Figure SUPP-1: Trial design

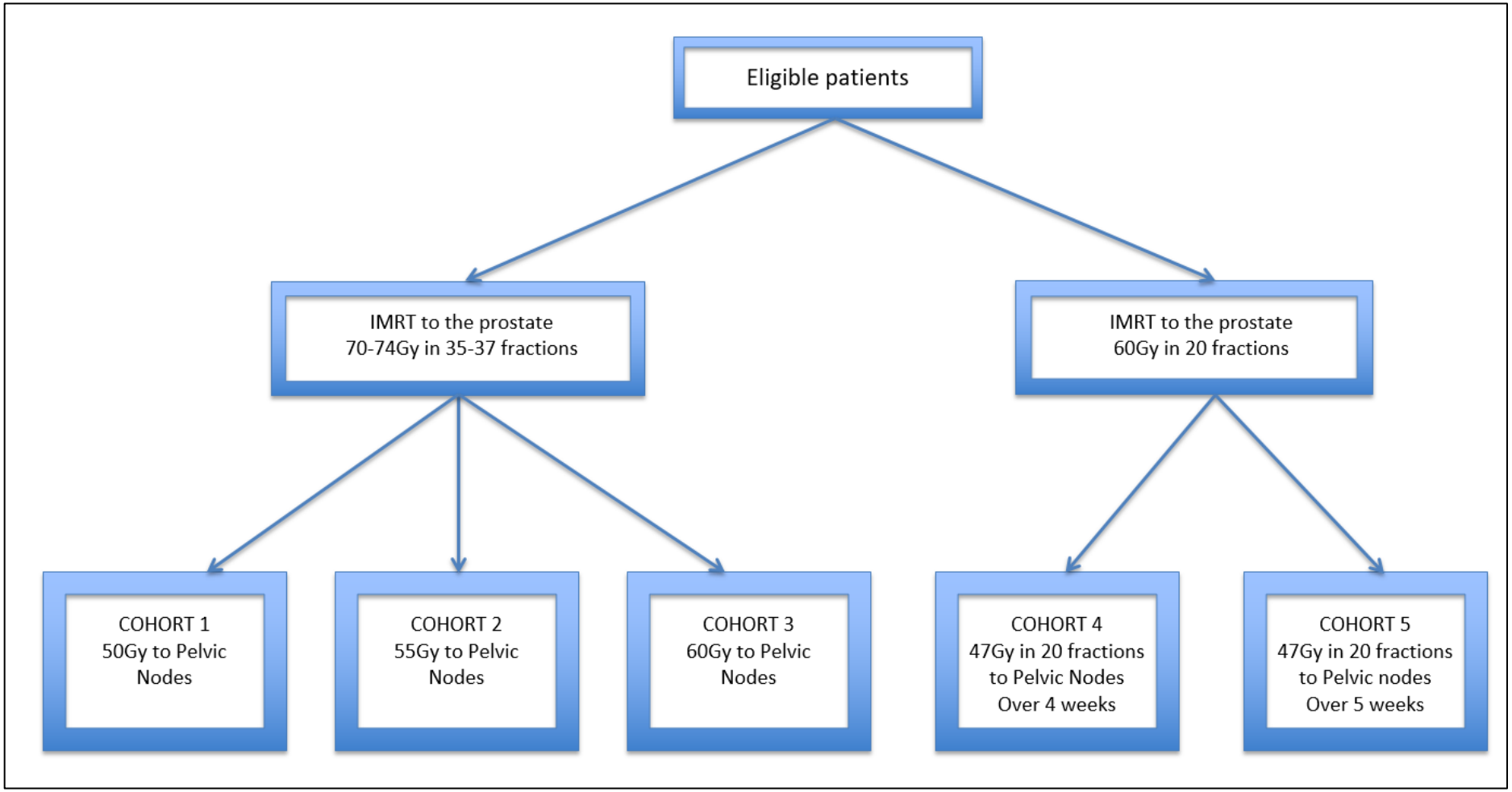

Table SUPP-1: Patient demographics (detailed)

	Cohort 1 50Gy to PLN (n=25)	Cohort 2 55Gy to PLN (n=70)	Cohort 3 60Gy to PLN (n=138)	Cohort 4 47Gy to PLN/4wks (n=64)	Cohort 5 47Gy to PLN/5wks (n=129)	Cohorts 1-5 (n=426)
Median follow-up in years	13.9	11.2	9.0	7.1	5.7	7.6
Median Age at Diagnosis in years (IQR)	63 (56-67)	62 (57-67)	65 (59-69)	66 (62-72)	67 (62-71)	65 (60-70)
PSA at Diagnosis - Median (IQR)	39.1 (24.7-78.0)	25.4 (12.4-44.7)	24.5 (10.2-47.1)	15.4 (8.5-31.4)	18 (8.1-37.9)	21.4 (10.2 – 42.8)
Nadir Pre RT PSA - Median (IQR)	0.5 (0.1- 1.2)	0.4 (0.1-1.2)	0.5 (0.1-1.1)	0.4 (0.1- 1.0)	0.6 (0.2-1.2)	0.5 (0.1 -1.2)
Gleason Score						
Gleason 6/7	13(52%)	34(48%)	60 (43%)	22(35%)	56(44%)	185(44%)
Gleason 8	4 (16%)	17 (24%)	29 (21%)	13(20%)	11(9%)	74(17%)
Gleason 9/10	6 (24%)	16 (22%)	48 (35%)	28(44%)	60(47%)	158(37%)
Unknown	2(8%)	3 (4%)	1(1%)	1(2%)	2(2%)	9(2%)
CT/MR N Stage						
N0	16 (64%)	49 (70%)	115 (83%)	51(80%)	110(85%)	341 (80%)
N1-3	9 (36%)	14 (20%)	22 (16%)	11(17%)	18(14%)	74 (17%)
Unknown	0 (0%)	7 (10%)	1 (1%)	2(3%)	1(1%)	11 (3%)
Clinical T Stage						
cT1/T2	8(32%)	23(33%)	60(43%)	6(9%)	42(32%)	156 (37%)
cT3	17 (68%)	34 (49%)	57 (41%)	17(27%)	56(43%)	192 (45%)
cT4	0 (0%)	2 (3%)	3 (2%)	28(44%)	1(1%)	6 (1%)
Unknown	0(0%)	11(16%)	18 (13%)	13(20%)	30(23%)	72 (17%)
MRI stage						
MRI T1/T2	2 (8%)	6(9%)	30(21%)	7(11%)	25(20%)	70 (17%)
MRI T3	13(52%)	34 (49%)	74 (54%)	30(47%)	78(60%)	229 (54%)
MRI T4	2(8%)	3 (4%)	6 (4%)	1(2%)	4(3%)	16 (4%)
Unknown	8 (32%)	27 (39%)	28 (20%)	26(41%)	22(17%)	111 (26%)
Pathological T stage	*n=0*	*n=7*	*n=16*	*n=4*	*n=6*	*n=34*
T1/T2	0	1(13%)	1(6%)	1(25%)	2(33%)	5(15%)
T3a/b	0	7(77%)	14(82%)	2(50%)	4(67%)	27(79%)
T4	0	0	0	0	0	0
Unknown	0	0	1(6%)	1(25%)	0	2(6%)
Pathological N stage		n=5	n=13	n=3	n=2	n=23
N0	0	3(60%)	10 (77%)	3(100%)	2(100%)	18(78%)
N1	0	2(40%)	3(23%)	0(0%)	0(0%)	5(22%)
Risk of LN Involvement (Roach Formula)						
<15%	1 (4%)	2 (3%)	10 (7%)	5(8%)	12(9%)	30 (7%)
15-≤29%	4 (16%)	25(36%)	32 (23%)	16(25%)	24(19%)	101(24%)
≤30%	18(72%)	40(57%)	95(69%)	42(66%)	91(71%)	286 (67%)
Unknown	2 (8%)	3 (4%)	1 (1%)	1(2%)	2 (2%)	9(2%)
NCCN risk group						
Low/Intermediate	1 (4%)	1(1%)	8(6%)	6(10%)	6(5%)	22(6%)
High	24 (96%)	67(96%)	126 (91%)	55 (86%)	118(91%)	390 (92%)
Unknown	0(0%)	2(3%)	4 (3%)	3(5%)	5(4%)	14 (3%)
Hormone Therapy						
LHRHa and short term anti-androgen	9(36%)	44(63%)	99(72%)	53(83%)	104(81%)	309(73%)
Anti-androgen alone (Bicalutamide 150mg/day)	1(4%)	9(13%)	15(11%)	3(5%)	4(1%)	32(8%)
Combined Androgen Blockade	15(60%)	17(24%)	24(17%)	8(12%)	21(16%)	85(20%)
Duration of hormone therapy (months)						
≤12 months	1(4%)	4(6%)	1(1%)	1(2%)	0(0%)	7(2%)
>12-≤24 months	2(8%)	0(0%)	8(6%)	2(3%)	4(3%)	16(4%)
>24 to ≤36 months	9(36%)	29(41%)	51(37%)	38(59%)	64(50%)	191(45%)
>36 to ≤48 months	5(20%)	21(30%)	52(38%)	14(22%)	48(37%)	140(33%)
>48 months	3(12%)	6(9%)	10(7%)	2(3%)	24(6%)	24(6%)
Incomplete (died or progressed on ADT)	5(20%)	10(14%)	16(12%)	7(11%)	10(8%)	48(11%)

