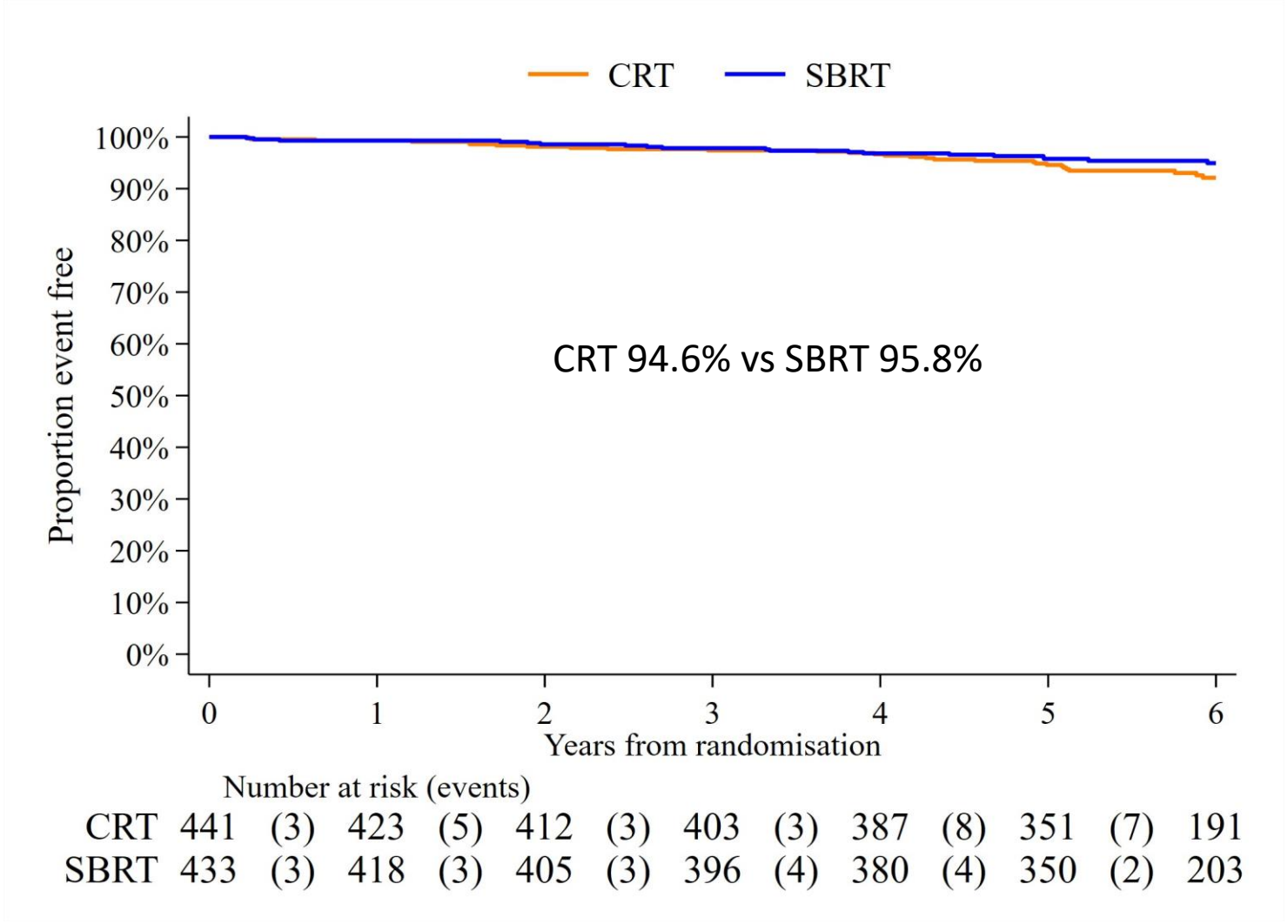
Nicholas van As, Alison Tree, Jaymini Patel, Peter Ostler, Hans van der Voet, Andrew Loblaw, William Chu, Daniel Ford, Shaun Tolan, Suneil Jain, John G Armstrong, Philip Camilleri, Kiran Kancherla, John Frew, Andrew Chan, Olivia Naismith, Georgina Manning, Stephanie Brown, Clare Griffin, Emma Hall

