Supplementary Table 1
Phase 3 Studies of radiotherapy technique and fractionation

Study	No.	Risk groups	Trial design	ADT	Recruitment period	Findings
Trials of Conformal RT and dose-escalation						
Conformal RT **ICR/RMH, London UK** **Dearnaley1999**	225	Int/high risk	Conventional vs conformal RT Dose 64Gy	3-6m LHRHa	1988-95	*Demonstrates Conformal RT reduces side effects* Efficacy unchanged
Dose Escalation Trial Pilot Study **ICR/RMH, London UK** **Dearnaley 2005, Creak 2013**	126	Int/high risk	Dose Escalation CFRT: Factorial design 1) 64Gy vs 74Gy 2)1.0cm vs 1.5cm margin	3-6m LHRHa	1995-7	*Suggests dose-escalation and CFRT improve PSA control* 12% increase in PSA control with 74Gy Higher dose and 1.5cm margin more GU and GI side effects
Medical Research Council UK **RT01 Dose Escalation Trial** **Dearnaley 2007,2014**	843	Int risk 37% High risk 43%	Dose Escalation CFRT: 64Gy vs 74Gy	3-6m LHRHa	1998-2002	*Demonstrates dose-escalation and CFRT improve PSA control* 12% increase in PSA control at 10 years 11% increase in GI side effects at 5 years Overall survival : no difference (11% PCa deaths)

CKVO96-10 **Netherlands** **Peeters 2006** **Heemsbergen 2014**	664	Int risk 27% High risk 55%	Dose Escalation CFRT: 68Gy vs 78Gy	LHRHa for 6 m in 21%	1997-2003	*Demonstrates dose-escalation and CFRT improve PSA control* 13% increase in PSA control at 10 years 5 % increase in GI side effects at 5 years (p=0.2) Overall survival: no difference (13%PCa deaths)
PROG 95-09 **Loma Linda University Medical Center and Massachusetts General Hospital** **Zeitman 2010**	393	Int risk 37% High risk 4%	Dose Escalation CFRT:50.4Gy 28f + Proton boost to 70.2GyE 39f vs 79.2GyE 44f	none	1996-9	16% increase in PSA control at 10 years (p<0.0001) 9 % increase in Grade ≥2 GI side effects at 5 years (p=0.09), 4%% increase in GU side effect at 5 years (p=0.79) Overall survival: no difference (1.5% PCa deaths)
MD Anderson Cancer Centre **USA** **Kuban 2008**	301	Int risk 46% High risk 34%	Dose Escalation CFRT: 70Gy vs 78 Gy	none	1993-98	*Demonstrates dose-escalation and CFRT improve PSA control* 19% increase in PSA control at 8 years 13 % increase in Grade ≥2 GI side effects at 10 years (p=0.013), 5%% increase in GU side effects at 10 years (p=NS) Overall survival : no difference (3%PCa deaths)
GETUG 06 **France**	306	Int risk not stated High risk 29%	Dose Escalation CFRT: 70gy 35f vs 80Gy 40f	none	1999-2002	*Demonstrates dose-escalation and CFRT*

Beckendorf 2011						*improve PSA control* 8.5%% increase in PSA control at 5 years 5 % increase in GI side effects at 5 years (p=0.2), 7.5 % increase in GU side effects at 5 years (p=0.039) Overall survival: no difference (3.3%PCa deaths)
RTOG 0126 **USA** **Michalski 2018**	1522	Int Risk: 100%	Dose Escalation CFRT: 70.2Gy 39f vs 79.2Gy 44f	none	2002-2008	*Demonstrates dose-escalation and CFRT improve PSA control* 15% decrease in PSA failure (35%vs 20% HR 0.054 p=0.001) At 5 yrs 6% increase in Grade≥2 GI HR1.39p=0.006, 5% increase in Grade≥2 GU HR1.59 p=0.003 DM: 4% vs 6% (NS) OS: 76% No difference at 8 years
Trials of image-guided RT						
France **De Crevoiser 2018**	470	Intermediate and high risk	Image Guided RT Daily vs weekly IGRT	ADT in 46%, short or longer course (non-randomised)	2007-12	Tocicity: Late rectal ≥1 RTOG GI reduced with daily IGRT HR 0.71, p=0.027 BPFS improved with daily IGRT HR 0.45, p=0.007 but non-prostate cancer deaths increased with daily IGRT