Table SUPP-2: Dose-volume constraints

DOSE CONSTRAINTS							
Conventionally fractionated cohorts				**Hypofractionated cohorts**			
Target volumes				Target volumes			
Structure	Volume constraint	Dose required		Structure	Volume constraint	Dose required	
Prostate PTV	99%	90%		Prostate PTV	99%	90%	
	98%	95%			98%	95%	
	95%	95%			95%	95%	
	50%	100%			50%	100%	
	<=5%	105%			<=5%	105%	
	2%	110%			2%	110%	
Nodal PTV	99%	90%		Nodal PTV	99%	90%	
	98%	95%			98%	95%	
	95%	95%			95%	95%	
	50%	100%			50%	100%	
Boost PTV to N1 disease (when appliccable)	99%	90%		Boost PTV to N1 disease (when appliccable)	99%	90%	
	95%	95%			95%	95%	
	50%	100%			50%	100%	
Organs at risk				Organs at risk			
Organ	Dose Constraint	Volume Required (%)		Organ	Dose Constraint	Volume Required (%)	
Rectum	50Gy	60%		Rectum	43Gy	60%	
	60Gy	50%			51Gy	50%	
	65Gy	30%			55Gy	30%	
	70Gy	15%			59Gy	15%	
	75Gy	3%			63Gy	0%	
Bladder	50Gy	50%		Bladder	43Gy	50%	
	60Gy	25%			51Gy	25%	
	70Gy	5%			59Gy	5%	
L Femoral Head	50Gy	50%		L Femoral Head	43Gy	50%	
R Femoral Head	50Gy	50%		R Femoral Head	43Gy	50%	
	Dose constraint	Optimal volume required (cc)	Mandatory volume required (cc)		Dose constraint	Optimal volume required (cc)	Mandatory volume required (cc)
Bowel	45Gy	78 cc	158 cc	Bowel	39Gy	78 cc	158 cc
	50Gy	17 cc	110 cc		43Gy	17 cc	110 cc
	55Gy	14 cc	28 cc		47Gy	14 cc	28 cc
	60Gy	0 cc	6 cc		51Gy	0 cc	6 cc
	65Gy	0 cc	0 cc		55Gy	0 cc	0 cc

Table SUPP-3: Physician-reported acute symptoms (cumulative and prevalence) compared to CHHiP and Holch et al.[1]

CLINICIAN-REPORTED OUTCOMES						
	BOWEL			BLADDER		
	No. of events *(0-18 weeks)* /N	Cumulative proportion with event 0-18 weeks	Prevalence with event at 18 weeks	No. of events/N	Cumulative proportion with event 0-18 weeks	Prevalence with event at 18 weeks
		%	% (n/n analyzed)		%	% (n/n analyzed)
RTOG - Event = Grade 2+ toxicity						
Cohort 1 - CFRT - 50 Gy to LN	10/25	40%	4% (1/25)	7/25	28%	0% (0/25)
Cohort 2 - CFRT - 55 Gy to LN	40/70	56%	10% (7/69)	31/70	43%	5% (4/68)
Cohort 3 - CFRT - 60 Gy to LN	75/138	54%	4% (5/134)	73/138	53%	6% (8/134)
Cohort 4 - HFRT - 47 Gy to LN (4 w)	42/64	66%	3% (2/61)	39/64	61%	8% (5/61)
Cohort 5 - HFRT - 47 Gy to LN (5 w)	61/127	48%	5% (6/120)	67/129	53%	6% (7/121)
CHHiP - 74Gy CFRT **(prostate-only)**	NA/129	NA	2.3% (3)	NA/129	NA	7% (9)
CHHiP - 60Gy HFRT **(prostate-only)**	NA/132	NA	2.3% (3)	NA/132	NA	7.6% (10%)
Holch et al. CFRT - **(prostate-only)**	NA	21-60%	NA	NA	40%	NA
Holch et al. HFRT - **(prostate-only)**	NA	35%*	NA	NA	47%	NA

* This result only includes grade 2 (ie, not grade 2+). For grade 2+, the result is 36% (obtained from original reference in the Holch et al. systematic review).[1]

Table SUPP-4: Physician and patient-reported late symptoms (cumulative) compared to CHHiP and Holch et al.[1]