Prof Nicholas van As
on behalf of the PACE Trial Investigators

PACE B trial schema & endpoints

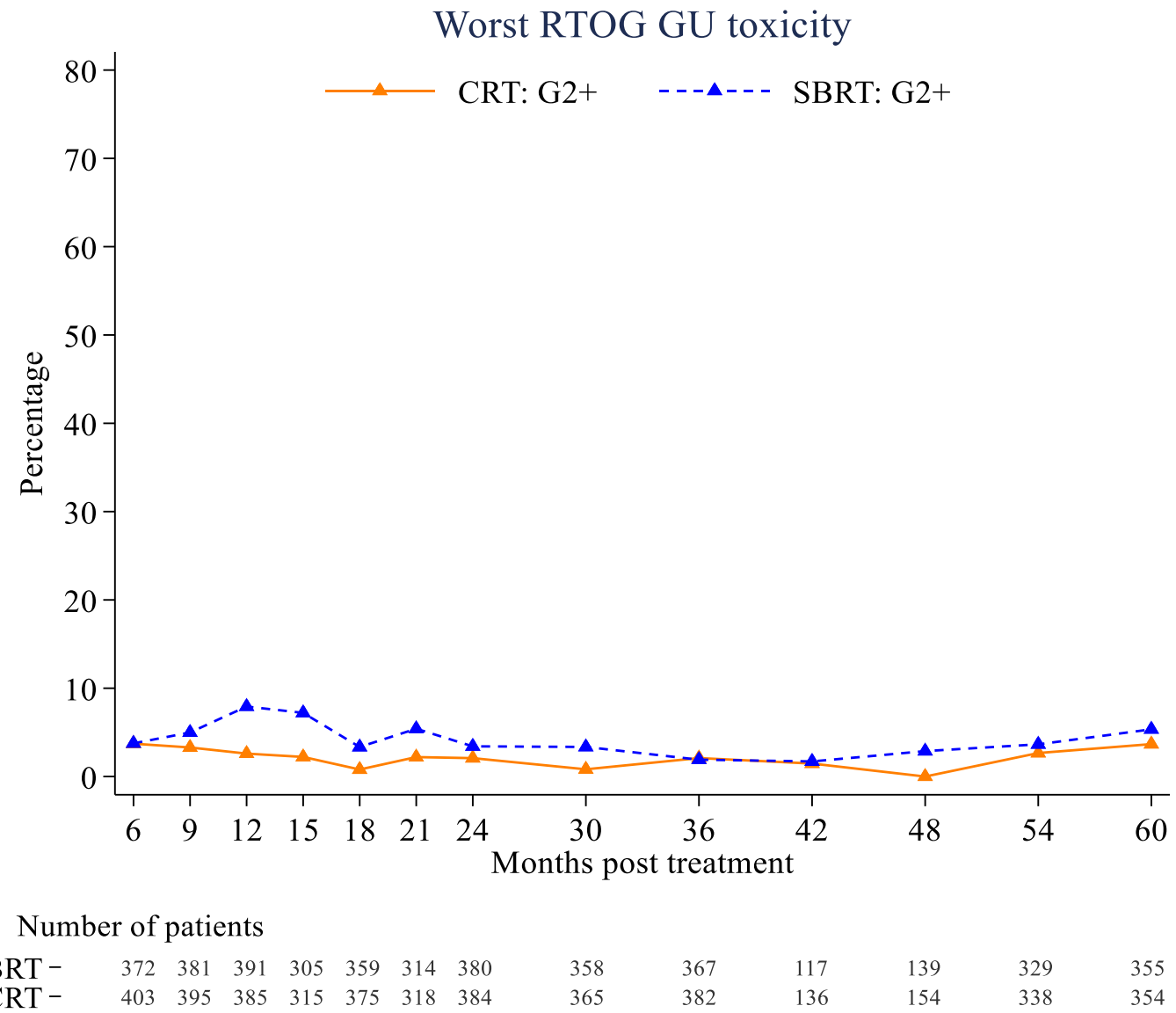


Biochemical/clinical failure – primary endpoint



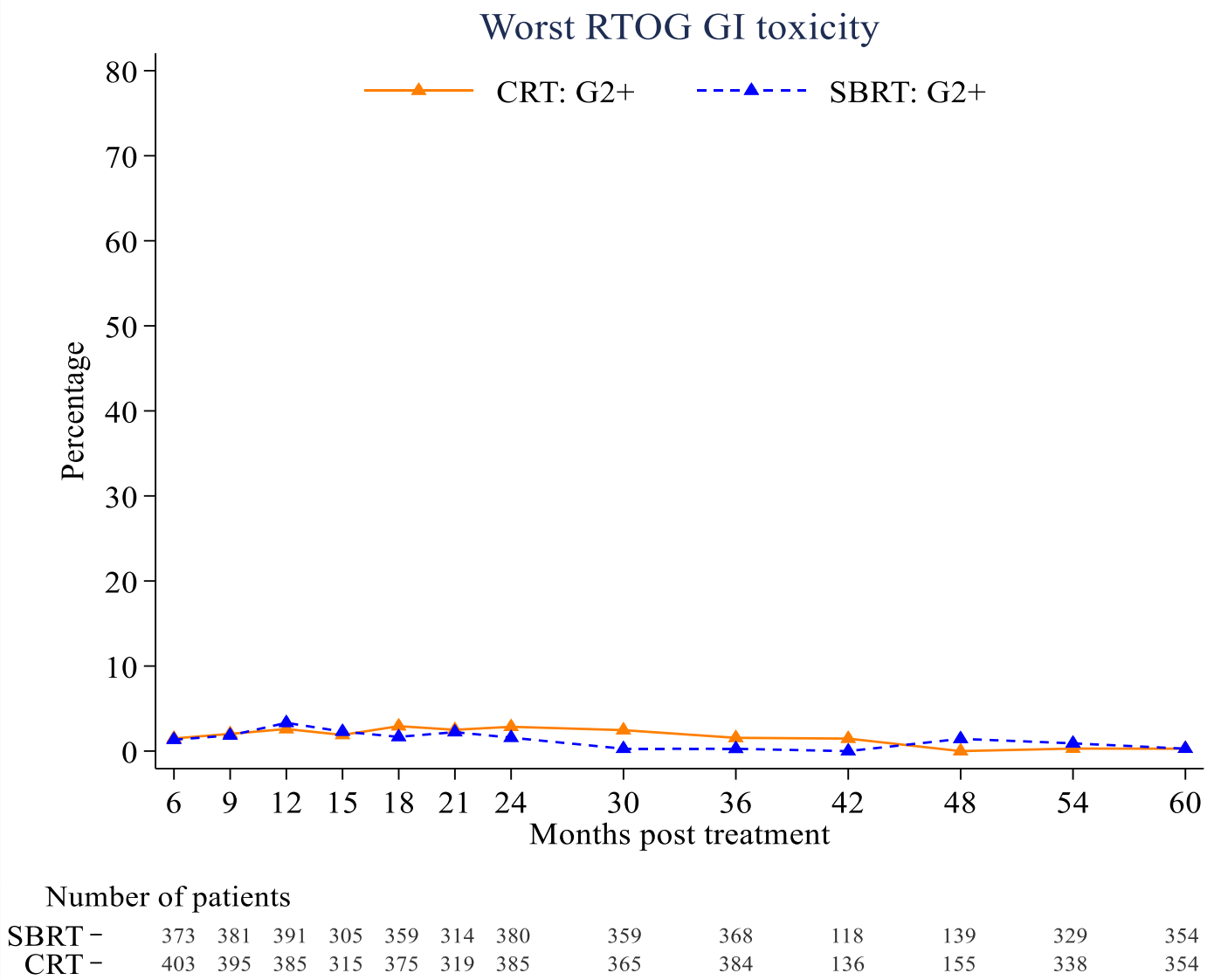
RTOG GU toxicity – up to 5 years

RTOG GU at 5 years	CRT N (%)	SBRT N (%)	P-value
Grade 0/1	341 (96.3)	336 (94.6)	0.28
Grade 2+	13 (3.7)	19 (5.4)	



RTOG GI toxicity – up to 5 years

RTOG GI at 5 years	CRT N (%)	SBRT N (%)	P-value
Grade 0/1	353 (99)	353 (99)	0.99
Grade 2+	1 (<1)	1 (<1)	



PATRIOT Study

- low or intermediate risk prostate cancer
- Exclusion :IPSS > 19 &> 90 cc prostate
- 152 Canadian men.
- Weekly SABR had better acute toxicity compared to EOD