						HR2.21, p=0.026 (anomalous result)
CHHiP IGRT **UK** **Murray**	293	T1b-T3a, N0, Gleason score <8, PSA<40	Image Guided RT CHHiP sub-study IMRT no IGRT vs IMRT with IGRT with standard (S) or reduced margins (R)	LHRHa 4-6m	2010-2011	Lower bladder and rectal DVH/DSH with IGRT(R) with lower GI and GU side effects No IGRTvs IGRT(S) vs IGRT (R) RTOG ≥2 GI 8.3% vs 8.3% vs 5.8%, GU 8.4%vs 4.6% vs 3.9%
Trials of modest Hypofractionation						
CHHiP **UK** **Dearnaley 2016, Syndikus 2025, Wilson 2018, Wilkins 2023a/b**	3216	T1b-T3a, N0, Gleason score <8, PSA<40	Non-inferiority design Moderate HFRT 74Gy 37f vs 60Gy 20f vs 57Gy 19f IMRT all cases, IGRT	LHRHa 4-6m	2002-2011	*Demonstrates non- inferiority of modest HFRT* 5/10yr BCF free: 74Gy 88.3%/76.0%, 60Gy 90.6%//79.8%, 57Gy 85.9%/73.3% HR_{60} P<0.001(non-inferiority) 10yr MFS: 74Gy 75.8%, 60Gy 80.0%, 57Gy 76.1% HR_{60} 0.85 P=0.05 10yr OS 74Gy 78.4%, 60Gy 83.0%, 57Gy 79.9% No differences. 15% deaths due to PCa 5yr Side effects ≥Grade 2: GI 74Gy 11.9%, 60Gy 10.9%, 57Gy 11.0%% No differences : GU 74Gy 8.1%, 60Gy 9.7%%, 57Gy

						7.0% $HR_{60/57}$ 1.45 p=0.02
PROFIT **Canada** **Catton 2017**	1206	Intermediate risk	Non-inferiority design Moderate HFRT 78Gy 39f vs 60Gy 20f IMRT all cases	none	2006-2011	*Demonstrates non-inferiority of modest HFRT* 5yr BCF free survival: 78Gy 85%, 60Gy 85%. 60 Gy non-inferior. No difference in survival. 14 % deaths due to PCa Late side effects RTOG ≥2: GI 78Gy 13.9% vs 60Gy 8.9% P=0.006, GU 20.0% vs 22.5% p=NS
HYPRO **Netherlands** **Incrocci 2016, Aluwini 2016**	804	High or Intermediate risk	Superiority design Dose escalated Moderate HFRT 64.6Gy19f 6.5wk vs 78Gy 39f 8wk IMRT 95%, IGRT94%	ADT in 67% (median 32m)	2007-2010	No difference in 5yr RFS:80.5% 64.6Gy vs 77.1% 78Gy, HR 0.86, p=0.36 . No difference in 5 yr OS 86% Increased RTOG ≥grade3 GU toxicity 19.0% 64.6Gy vs 12.9%78Gy p=0.021. No difference GI toxicity RTOG ≥grade2 GI toxicity 21.9% 64.6Gy vs 17.7%78Gy HR 1.19
NRG/RTOG-0415 **USA** **Lee 2024**	1092	Low risk	Non-inferiority design Dose escalated Moderate HFRT 70Gy 28f vs 73.8Gy 41f IMRT 79%	none	2006-2009	12yr DFS HR (H-RT/C-RT) is 0.85 ($P < .001$ for non-inferiority). 12yr BCF 17.0% for C-RT and 9.9% H-RT. HR 0.55, p<0.001 Late grade ≥3 GI 3.2% (C-RT) versus 4.4% (H-RT), RR 1.39 . Late grade ≥3 GU 3.4% (C-RT)