	BOWEL			BLADDER			SEXUAL FUNCTION		
CLINICIAN-REPORTED OUTCOMES	N(events) / N(total)	Cumulative proportion with event by 2 years % (95% CI)	Cumulative proportion with event by 5 years % (95% CI)	N(events) / N(total)	Cumulative proportion with event by 2 years % (95% CI)	Cumulative proportion with event by 5 years % (95% CI)	N(events) / N(total)	Cumulative proportion with event by 2 years % (95% CI)	Cumulative proportion with event by 5 years % (95% CI)
RTOG - Event = Grade 2+ toxicity									
Cohort 1 - CFRT - 50 Gy to LN	3/24	8.3% (2.7-24.3)	8.3% (2.2-29.4)	5/24	4.2% (0.6-26.1)	4.2% (0.6-26.1)			
Cohort 2 - CFRT - 55 Gy to LN	18/70	8.9% (4.1-18.7)	15.7% (8.7-27.3)	14/70	5.9% (2.3-15)	9.2% (4.3-19.5)			
Cohort 3 - CFRT - 60 Gy to LN	25/138	13.2% (8.6-20.2)	15.7% (10.5-23.1)	12/138	2.9% (1.1-7.7)	5.4% (2.6-11.1)			
Cohort 4 - HFRT - 47 Gy to LN (4 w)	16/63	16.4% (9.2-28.4)	20% (11.8-32.4)	8/63	4.8% (1.6-14.3)	6.6% (2.5-16.8)			
Cohort 5 - HFRT - 47 Gy to LN (5 w)	24/124	12.2% (7.6-19.5)	18.5% (12.6-26.7)	13/124	7.3% (3.9-13.6)	9.3% (5.2-16.1)			
CHHiP - 74Gy CFRT **(prostate-only)**	111/1040	8% (6.5-9.9)	13.7% (10.8-17.4)	66/1040	3.9% (2.9-5.3)	9.1% (6.5-12.8)			
CHHiP - 60Gy HFRT **(prostate-only)**	105/1049	8.6% (7.1-10.5)	11.9% (9.6-14.8)	88/1049	5.7% (4.5-7.3)	11.7% (8.4-16.1)			
Holch et al. CFRT - **(prostate-only)**	NA	NA	14-19.5% (NA)	NA	NA	NA			
Holch et al. HFRT - **(prostate-only)**	NA	NA	NA	NA	NA	NA			
RMH - Event = Grade 2+ toxicity									
Cohort 1 - CFRT - 50 Gy to LN	2/24	8.3% (2.2-29.4)	8.3% (2.2-29.4)	15/24	20.8% (9.3-43)	30.2% (15.6-53.3)	21/24	83.3% (66.3-94.8)	87.5% (71.4-96.9)
Cohort 2 - CFRT - 55 Gy to LN	15/70	13.5% (7.3-24.4)	18.5% (10.9-30.4)	33/70	23.9% (15.4-36.1)	27.4% (18.2-39.9)	63/70	85.2% (75.8-92.4)	90.5% (81.6-96.3)
Cohort 3 - CFRT - 60 Gy to LN	30/138	9.6% (5.7-15.9)	15.4% (10.2-22.9)	38/138	16.8% (11.5-24.2)	21.9% (15.7-30)	131/138	80.3% (73.1-86.7)	88.9% (82.6-93.6)
Cohort 4 - HFRT - 47 Gy to LN (4 w)	16/63	16.3% (9.1-28.2)	21.5% (13.1-34.2)	21/63	22.9% (14.3-35.7)	31.9% (21.6-45.4)	57/63	90.3% (81.5-96.1)	91.9% (83.5-97)
Cohort 5 - HFRT - 47 Gy to LN (5 w)	26/124	14.7% (9.5-22.3)	17.2% (11.6-25.1)	56/124	32.5% (25-41.6)	42.3% (34-51.7)	119/124	94.4% (89.3-97.5)	96.8% (91.6-99.1)
CHHiP - 74Gy CFRT **(prostate-only)**	133/1040	10.4% (8.7-12.4)	15.9% (12.7-19.8)	260/1040	18.8% (16.5-21.3)	31% (26.3-36.3)	NA	NA	NA
CHHiP - 60Gy HFRT **(prostate-only)**	136/1049	10.5% (8.7-12.5)	15.3% (12.5-18.8)	286/1049	21.3% (18.9-23.9)	34.1% (28.8-40)	NA	NA	NA
Holch et al. CFRT - **(prostate-only)**	NA	NA	14-20% (NA)**	NA	NA	NA	NA	NA	NA
Holch et al. HFRT - **(prostate-only)**	NA	NA	NA	NA	NA	NA	NA	NA	NA
LENT-SOM - Event = Grade 2+ toxicity									
Cohort 1 - CFRT - 50 Gy to LN	4/24	12.5% (4.2-33.9)	17.4% (6.9-40.1)	10/24	33.8% (18.5-56.5)	43.3% (26-65.7)	22/24	85.9% (68.6-96.4)	95.3% (80.7-99.7)
Cohort 2 - CFRT - 55 Gy to LN	19/70	19.5% (11.8-31.2)	30.1% (20.2-43.2)	33/70	35.3% (25.2-47.9)	48.4% (37.1-61.1)	68/70	98.6% (93.1-99.9)	N/A (N/A)*
Cohort 3 - CFRT - 60 Gy to LN	30/138	19.8% (14-27.6)	22.3% (16.2-30.4)	60/138	35.2% (27.8-43.9)	45.3% (37.2-54.2)	133/138	94.7% (89.9-97.6)	96.4% (92.1-98.8)
Cohort 4 - HFRT - 47 Gy to LN (4 w)	23/63	34.2% (23.8-47.5)	37.6% (26.8-51)	32/63	35.6% (25.1-48.9)	52.2% (40.1-65.4)	63/63	100% (NA)	N/A (N/A)*
Cohort 5 - HFRT - 47 Gy to LN (5 w)	39/124	24.5% (17.8-33.1)	32.1% (24.6-41.2)	64/124	39.6% (31.6-48.8)	51.6% (43-60.8)	123/124	98.4% (94.8-99.7)	N/A (N/A)*
CHHiP - 74Gy CFRT **(prostate-only)**	210/1040	16% (13.9-18.4)	24.3% (20.2-29.1)	390/1040	28.8% (26.2-31.7)	49.1% (42.9-55.8)	899/1040	82.4% (80-84.7)	93.3% (87.8-96.9)
CHHiP - 60Gy HFRT **(prostate-only)**	228/1049	17.6% (15.4-20.1)	25.8% (22.6-29.5)	409/1049	30.9% (28.2-33.8)	49.9% (43.8-56.4)	892/1049	80.1% (77.6-82.5)	89.3% (86.1-92.1)
Holch et al. CFRT - **(prostate-only)**	NA	NA	20-27% (NA)**	NA	NA	NA	NA	NA	NA
Holch et al. HFRT - **(prostate-only)**	NA	NA	NA	NA	NA	NA	NA	NA	NA

