## Hypofractionated vs. conventionally fractionated radiotherapy for prostate cancer: A meta-analysis

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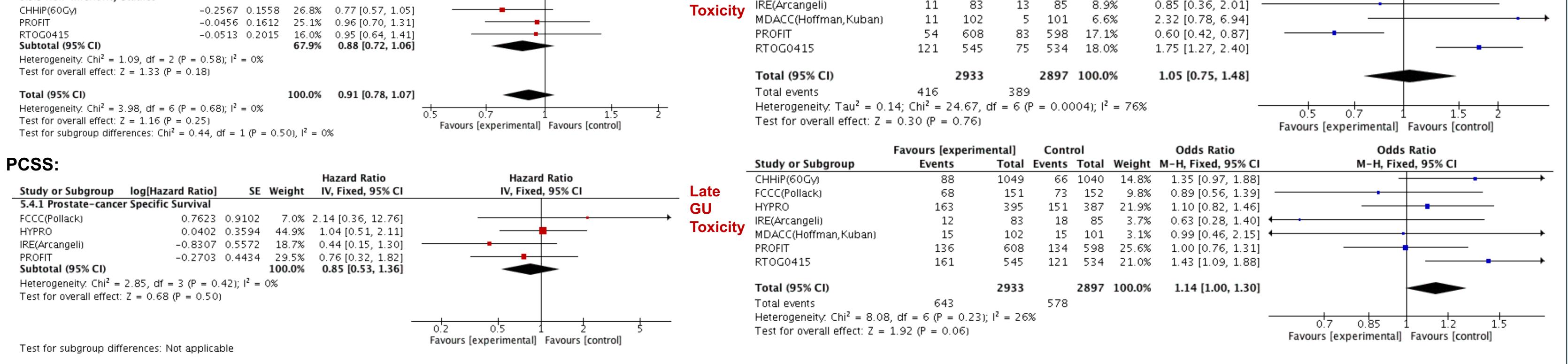
Objectives:	We conducted a meta-analysis of currently reported randomized clinical trials (RCT) to investigate the biochemical and/or clinical progression free survival (BCPFS) benefit and safety of hypofractionated radiotherapy (HFRT) compared to conventionally fractionated dose-escalated radiotherapy (CFRT) for localized prostate cancer.
Methods:	A comprehensive Medline and conference abstracts search was conducted to identify RCT reporting efficacy and toxicity of HFRT. Studies were included if they compared HFRT (2.4-4.5 Gy per fraction) with CFRT (1.8-2.0 Gy per fraction) for patients with localized prostate cancer. Studies that used CFRT dose less than 74 Gy or HFRT dose with EQD2 of less than 74 Gy, rounded to nearest whole number, were excluded. Primary endpoint was BCPFS defined as freedom from biochemical failure or clinical progression. Secondary endpoints were prostate-cancer specific survival, overall survival, and acute/late genitourinary (GU) and gastrointestinal (GI) toxicity. Hazard ratio (HR) was the effect size of choice for survival endpoints and odds ratio (OR) for toxicities. Event rates were assumed to be constant for HR estimations under the
	proportional hazard model. Either random-effects model (RE) or fixed-effect model (FE) was used based on the test of heterogeneity.