						versus 4.2% (H-RT), RR 1.26
Trials of extreme hypofractionation and SBRT						
HYPO-RT **Sweden** **Widmark 2019, Fransson 2021**	1200	Intermediate risk 89% High risk 11%	Non-inferiority design Extreme HFRT IGRT 42.7Gy 7f vs 78Gy 39f	none	2005-2015	*Demonstrates non- inferiority of extreme HFRT* 5yr FFS 84% in both groups HR 1.002, p=0.99 Toxicity *at* 5 yr: ≥2 RTOG GI 42.7Gy vs 78Gy, 1% vs 5%, ≥2 RTOG GU toxicity 5% vs 5% but increased GU toxicity at 1 year 6% vs 2% p=0.0037 QoL:Acute GI scores worse with 42.7Gy Overall bother at 6 yrs 78 Gy vs 42.7Gy: GU 33% ve 28% p=0.38, Overall bother GI 33% vs 28% p=0.33
PACE **UK, Ireland, Canada** **van As 2024, Tree 2022**	874	Low risk 8.4% Intermediate risk 91.6%	Extreme HFRT Non-inferiority SBRT 36.25Gy 5f 1-2wk vs 78Gy 39f 7.5wk or 62Gy 20f 4wk IGRT	none	2012-2018	*Demonstrates non- inferiority of extreme HFRT* 5-year FFBCF 95.8% SBRT vs 94.6%, HR 0.73, P=0.004 for noninferiority) Late Toxicity: Increased 1-2yr GU toxicity with SBRT, cumulative 5yr RTOG grade ≥2 GU 26.9% SBRT vs 18.3% control p<0.001, cumulative 5 yr RTOG grade ≥2 GI 10.7% SBRT vs 10.2% p=0.94 QoL EPIC at 5 yr no differences SBRT vs Control urinary

						incontinence 96.9 vs 100 p=0.45, bowel sub-domain 100vs 85.8 p=0.10 or sexual sub-domain
Trials of Pelvic RT						
GETUG-01 **France** **Pommier 2016**	446	T1b-T3 N0, Stratified low risk 92 High risk 354	Prostate only vs prostate and pelvis RT CFRT Prostate 66-70Gy Pelvis 46 Gy	6m ADT for high-risk group only	1998-2004	10-year OS, P alone vs P+pelvis: 74.9% vs 73.6%, p=NS 10yr EFS, 57.6% vs 55.6, p=NS.Low risk 77.2%, vs 62.5% *p*=0.178). Post hoc subgroup analysis significant benefit of pelvic RT without ADT for LN <15%
NRG/RTOG 9413 **USA** **Roche 2018**	1322	LN risk >15%	2 by 2 factorial design a)Prostate(PORT) CFRT 70Gy vs Prostate and pelvis (WPRT) 46Gy b) 4m neoadjuvant ADT (NHT) vs 4m post RT adjuvant ADT(AHT)	ADT 2m before and during RT(NHT) vs ADT for 4m after ADT(AHT)	1995-1999	10 yr PFS 28·4% NHT plus WPRT vs 23·5% NHT plus PORT group vs 19·4% WPRT plus AHT vs 30·2% in the PORT plus AHT group. Toxicity: RTOG GU≥3: 6.5% WPRT vs 4.5% PORT, RTOG GI ≥3 WPRT 5% vs PORT 2%
POP-RT **Tata Memorial Mumbai** **Murthy 2021**	224	LN Risk ≥20% 50% NCCN Very High Risk PSMA PET in 80%	Single Centre Phase 3 trial Prostate only RT (PORT) 68Gy 25f vs Prostate and pelvis RT (WPRT) 50Gy 25f IMRT with IGRT	24m + ADT	2011-2017	*Suggests benefit of pelvic RT in high-risk groups* 5yr BFFS: WPRT 95.0% vs 81.2% PORT HR 0.23, p<0.0001 5yr DFS: WPRT 89.5% v PORT 77.2%; HR 0.40, p=0.002