	BOWEL			BLADDER		
PATIENT-REPORTED OUTCOMES	N(events) / N(total)	Cumulative proportion with event by 2 years % (95% CI)	Cumulative proportion with event by 5 years % (95% CI)	N(events) / N(total)	Cumulative proportion with event by 2 years % (95% CI)	Cumulative proportion with event by 5 years % (95% CI)
UCLA-PCI - Event = Small or worse bother						
Cohort 1 - CFRT - 50 Gy to LN	6/24	21% (9-43)	26% (13-50)	7/24	8% (2-29)	37% (19-63)
Cohort 2 - CFRT - 55 Gy to LN	29/64	38% (27-52)	49% (37-63)	22/64	33% (23-47)	35% (24-49)
Cohort 3 - CFRT - 60 Gy to LN	48/128	28% (21-37)	38% (30-48)	41/128	25% (18-34)	35% (27-45)
Cohort 4 - HFRT - 47 Gy to LN (4 w)	33/62	53% (41-66)	56% (43-69)	26/62	35% (25-49)	45% (32-59)
Cohort 5 - HFRT - 47 Gy to LN (5 w)	58/120	43% (35-53)	54% (44-64)	52/120	35% (27-44)	46% (37-57)
CHHiP - 74Gy CFRT (prostate-only)	202/677	24.6% (21.4-28.2)	45.2% (36.6-54.8)	202/677	23.9% (20.7-27.5)	42.5% (34.6-51.3)
CHHiP - 60Gy HFRT (prostate-only)	225/682	27.1% (23.8-30)	44.7% (37.4-52.6)	200/682	23.2% (20.1-26.7)	43.2% (35.6-51.6)
Holch et al. CFRT - **(prostate-only)**	NA	NA	78-83% (NA)**	NA	NA	NA
Holch et al. HFRT - **(prostate-only)**	NA	NA	NA	NA	NA	NA

* All patients in these cohorts had either experienced a grade 2+ event or been censored before 5 years, so no 5 year estimates are available for this cohort.

** These results are ranges stemming from a systematic review.[1]

Table SUPP-5: Physician and patient-reported late symptoms (prevalence) compared to CHHiP and Holch et al.[1]

	CLINICIAN-REPORTED OUTCOMES								
	BOWEL			BLADDER			SEXUAL FUNCTION		
	N (2 years) / N (5 years)	Prevalence with event by 2 years % (n)	Prevalence with event by 5 years % (n)	N (2 years) / N (5 years)	Prevalence with event by 2 years % (n)	Prevalence with event by 5 years % (n)	N (2 years) / N (5 years)	Prevalence with event by 2 years % (n)	Prevalence with event by 5 years % (n)
RTOG - Event = Grade 2+ toxicity									
Cohort 1 - CFRT - 50 Gy to LN	22/13	0% (0)	0% (0)	22/13	0% (0)	0% (0)			
Cohort 2 - CFRT - 55 Gy to LN	57/49	11% (6)	2% (1)	57/49	6% (3)	4% (2)			
Cohort 3 - CFRT - 60 Gy to LN	126/111	8% (10)	5% (5)	126/111	2% (2)	1% (1)			
Cohort 4 - HFRT - 47 Gy to LN (4 w)	56/52	9% (5)	6% (3)	56/52	0% (0)	4% (2)			
Cohort 5 - HFRT - 47 Gy to LN (5 w)	115/92	5% (5)	2% (2)	115/92	2% (2)	3% (3)			
CHHiP - 74Gy CFRT **(prostate-only)**	922/534	4% (35)	1% (7)	922/534	1% (13)	2% (9)			
CHHiP - 60Gy HFRT **(prostate-only)**	959/569	3% (28)	2% (13)	959/569	2% (16)	2% (10)			
Holch et al. CFRT - **(prostate-only)**	NA	NA	NA	NA	10-17%	NA			
Holch et al. HFRT - **(prostate-only)**	NA	NA	NA	NA	15%	NA			
RMH - Event = Grade 2+ toxicity									
Cohort 1 - CFRT - 50 Gy to LN	22/13	0% (0)	0% (0)	22/13	9% (2)	8% (1)	22/13	77% (17)	77% (10)
Cohort 2 - CFRT - 55 Gy to LN	57/48	14% (8)	2% (1)	56/48	18% (10)	11% (5)	55/48	73% (40)	56% (27)
Cohort 3 - CFRT - 60 Gy to LN	125/107	6% (7)	4% (4)	123/107	12% (14)	8% (9)	119/100	78% (93)	63% (63)
Cohort 4 - HFRT - 47 Gy to LN (4 w)	55/51	6% (3)	10% (5)	55/51	15% (8)	10% (5)	51/49	84% (43)	61% (30)
Cohort 5 - HFRT - 47 Gy to LN (5 w)	114/89	4% (4)	8% (7)	115/90	12% (14)	18% (16)	112/83	81% (91)	58% (48)
CHHiP - 74Gy CFRT (prostate-only)	919/524	5% (49)	2% (12)	918/522	9% (83)	8% (41)	NA	NA	NA
CHHiP - 60Gy HFRT (prostate-only)	953/563	4% (36)	3% (18)	955/563	10% (92)	8% (41)	NA	NA	NA
Holch et al. CFRT - **(prostate-only)**	NA	6%	NA	NA	11%	NA	NA	NA	NA
Holch et al. HFRT - **(prostate-only)**	NA	1-3%	NA	NA	6-7%	NA	NA	NA	NA
LENT-SOM - Event = Grade 2+ toxicity									
Cohort 1 - CFRT - 50 Gy to LN	22/12	0% (0)	0% (0)	22/12	23% (5)	8% (1)	22/12	91% (20)	100% (12)
Cohort 2 - CFRT - 55 Gy to LN	55/47	12% (7)	6% (3)	54/46	26% (14)	31% (14)	54/45	97% (52)	93% (42)
Cohort 3 - CFRT - 60 Gy to LN	123/104	4% (5)	4% (4)	123/103	19% (24)	17% (17)	116/100	95% (110)	85% (85)
Cohort 4 - HFRT - 47 Gy to LN (4 w)	53/51	17% (9)	14% (7)	54/51	21% (11)	24% (11)	52/48	99% (51)	81% (39)
Cohort 5 - HFRT - 47 Gy to LN (5 w)	113/88	13% (14)	6% (5)	113/89	19% (22)	8% (7)	110/83	91% (100)	82% (68)
CHHiP - 74Gy CFRT (prostate-only)	919/524	5% (49)	2% (12)	891/518	13% (114)	13% (70)	826/454	67% (550)	67% (305)
CHHiP - 60Gy HFRT (prostate-only)	953/563	4% (36)	3% (14)	928/555	14% (60)	13% (73)	864/499	65% (562)	51% (187)
Holch et al. CFRT - **(prostate-only)**	NA	9%	NA	NA	15%	NA	NA	91%	NA
Holch et al. HFRT - **(prostate-only)**	NA	4-5%	NA	NA	12%	NA	NA	89-91%	NA