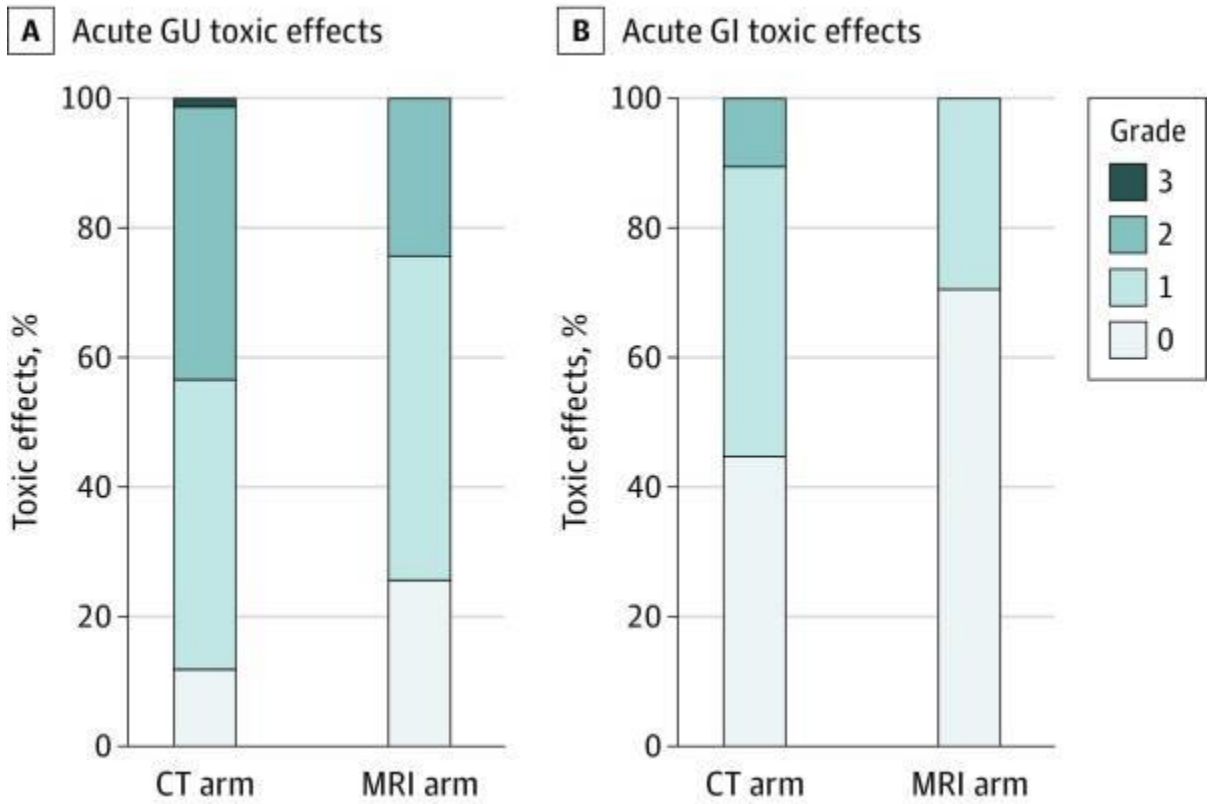
- Quon HC et al. Once-weekly versus every-other-day stereotactic body radiotherapy in patients with prostate cancer (PATRIOT): A phase 2 randomized trial. Radiother Oncol. 2018 ;127(2):206-212.

Mirage trial . A Kishan

- SBRT CT guided (4 mm PTV) and MRI guided (2mm PTV)SBRT compared
- 156 patients
- 40 Gy in 5 fractions .
- Acute Toxicity less for MRI guided SBRT
- Late toxicity and outcome not reported yet.

- Kishan AU, Magnetic Resonance Imaging-Guided vs Computed Tomography-Guided Stereotactic Body Radiotherapy for Prostate Cancer: The MIRAGE Randomized Clinical Trial. JAMA Oncol. 2023 ;9(3):365-373.

MIRAGE trial . AU Kishan UCLA 2023.



Two fractions ?

- A randomized phase II trial of MR-guided prostate stereotactic body radiotherapy administered in 5 or 2 fractions for localized prostate cancer (FORT)

Wolfe S et al . A randomized phase II trial of MR-guided prostate stereotactic body radiotherapy administered in 5 or 2 fractions for localized prostate cancer (FORT). BMC Cancer. 2023 Sep 30;23(1):923

Finally single fraction ?

- ONE SHOT trial ?
- PROSINT Trial ?

- Ong WL, Loblaw A. The march toward single-fraction stereotactic body radiotherapy for localized prostate cancer-Quo Vadimus? World J Urol. 2023 Nov 3. doi: 10.1007/s00345-023-04663-x.

Oligometastatic disease

De Novo Oligometastatic Prosate cancer .

- PLATON/TERPS/METRO/START PRESTO study results are awaited .

Oligorecurrence HSPC

- SABR-COMET, STOMP, ORIOLE etc.

Conclusions

- Moderately and Utra hypofractionaterd RT appear as effective as Conventional fractionation . Superiority is not proven.
- Acute side effects appears higher.
- Late side effects are higher in some subset of patients
- Patients with higher IPSS and h/o TURP are at higher risk of Urinary toxicity
- Toxicity is related to PTV margins, SV dose , Image Guidance etc.
- More data is needed for less than 5 fractions of RT
- SBRT for Oligometastatic prostate disease is also evolving.

Thank You