						5 yr DMFS WPRT 95.9% vs PORT 89.2%, HR 0.35, p=0.01 5yr OS 92.5% v 90.8%, HR 0.92; p= 0.83 Toxicity: Cumulative late RTOG≥2 WPRT vs PORT: GU 20.0% vs 8.9%p=0.02, GI 8.2% vs 4.5% p=0.28
Dearnaley **UK** **PIVOTAL 2019**	124		Randomised phase 2 IMRT: Prostate only (74Gy) vs Prostate + pelvis (74Gy+60Gy)	6-24m ADT	2011-13	No difference in acute or late toxicity using physician or patient reported outcomes
Trials of dominant lesion focal boosts						
FLAME **Netherlands,Belgium** **Kerkmeijer 2021**	571	Intermediate (15%) and high risk (84%)	Dominant lesion boost Phase 3 Whole prostate 77Gy 35f (2.2Gy/f) vs whole prostate + integrated boost 95Gy 35f (2.7Gy/f)	ADT in 65% 6m-36m	2009-2015	*Demonstrates improved PSA control with focal boost* 5yr bDFS focal boost vs no boost 92% and 85% HR 0.45, p < .001. No difference in PCSS or OS Toxicity: cumulative incidence late GU and GI toxicity grade ≥ 2, 23% and 12% no boost vs 28% and 13% focal boost, p=NS
Hypo-FLAME **Netherlands, Belgium** **Draulans 2024**	100	Intermediate (32%) and high risk (68%)	Dominant lesion boost Phase 2 Whole prostate 35Gy 5f (7.0Gy/f) 5wk + integrated boost 50Gy 5f (10.0Gy/f)	ADT in 62% 6m-36m	2016-2024	5-year bDFS focal boost 93% Toxicity: 5yr prevalence late GU and GI toxicity grade ≥ 2, 12%and 14%
DELINEATE	265	Three groups	Dominant lesion boost Phase 2	ADT in 100% short course 95%/79%/15%	2011-2020	5 yr FFBCF: a) 98.2% b) 96.7% c) 95.1%

RMH UK **Tree 2022**		a)Intermediate/high risk 73%/27% b)Intermediate/high risk 46%/54% c)High risk 100%	Whole prostate a)74Gy 37f + boost 82Gy 37f (2.2Gy/f) b)60Gy 20f + boost 67Gy 20f (3.35Gy/f) c) as a) with 60Gy 37f (1.62Gy/f) to pelvis	or long course 6%/20%/85%		Toxicity: Cumulative 5yr late RTOG grade 2+ GI a) 12.8% b), 14.6% c) 20.7% Cumulative 5 yr RTOG grade 2+ GU a) 12.9 b) 18.2% c) 18.2%
Trials of Post Prostatectomy radiotherapy						
SWOG 8794 **USA** **Thomson 2009**	431	pT3N0 +/-positive SM	Post - prostatectomy RT 60-64Gy vs observation	No ADT	1988-1997	10 yr MFS greater with RT 71%vs 61% HR 0.71, p=0.016). Survival improved with RT 74% vs 66% HR 0.72, p=0.023)
EORTC 22991 **European multicentre** **Bolla 2005**	1005	pT3N0 +/- positive SM, pT2 + positive SM	Post - prostatectomy RT 60Gy vs observation	No ADT	1992-2001	10yr BPFS improved with RT 60.6% vs 41.0% HR 0·49 p<0·0001). No difference in metastases 10.1% vs11% or 10yr OS 76.9% vs 80.7% Toxicity: Increased 10 year cumulative incidence with RT all grades 70·8% vs 59·7% p=0.001.
ARO 96-02/AUO AP 09/95 **Germany** **Wiegel 2009**	388	pT3N0 +/-positive SM	Post - prostatectomy RT 60Gy vs observation	No ADT	1997-2004	10 yr PFS 56% for RT and 35% for observation $p < 0.000110$yr OS 86% vs 82% p=NS
Finn Prostate **Finland** **Hackman 2019**	250	pT3a, pT2 SM positive N0	Post - prostatectomy RT 66.6Gy vs observation	No ADT	2004-2012	10yr BPFS 82% with RT vs 61% observation HR 0.26 p < 0.001. 10 yr OS 92% vs 87% HR 0.69, p = 0.4. Toxicity: 56% grade 3 with RT vs 40% observation p = 0.016