	PATIENT-REPORTED OUTCOMES					
	BOWEL			BLADDER		
	N (2 years) / N (5 years)	Prevalence with event by 2 years % (95% CI)	Prevalence with event by 5 years % (95% CI)	N (2 years) / N (5 years)	Prevalence with event by 2 years % (95% CI)	Prevalence with event by 5 years % (95% CI)
UCLA-PCI - Event = Small or worse bother						
Cohort 1 - CFRT - 50 Gy to LN	22/12	14% (3)	8% (1)	22/12	19% (9)	8% (1)
Cohort 2 - CFRT - 55 Gy to LN	47/42	14% (7)	16% (7)	47/42	19% (9)	14% (6)
Cohort 3 - CFRT - 60 Gy to LN	84/76	13% (11)	5% (4)	85/78	13% (11)	10% (8)
Cohort 4 - HFRT - 47 Gy to LN (4 w)	45/35	25% (11)	12% (4)	47/35	19% (9)	20% (7)
Cohort 5 - HFRT - 47 Gy to LN (5 w)	85/54	26% (22)	17% (9)	85/57	30% (25)	16% (9)
CHHiP - 74Gy CFRT (prostate-only)	431/341	12% (53)	14% (49)	425/333	12% (50)	17% (56)
CHHiP - 60Gy HFRT (prostate-only)	426/375	14% (58)	15% (57)	425/371	14% (60)	17% (63)
Holch et al. CFRT - **(prostate-only)**	NA	NA	NA	NA	NA	NA
Holch et al. HFRT - **(prostate-only)**	NA	NA	NA	NA	NA	NA

* All patients in these cohorts had either experienced a grade 2+ event or been censored before 5 years, so no 5 year estimates are available for this cohort.

** These results are ranges stemming from a systematic review.[1]

Table SUPP-6: Physician and patient-reported late symptoms (cumulative) and overall proportion of patients treated post-prostatectomy per cohort.

Cohort no.			Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Total
Proportion of post-RP patients			0%	8%	16%	4%	6%	34%
Bowel toxicity	**G2+ RTOG bowel toxicity** cumulative proportion (95% CI)	2 years	-	13% (2-61)	13% (3-41)	25% (4-87)	0% (NA)	12% (5-29)
		5 years	-	27% (7-72)	20% (7-50)	50% (16-94)	17% (3-73)	25% (13-44)
	Small or worse bowel problem cumulative proportion (95% CI)	2 years	-	67% (34-94)	36% (17-66)	75% (33-99)	33% (10-81)	48% (32-67)
		5 years	-	83% (49-99)	44% (22-73)	75% (33-99)	67% (25-99)	63% (44-81)
Bladder toxicity	**G2+ RTOG bladder toxicity** cumulative proportion (95% CI)	2 years	-	13% (2-61)	6% (1-37)	0% (NA)	17% (3-73)	9% (3-25)
		5 years	-	25% (7-69)	13% (4-44)	0% (NA)	17% (3-73)	15% (7-33)
	Small or worse bladder problem cumulative proportion (95% CI)	2 years	-	75% (44-96)	47% (24-77)	25% (4-87)	67% (32-95)	55% (39-73)
		5 years	-	75% (44-96)	60% (33-88)	25% (4-87)	83% (48-99)	64% (46-81)

Text SUPP-1: Outlining protocol for pelvic lymph nodes and uninvolved seminal vesicle.

Lymph nodes are not readily identifiable on the planning CT scans. The relationship between the nodes and the vasculature is therefore used to ensure that the nodes are included within the CTV_2. Before outlining it is advisable to identify the various structures – especially the vessels and bowel. This can be done with more confidence by following their course over several scans.

Three distinct sections of the outlining process for CTV_2 are identified. The outlining procedure starts cranially, and the outline is drawn separately on each subsequent scan.

a) Sacral promontory to bottom of anterior extent of S3/4 junction – pre-sacral and upper pelvic nodes.

During this section, there is a single outline.

- The outline starts at the sacral promontory, which is defined from the sagittal scout film as the most anterior point of S1. The outline starts at the anterior extent of iliac vessels. It follows the anterior wall of the vessels. The plane between the vessels and psoas muscle should be identified. The lateral extent of the outline follows this plane or the medial border of the psoas muscle if there is a distinct fat plane between the vessels and psoas. Posteriorly the outline extends onto the sacrum and stops at the anterior extent of the sacrum and crosses the midline.

- The contralateral outline is effectively a mirror. The outline continues to run laterally until it has reached a point equivalent to the lateral extent of the iliac vessels. At this point the outline runs anteriorly and again runs along the tissue plane between the vessels and the psoas. The outline then follows the anterior curvature of the vessels and then runs posteriorly along the medial edge of the vessels.

- To cross the midline anteriorly, three situations occur. Firstly, if there is a vessel crossing the midline, the outline should follow the anterior extent of this vessel and continue anterior to the wall of the vessel until it joins the starting point. Secondly, if there is no vessel crossing the midline, the anterior extent of the outline crossing the midline should be 15mm anterior to the sacrum. This will include the pre-sacral nodes. Thirdly, if there is bowel in this pre-sacral space it should be specifically excluded from the wall of the bowel. The first outline should now be complete.

- The outline on subsequent scans follows the same path until it reaches the anterior aspect of the S3/4 junction apart from one point. As the sacral promontory becomes less prominent, the anterior extent of the sacrum becomes almost horizontal. At this point the lateral extent of the sacrum is defined by the sacro-iliac joints and usually corresponds to the point where the psoas muscle meets the pelvic bone. A corner is created. This corner marks the postero-lateral extent of the outline. The lateral outline, running between the iliac vessels and the psoas should follow the medial border of psoas posteriorly onto the bone, and the outline should then continue medially.

- Proceeding caudally, the sacrum has hollows, which correspond to the exit foramina of the sacral nerves. These hollows are included within the volume, i.e. the outline continues to follow the anterior extent of the bone. The pyriformis muscle lies anterior to the sacrum and becomes bulkier caudally. Its anterior border becomes the posterior border of the outline, i.e. it is excluded from the volume.

- During this section the common iliac vessels bifurcate. The external iliac vessels become more anterior on caudal slices. The anterior extent of the outline should follow anterior wall of the external iliac vessel.

- The bottom of this section corresponds to the anterior extent of the S3/4 junction, which is identified from the sagittal scout film and approximates to the bottom of the sacro-iliac joints.

b) S3/4 junction to the tips of the seminal vesicles – mid pelvic nodes

- At the anterior extent of S3/4 junction (defined form lateral scout view) the outline now excludes the remaining inferior extent of the pre-sacral space. This point approximates to the bottom of the sacro-iliac joints and the top of the sciatic notches. This results in two disconnected outlines. The outlining procedure for each side is identical, although the volumes are usually not mirror images.