## TOXICITY:

## **BCPFS**:

Study or Subgroup	Hazard Ratio log[Hazard Ratio] SE Weight IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI		Study or Subgroup	Favours [ex] Events	-			Odds Ratio ght M-H, Random, 95% C	Odds Ratio M-H, Random, 95% CI
	tudies (Dose: CFRT >= 74Gy & HFRT EQD2 >= 74 Gy)		—	CHHiP(60Gy)	277	72				
FCCC(Pollack)	0.3199 0.2835 4.8% 1.38 [0.79, 2.40]		Acute	FCCC(Pollack)		15			• /	-
HYPRO	-0.1568 0.1557 15.9% 0.85 [0.63, 1.16]			•	15				• •	-
IRE(Arcangeli)	-0.4834 0.3114 4.0% 0.62 [0.33, 1.14]		GI	HYPRO	169	40			• /	
MDACC(Hoffman,Kuban)	-0.755 0.36 3.0% 0.47 [0.23, 0.95]	•	Toxicity	IRE(Arcangeli)	29	8			.5% 2.00 [1.00, 3.98	-
Norkus, HypoFx Cap, 2009 Subtotal (95% CI)	-0.5123 0.9129 0.5% 0.60 [0.10, 3.59] 28.2% 0.83 [0.66, 1.04]			PROFIT RTOG0415	99 58	60 54		598 19 542 17	.4% 1.68 [1.20, 2.36 .2% 1.05 [0.71, 1.56	-
Heterogeneity: Chi <sup>2</sup> = 6.76,	$df = 4 (P = 0.15); I^2 = 41\%$									
Test for overall effect: $Z = 1$	.63 (P = 0.10)			Total (95% CI)		250	9	2483 100	.0% 1.51 [1.20, 1.91	
5 3 3 BCPES - Non-inferior	ity Studies (Dose: CFRT >= 74Gy & HFRT EQD2 >= 74 Gy)			Total events	647		452			
CHHiP(60Gy)	-0.1816 0.1272 23.9% 0.83 [0.65, 1.07]			Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 11.24, df = 5 (P = 0.05); I <sup>2</sup> = 56%						
PROFIT	-0.0395 0.1132 30.1% 0.96 [0.77, 1.20]			Test for overall effect:			·			Favours [experimental] Favours [control]
RTOG0415	-0.1576 0.1473 17.8% 0.85 [0.64, 1.14]									
Subtotal (95% CI)	71.8% 0.89 [0.77, 1.03]				Experime	ntal C	Control		Odds Ratio	Odds Ratio
Heterogeneity: Chi <sup>2</sup> = 0.80,	$df = 2 (P = 0.67); I^2 = 0\%$			Study or Subgroup	Events	Total Eve	ents Tota	al Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% CI
Test for overall effect: $Z = 1$	.58 (P = 0.11)			CHHiP(60Gy)	331	715	356 72	0 33.4%	0.88 [0.72, 1.08]	<b>_</b>
			Acute	FCCC(Pollack)	87	151	87 153		1.02 [0.64, 1.60]	
Total (95% CI)	100.0% 0.87 [0.77, 0.98]		- GU	•					• • •	
Heterogeneity: $Chi^2 = 7.85$ ,		0.5 0.7 1 1.5 2		HYPRO	244		226 39		1.12 [0.84, 1.49]	
Test for overall effect: Z = 2.	P = 0.03 es: Chi <sup>2</sup> = 0.29, df = 1 (P = 0.59), I <sup>2</sup> = 0%	Favours [experimental] Favours [control]	Toxicity	IRE(Arcangeli)	39	83	34 8		1.33 [0.72, 2.45]	
rest for subgroup unterence	1 = 0.29, u = 1 (r = 0.39), r = 0.8			PROFIT	185	608	183 598	8 22.5%	0.99 [0.78, 1.27]	
				RTOG0415	147	545	145 53-	4 18.7%	0.99 [0.76, 1.30]	
OS:										
	Hazard Ratio	Hazard Ratio		Total (95% CI)		2505	248	0 100.0%	0.99 [0.88, 1.11]	
Study or Subgroup	log[Hazard Ratio] SE Weight IV, Fixed, 95% CI	IV, Fixed, 95% CI		Total events	1033	1	031			
5.5.2 Superiority Studies								~		
FCCC(Pollack)	0.3382 0.3473 5.4% 1.40 [0.71, 2.77]		Heterogeneity: $Chi^2 = 2.84$ , $df = 5 (P = 0.72); I^2 = 0\%$ 0.7  0.85  1  1.2  1.5							
HYPRO	$V_{ij} = V_{ij} = V$						Favours [experimental] Favours [control]			
IRE(Arcangeli)	-0.3715 0.3034 7.1% 0.69 [0.38, 1.25]	• • • • • • • • • • • • • • • • • • • •					<b>6</b>			
Norkus, HypoFx Cap, 2009			+		Experin		Control		Odds Ratio	Odds Ratio
Subtotal (95% CI)	32.1% 0.99 [0.74, 1.30]		_	Study or Subgroup	Events	Total E	vents To	tal Weight	: M-H, Random, 95% CI	M-H, Random, 95% Cl
Heterogeneity: $Chi^2 = 2.45$ , $df = 3 (P = 0.48)$ ; $I^2 = 0\%$				CHHiP(60Gy)	105	1049	111 10	40 18.6%	0.93 [0.70, 1.23]	
Test for overall effect: $Z = 0.11$ (P = 0.92)			Late	FCCC(Pollack)	27	151	34 1	.52 13.4%		<b>_</b>
			GI	HYPRO	87	395		87 17.3%		
5.5.3 Non-inferiority Stud	ies			IRF(Arcandeli)	11	222	12	85 8.9%	• • •	





- Eight RCT (CHHiP<sup>1</sup>, Pollack<sup>2</sup>, HYPRO<sup>3</sup>, Arcangeli<sup>4</sup>, Norkus<sup>5</sup>, Hoffman<sup>6</sup>, PROFIT<sup>7</sup> & RTOG0415<sup>8</sup>) were identified with total of 6007 patients.
  - One of the two HFRT arms (i.e. 57 Gy in 19 fraction) in the three-arm CHHiP trial was excluded, as the EQD2 was less than 74 Gy.

## **EFFICACY:**

- Pooled analysis showed that the BCPFS was significantly better in the HFRT compared to CFRT (HR = 0.87; 95% CI: 0.77, 0.98, p=0.03, FE).
- There was no difference in prostate-cancer specific survival (p=0.5, FE) or overall survival (p=0.25, FE).

<b>TOXICITY:</b>
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- Patients treated with HFRT compared to CFRT, demonstrated:
  - statistically significant increased acute grade 2+ gastrointestinal toxicity (26% vs. 18%, OR=1.51, p=0.0005, RE)
  - no difference in grade 2+ acute genitourinary toxicity (41% vs. 42%, p=0.83, FE)
  - no difference in grade 2+ late gastrointestinal toxicity (14% vs. 13%, p=0.76,RE)
  - a trend toward worse grade 2+ late genitourinary toxicity (22% vs. 20%, OR=1.14, p=0.06, FE).

Conclusions:	<ul> <li>HFRT for localized prostate cancer results in statistically significant superior BCPFS when compared to CFRT.</li> <li>With currently reported follow up, there was no difference in prostate-cancer specific survival and overall survival.</li> <li>The improvements in biochemical control come at a modest and acceptable increase in acute and late toxicity</li> <li>Grade 2+ acute GI toxicity was significantly higher with an absolute increase of 8% with HFRT and Grade 2+ late GU toxicities showed a trend toward worse outcome with HFRT.</li> </ul>
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