Medical Research Council UK RADICALS-RT **UK, Denmark, Canada, Ireland** **Parker 2024a**	1396	≥1 risk factor (pT3/4, Gleason 7-10, positive margins, preoperative PSA≥10 ng/ml)	Post-prostatectomy Adjuvant RT vs Salvage RT EBRT to prostate bed. 66Gy 33f or 52.5Gy 20f daily (non-randomised	Clinical preference or 2nd randomisation 0m vs 6m vs 24m ADT (see Table3)	2007-2016	*Demonstrates no advantage for adjuvant RT* 10-year FFDM not improved 93% Adjuvant-RT vs 90% Salvage-RT: HR=0.68, p=0.095. OS not improved (HR=0.980, P=0.917). Adjuvant-RT worse urinary and faecal incontinence 1 year after randomisation (P=0.001); faecal incontinence significant after 10 years (P=0.017).
TROG 08.03/ANZUP RAVES **Australia, New Zealand** **Kneebone 2020**	333	pT3a/b or SM positive	Post-prostatectomy Adjuvant RT vs Salvage RT EBRT to prostate bed. 64Gy 32f	No ADT	2009-2015	5-year BPFS 87% SRT with ART vs 86% ART HR 1.12, p = 0.15 (non-inferiority) Toxicity: grade ≥2 GI 10%SRT vs 14%
GETUG-AFU 17 **France** **Sargos 2020**	424	pT3a/b, T4a, pNx/0	Post-prostatectomy Adjuvant RT vs Salvage RT EBRT to prostate bed. 66Gy 33f +/- pelvic RT 46Gy 23f	ADT for 6 months	2008-2016	5yr EFS 92% ART vs 90% SRT HR 0·81, p=0·42. 5yr OS 96% ART vs 99% SRT HR1.60 p=0.25 Toxicity: Late grade≥ 2 GI 8% ART vs 5% SRT ,: Late grade≥ 2 GU 27% ART vs 7% SRT p<0·0001. Late erectile dysfunction ≥Grade 2 36% ART vs 13% SRT p<0·0001
ARTISTIC International Vale 2020	2153	As above	Post-prostatectomy Adjuvant RT vs Salvage RT	see 3 trials above)	2007-2016	39% had SRT No evidence that EFS was improved by ART 89% vs SRT 88% HR 0·95; p=0·70

			Meta-analysis (see 3 trials above)			
Trials of Prostatectomy and radical radiotherapy						
ProtecT **UK** **Hamdy 2023** **Donovan 2023**	1643	Sceen detected Low -High Risk	RT vs prostatectomy 1)Active monitoring 2)Radical prostatectomy 3) Radical Radiotherapy + 3-6m ADT	CFRT 74Gy 37f + 3-6m ADT	1999-2009	*Demonstrates similar control and survival for radical RT and prostatectomy* 15yr F-U: No difference on deaths from PCa (2.7%) or OS 21.7% RP and RT no difference in development of metastases (4.6./5.0%), long-term ADT,7.2%/7.7% or clinical progression (10.5%/11.0%) AM had about double DM and additional ADT Urinary leakage RP24%vs RT 8% AM 11%; Faeccal leakage RP 6%, RT 12%, AM 6%; Erectile potency RP 18%, RT 27%, AM 30%
PACE-A **UK** **van AS 2024b**	123	Low-Intermediate risk (92%)	SBRT vs Prostatectomy	none	2002-2012	Toxicity (EPIC): 2yr pad use 50% prostatectomy vs 6.5% SBRT p<0.001, bowel domain 100 vs 87.5 p<0.001, sexual scores 18 vs 62.6
Trials of prostate radiotherapy in metastatic disease						
HORRAD **Netherlands** **Boeve 2021**	432	Bone metastases	Prostate RT in M1 ADT vs ADT and prostate RT	Long term ADT	EBRT to prostate 72Gy 36f	No difference in overall survival but prolonged time to PSA progression (HR 0.78 p=0.02)