- The outline starts at the anterior extent of the external iliac vessels. Laterally it follows initially the medial edge of the psoas muscle, and then the medial wall of the pelvis. The posterior edge of the ilium marks the anterior portion of the sciatic notch. The pre-sciatic nodes (also known as the internal pudendal nodes) accompanying vessels (continuation of the internal iliac vessels) and the sciatic nerve lie in this area. The outline extends down from the bony pelvis and passes lateral to these structures (i.e. they are included). The outline runs along the visible musculature (obturator externus), which forms the postero-lateral border of the volume. The posterior extent of the outline runs along the most posterior of the previously mentioned structures. This usually involves outlining as much as 2/3rds of the sciatic foramen. The outline then runs up the medial border of the internal iliac vessels.

- The next part of the medial outline is variable. The outline eventually follows the medial border of the external iliac vessels. The outline between the internal and external iliac vessels is drawn to include branches of the internal iliac vessels but excludes bowel.

- During this section, the external iliac arteries become gradually more anterior. The anterior extent of the outline continues to be the anterior wall of the vessels, but it should not extend more than about 2cm anterior to the most anterior point of the bony pelvis. It should include both artery and vein. Eventually both vessels are anterior and lateral to the pelvic brim, as they descend into the groin. At this point, the anterior extent of the outline corresponds to the antero-medial point of the bony pelvis and usually approximates to the level of the acetabulum.

- Caudally, the tips of the seminal vesicles or small vascular structures may become visible medially. At this point the medial edge of the outline follows the medial edge of the vessels/seminal vesicles. The outlines may stay separate. If the vessels/seminal vesicles meet in the midline, the outlines join to form a single volume. This outlining process for this volume is described in the next section.

c) <u>Tips of seminal vesicles to prostate GTV_1 - lower pelvic nodes and uninvolved seminal vesicle.</u>

- Caudally, the tips of the seminal vesicles or small vascular structures may become visible in the midline. At this point the two separate volumes join medially into a single outline.

- The anterior extent of the outline follows the medial edge of the obturator internus muscle and posteriorly the bony pelvis. When the structures in the pre-sciatic notch become invisible, the posterior extent of the outline becomes the posterior point of the ilium. The medial outline follows the medial border of the small vessels and curves into the midline. As much distance as possible is kept between the outline and rectum at this point. The outline is drawn across midline and the process is repeated on the other side.

- Contralaterally, the anterior extent is again the antero-medial bony pelvis. the antero-medial outline is drawn to cover the medial aspect of the small vessels. The outline is drawn as far away from the bladder as possible. The outline crosses the midline, becomes more anterior again, as it follows the small vessels, and joins the starting point.

- As the superior pubic ramus starts to appear, the nodal volume reduces further in size. The anterior extent of the nodal volume becomes the anterior extent of the vessels on the pelvic sidewalls, and the posterior extent becomes the posterior extent of the vessels. The lateral

border remains the musculature and bony pelvis. The outline stops extending to the pelvic side walls 0.5-1cm above the top of the acetabulum.

- Throughout this stage of the outlining process, all of the seminal vesicles should be included in CTV_2 unless they are included in GTV_1. As GTV_1 may include the central portion (base) of the seminal vesicles, any remaining seminal vesicles should be outlined as CTV_2.

References (Appendix)

1 Holch P, Henry AM, Davidson S, et al. Acute and Late Adverse Events Associated With Radical Radiation Therapy Prostate Cancer Treatment: A Systematic Review of Clinician and Patient Toxicity Reporting in Randomized Controlled Trials. Int J Radiat Oncol Biol Phys 2017 Mar 1; 97(3): 495–510.

Text SUPP-2: Trial protocol (version 6.0, April 2010).

STATEMENT BY THE AUTHORS: For clarity, cohort numbers in the manuscript have been modified from the protocol, separating the hypofractionated 4 and 5 week schedules but including lymph node positive patients in their respective overall pelvic lymph node dose cohorts. Cohorts are numbered in the protocol and in the manuscript as in the table (table SUPP-6).

Table SUPP-6: Cohort numbering in protocol and manuscript

Cohort number (protocol)	Cohort number (manuscript)	Dose/fractionation	Notes
Cohort 1	Cohort 1	CFRT 70-74 Gy to P+SV 50Gy to PLN	-
Cohort 2	Cohort 2	CFRT 70-74 Gy to P+SV 55Gy to PLN	-
Cohort 3	Cohort 3	CFRT 70-74 Gy to P+SV 60Gy to PLN	-
Cohort 4	Cohort 4	HFRT – 4 weeks schedule 60 Gy to P+SV 47Gy to PLN	-
	Cohort 5	HFRT – 5 weeks schedule 60 Gy to P+SV 47Gy to PLN	-
Cohort 5	*Not reported independently in the manuscript*	CFRT and HFRT with 4 Gy boost to any positive lymph node as described in the methods section of the manuscript	Node-positive patients

FULL TITLE OF PROJECT:

A Phase 1 dose escalation study of the use of intensity modulated radiotherapy (IMRT) to treat the prostate and pelvic nodes in patients with prostate cancer

SHORT TITLE:

Pelvic IMRT for prostate cancer

1) SUMMARY OF PROJECT

Intensity Modulated Radiotherapy (IMRT) is a new development of conformal radiotherapy. It allows the irradiation of concave tumours, and reduces the radiation dose to radiosensitive normal tissues close to or even surrounded by a tumour.

In the treatment of the pelvis with current radiation techniques, patients commonly experience side effects due to irradiation of small bowel, colon, bladder and rectum. In around 5% of patients these side effects can be serious enough to require surgical correction, and in addition this risk of side effects limits the dose that can safely be prescribed.

We have performed radiotherapy planning studies of pelvic irradiation, which suggest that IMRT reduces the volume of small bowel treated to radiation tolerance from 20% to 4-6%. Five fold reductions in the dose to rectum and bladders were also measured. We have delivered these treatments to phantoms showing a delivery accuracy of ≤2%. This project is to test the feasibility of delivering this novel radiotherapy technique to patients, and to perform a dose escalation study of pelvic node irradiation in men with prostate cancer to ascertain the optimal dose level for future studies.

2) BACKGROUND

Current techniques for pelvic radiotherapy are associated with considerable morbidity. This limits the dose of radiation that can be prescribed to 45-50 Gy using conventional 1.8-2.0 Gy daily fractions if significant quantities of bowel lie in the field. IMRT reduces the dose to bowel, and is likely to reduce treatment-related complications, and should allow dose escalation. If clinically proven, this would have a major impact on the treatment of prostate cancer on a National and International level. Additionally, the technique would have application to other pelvic tumours such as rectal cancer, anal cancer, and gynaecological tumours in the pelvis.

Results using pelvic lymph node irradiation in prostate cancer

Two large phase III trials evaluating the role of whole pelvic radiotherapy in patients with intermediate and high risk prostate cancer have been recently published(1, 2). Initial results of the 1,323 patient Radiation Therapy Oncology Group (RTOG) 94-13 trial(3), suggested pelvic radiotherapy (dose to whole pelvis 50.4 Gy in 1.8 Gy fractions) improved progression-free survival compared with prostate only radiotherapy (dose received 70.2 Gy in 1.8Gy fractions) among patients with a greater than 15% chance of pelvic lymph node involvement (as per the Roach formula)(4). With five year median follow-up, pelvic radiotherapy was associated with a 4 year progression-free survival rate of 54% (95% CI: 50-59) compared with 47% (42-52) in patients treated with prostate only (p=0.02). This study changed clinical practice for high risk patients in North America such that intermediate and high risk patients now receive whole pelvic radiotherapy. However, interpretation of this trial's results are complicated by the finding of a significant interaction between field size and timing of hormonal therapy (the trial also randomised patients, in a 2x2 factorial design, to neoadjuvant versus adjuvant hormone therapy, but was not powered to compare the four treatment arms one against the other). Recently updated results

are less convincing, with no statistically significant difference seen between the two radiotherapy treatment groups: 5 year biochemical progression free survival was just under 50% in both groups (p=0.72; p=0.07 in favour of pelvic radiotherapy for patients receiving neo-adjuvant hormone therapy, p=0.06 in favour of prostate only radiotherapy in patients receiving adjuvant hormone therapy (2). A detailed analysis of the toxicity of pelvic radiotherapy in this trial is not yet available.

GETUG-01, a smaller phase III trial of 444 patients conducted by the French FNLCC group, failed to show any difference between whole pelvic and prostate only radiotherapy: after a median follow-up of 42 months, five year progression-free survival was 63% (95% CI: 54-73) and 60% (51-69) in the high risk prostate alone and pelvis and prostate groups respectively (p=0.20) (1). The dose to the whole pelvis was 46Gy in 2Gy fractions and in both treatment groups the dose to the prostate was 66-70Gy in 2 Gy fractions. The GETUG group used a lower radiotherapy dose than RTOG, with a significant cohort being treated to 66Gy; median dose to the prostate was 68Gy. The superior border of the pelvic field was approximately 2cm lower (S1/S2 interspace) than in the RTOG trial. The GETUG trial included patients with high and low risk of lymph node involvement (<15/≥15% as per Roach formula) : >50% of patients had <15% risk - this may have contributed to the lack of an observed effect. The French study, by treating the prostate to a low dose by contemporary standards, may have a higher local failure rate diluting any possible benefit on regional control.

In general, the use of lymph node irradiation is limited to between 44 and 50Gy to avoid side effects which is probably a sub-optimal dose to destroy all micro metastases. Pre-clinical studies have shown that IMRT techniques can substantially reduce the bowel and bladder volume irradiated during pelvic radiotherapy. Bowel and colon irradiated to the 90% isodose level is reduced from 24% using conventional radiotherapy to 18% using conformal techniques but only 5% reaches this dose level using IMRT (5). Initial acute and late toxicity results are now available for the first two cohorts treated in this current study of IMRT. Low levels of both acute and late toxicity with target lymph node doses of 50 and 55 Gy (6) have been observed.

Treatment of lymph node positive patients

Despite the inevitable stage migration associated with PSA testing for asymptomatic patients, there is a sub-population of patients, who present with locally advanced node positive (N1) disease, whose optimal management remains uncertain. Various management approaches have been put forward in the literature; from not treating the primary tumour definitively and comparing timings of the initiation of hormonal deprivation therapy (7, 8) to aggressive surgical approaches (9, 10). Surgically treating patients has been shown to demonstrate a survival advantage for patients who have had a radical prostatectomy (RP) and a pelvic lymph node dissection (PLND) compared with a similar cohort whose pathologically positive nodes were not removed at the time of surgery(9).

There is limited evidence describing the use of radiotherapy and hormonal suppression in patients with locally advanced node positive prostate cancer. Non-randomised series (11, 12) have described overall and actuarial prostate cancer specific survival at 8 years of 72% and 87%. 50.4Gy in 1.8Gy fractions was delivered to the pelvic lymph node regions. These series compare more favourably to RTOG data on a separate group of patients who received radiotherapy as monotherapy with a similar dose delivered to the pelvic nodal regions (13), however, direct comparisons cannot be made. RTOG 85-31(14) evaluated the use of radiotherapy +/- hormonal therapy in patients with locally advanced prostate cancer; a subset analysis on patients who were node positive, with a median follow-up of 6.5 years for all patients and 9.5 years for living patients, estimated progression-free survival with prostate-specific antigen (PSA) level less than 1.5 ng/mL at 5 and 9 years was 54% and 33%, respectively, for patients who received immediate LHRH agonist versus 10% [corrected] and 4% for patients who received radiation alone with hormonal manipulation instituted at time of relapse (P < .0001) (15). In the absence of results from randomised trials it appears appropriate to treat patients with locally advanced node positive disease with external beam radiotherapy and hormonal suppression.

Recently, Da Pozzo and colleagues (16) reported a retrospective study including 250 consecutive patients with pathologic lymph node invasion. All patients underwent RP and PLND plus adjuvant hormones &/or radiotherapy. After a mean follow-up of 95.9 months, the 51.6% (129) patients who received hormones and radiotherapy had a prostate cancer specific survival of 80% at 10 years compared to 53% in the cohort who received hormones alone.

The impressive long-term survival data from the Italian group (16) further supports the role for treating patients with node positive prostate cancer aggressively. It has been demonstrated that dose escalation in radical radiotherapy for localised prostate cancer results in an increase in biochemical disease control (17-19)

In the pelvic node positive cohort, the pelvic lymph node regions will receive 60Gy in 37 fractions over 7.5 weeks to the lymph node regions; pathologically enlarged nodes will receive 65Gy as an integrated boost. The prostate and involved seminal vesicles will be treated to 74Gy, which is current standard care in the UK[25].

3) PART 1 - FEASIBILITY STUDY

Initially a feasibility study will be undertaken. Men with localised prostate cancer stage T3a/b or T2 with PSA >20ng/ml or Gleeson score ≥8 will be recruited. Planning CT scan will be performed, and the clinicians will segment the images for treatment planning. The anatomical location of the planning target volume will be based on published atlases of pelvic nodal anatomy, supplemented with our own experience and that of radiologist colleagues. Inverse treatment planning will be undertaken using the CORVUS Planning System (NOMOS Corporation, Pittsburgh, USA) to deliver 70Gy to the prostate, 64Gy to the seminal vesicles, and 50Gy to the pelvic lymph nodes. Intensity maps will be produced for delivery with the dynamic MLC (Elekta Oncology Systems, Crawley, UK). For the first 5-10 patients, the treatment plan will be delivered to a phantom, and dosimetry verified using radiographic film in 2 and 3 dimensions. Thereafter, the phantom studies will be continued on patients where there is any concern regarding the delivery of the planned dose distribution. In addition, for all patients, portal images of each treatment field will be taken using radiographic film to verify the correct dose intensity map is delivered from each beam direction, and exit portal images will be used to check that the patient is correctly positioned. Current levels of treatment set-up accuracy and protocols for patient movement will be applied. i.e. If a field set-up error of greater than 3mm is detected on three consecutive days, then the patients position will be adjusted accordingly. Acute and late radiotherapy toxicity data will be collected using the EORTC/RTOG LENT/SOM and RTOG standard toxicity survey systems. Data collected from this cohort of men will act as a base-line for the dose escalation protocol.