STAMPEDE **UK, Switzerland** **Parker 2018,2022**	2061	Bone metastases 40% low metastatic burden	Prostate RT in M1 SOC vs SOC + prostate RT	Long term ADT (Docetaxel in 18%)	EBRT to prostate 55Gy 20f or 36Gy 6f	*Demonstrates improved survival with prostate RT in low metastatic volume* FFS improved: HR 0.76 p<0.0001 OS all patients: overall no difference OS benefit in low burden disease: HR 0.65, p0.010
STOPCAP **Metanalysis** **Burdett 2019**	2126	Bone metastases	Prostate RT in M1 Metanalysis STAMPEDE and HORRAD SOC vs SOC + prostate RT	Log term ADT +/- docetaxel	EBRT to prostate	*Demonstrates improved survival with prostate RT in low metastatic volume* No overall survival benefit FFS HR 0.76 $p=0.9*10^{-8}$ Low metastatic burden (<5mets) OS benefit HR 1.47, p=0.007. 7% improvement at 3 yrs
PEACE 1 **France, Belgium Ireland, Italy, Romania, Spain, Switzerland** **Bossi 2024**	1173	Bone metastases Low metastatic burden 43%	Prostate RT in M1 2*2 factorial	1)SOC: ADT alone/docetaxel 2)SOC+ abiraterone 3)SOC + prostate RT 4)SOC+abi.+RT	74Gy 37f to prostate	RT +SoC +abiraterone improves RPFS HR 0.65 p=0.019 in low volume met.disease. No advantage in group treated without abiraterone. Time to CRPC increased by RT + abiraterone in low metastatic burden (HR 0.62,p=0.0056) and overall population (HR 0.79, p=0.028) No benefit on OS

						RT reduces genitourinary side effects

Supplementary Table 1, Abbreviations: ADT androgen deprivation treatment; AM active monitoring; ART adjuvant radiotherapy; AHT adjuvant hormone therapy BCF biochemical and clinical failure; bDFS biochemical disease free survival; BPFS biochemical and progression free survival; CFRT conformal radiotherapy; CRPC castration resistant prostate cancer; DFS disease free survival; DM distant metastases; DSH dose surface histogram; DVH dose volume histogram; EBRT external beam radiotherapy; EFS event free survival; EPIC Expanded Prostate Cancer Index Composite; fractions; FFBCF freedom from biochemical or clinical failure; FFS failure free survival; F-U follow up; GI gastrointestinal; GU genitourinary; Gy Gray; GyE Gray equivalent; HFRT hypofractionated radiotherapy; HR hazard ratio; ICR The Institute if Cancer Research, London; IGRT image guided radiotherapy; IMRT intensity modulated radiotherapy; LHRHa luteinising hormone releasing hormone analogue; LN lymph node; MFS metastases free survival; MRC Medical Research Council, London UK; NHT neoadjuvant hormone therapy; NS non-significant; OS overall survival; PCa prostate cancer; PORT prostate only radiotherapy; PSA prostate specific antigen; RP radical prostatectomy; RFS recurrence free survival; RMH Royal Marsden NHS Foundation Trust, London; RT radiotherapy; RTOG Radiotherapy and Oncology Group; QoL quality of life; SBRT stereotactic body radiotherapy; SM surgical margin; SOC standard of care; SRT salvage radiotherapy; WPRT whole pelvis radiotherapy