4) PART 2 - DOSE ESCALATION TRIAL

A. DESIGN

Once feasibility of treatment delivery has been established, a cohort dose escalation study will be performed. Dose to the pelvic nodes will be escalated in 5Gy increments from 50Gy to, 55Gy, and subsequently 60Gy. In patients thought to have radiologically suspicious lymph nodes, IMRT would allow the delivery of an additional 5Gy boost to these nodes. The 60Gy cohort will be expanded provided there is no evidence of dose limiting toxicity in the first 30 patients (see below).

5) PART 3 – HYPOFRACTIONATED COHORT

Following completion of recruitment to the 60Gy cohort, an hypofractionated 4 week schedule will be studied, using the same initial and then expanded patient groups provided no significant toxicity is observed in the first 30 patients. This hypofractionated schedule was modified after an interim analysis demonstrated an increase in acute toxicity. This hypofractionated schedule was modified to a five weeks schedule.

6) Part 4 – PELVIC NODE POSITIVE COHORT

Parts 1-3 of the study have demonstrated the feasibility of delivering escalated doses of radiotherapy using IMRT to the pelvic lymph node regions. Patients with radiologically node positive disease have also been treated within each cohort; however, a separate toxicity analysis was not planned for this sub-set of patients. Radiotherapy will be delivered using a simultaneous integrated boost technique; 74Gy in 37 fractions to the prostate and pathologically involved seminal vesicles, 60Gy in 37 fractions to lymph node regions and uninvolved seminal vesicles and 65Gy in 37 fractions to the radiologically pathological nodes.

Reported Toxicity to date

Successive cohorts of patients with locally advanced prostate cancer have been treated with radiotherapy receiving 70Gy in 35 fractions to the prostate and seminal vesicles and 50Gy (n=25), 55Gy (n=55) or 60Gy (n=135) to the pelvic lymph node region. Acute and late toxicity rates were low in the 50Gy and 55Gy groups (20, 21). In the 60Gy group, acute (RTOG ≥2) bladder and bowel toxicity peaked at 40% and 38% respectively at week 6/7 of follow-up. The 2-year actuarial rate of late bladder and bowel toxicity (RTOG ≥2) was favourable at 2.5% (95% CI: 0.8% - 7.6%) and 12.5% (7.7% - 20%) respectively(22).

B. ELIGIBILITY CRITERIA

1 Cohorts 1 – 4

i. **Men with prostate cancer** with either:

1. Radiological or pathological pelvic nodal metastases or T3b/T4 disease or
2. Localized prostate cancer (pT2-T4) with a >30% estimated risk of pelvic nodal metastases* or
3. National Collaborative Cancer Network (NCCN) High Risk (Gleason score ≥8 or ≥2 risk factors) or Very High Risk Disease (23) (Appendix 1)
4. Post-prostatectomy patients (T2-T3a, N0) with extensive high grade disease (Gleason score ≥8) or seminal vesicle involvement or lymph node involvement.

*Risk of pelvic nodal metastases = (Gleason score – 6) x 10 + 2/3 PSA

2 **Cohort 5 (NODE POSITIVE COHORT)**

i. **Men with prostate cancer** with either:

1. Radiological or pathological proven pelvic nodal metastases
2. Post-prostatectomy patients with residual nodal disease on post-operative Imaging

ii. **Informed consent**

iii. **Exclusion criteria**:

Patients unsuitable for radical radiotherapy

Previous pelvic radiotherapy or surgery (excluding prostatectomy)
Inflammatory bowel disease or other small bowel disease

C. MEASUREMENT OF RADIATION TOXICITY

Acute side effects will be documented weekly using the RTOG scoring system.

Late side effects will be monitored by RTOG, LENT SOM and Quality of Life assessments using the FACT-P and UCLA prostate instruments. Late side effects will be monitored 6, 12, 18 and 24 months after treatment, and annually thereafter.

D. TUMOUR CONTROL

Tumour control will be monitored clinically and by PSA estimation taken 6 months after treatment and at six monthly intervals for 5 years and thereafter annually.

E. END POINTS

i. **Primary endpoint**:
Late RTOG radiotherapy toxicity.

ii. **Secondary endpoints**:
Overall survival

Local control

PSA control

Acute side effects

Quality of Life

Patterns of recurrence

F. PATIENT NUMBERS AND STATISTICS

i. Cohorts 1 – 4
At each dose/volume level a total of 15 men will be treated and followed up for at least 1 year, to exclude a ≥20% Grade ≥3 late toxicity rate. If 0/15 men have Grade

≥3 RTOG complications then a ≥20% Grade≥3 toxicity rate is excluded with 95% power.

In order to speed up the recruitment process, patients in the low small bowel volume group in the feasibility study will be able to be recruited to the next dose level once at least 7 men have had ≥12 months follow-up, and 0/7 grade≥3 complications have been recorded (excludes ≥20% Grade≥3 toxicity rate with 80% power). If 1/7 Grade≥3 complications is seen, dose escalation will not be attempted, and a total of 15 men will be recruited into that group.

Cohort 3 (60Gy to pelvic nodes) will be expanded (see below) provided 0/15 men have Grade ≥3 bowel complications after ≥1 year's follow up.

Cohort 4 (hypofractionated schedule 47Gy to pelvic lymph nodes) will recruit at least 15 men at each volume level and be expanded (see below) provided 0/15 men have Grade ≥3 bowel after ≥1 year's follow up. In this cohort, a 4Gy boost will be given to patients with radiologically involved lymph nodes.

We expect a late toxicity rate of ≥ grade 2 RTOG toxicity rate at 2 years would be around 15% (p1 = 85%) and that a rate in excess of 25% would be unacceptable (p0 = 75%). Then with 80% power and a 1 sided alpha of 0.05 we would require that at least 85 patients or more, out of a total of 103 eligible patients, are free from toxicity. This would ensure that the 95% Confidence interval of the grade 2 or more RTOG toxicity rate will be less than and exclude 25%. Approximately 20% of patients may not be assessable at 2 years for all trial end points (personal communication from MRC RT01 Trial) so 123 men will be recruited to cohorts 3 and 4.

ii. Cohort 5 (node positive cohort)

We expect ≥ grade 2 RTOG late toxicity rate at 2 years to be around 15% (p1 = 85%) and that a rate in excess of 30% would be unacceptable (p0 = 70%). Then with 80% power and a 1 sided alpha of 0.05 we would require that at least 35 patients or more, out of a total of 49 eligible patients, are free from toxicity. This would ensure that the 95% confidence interval of the grade 2 or more RTOG toxicity rate will be less than and exclude 30%. Approximately 20% of patients may not be assessable at 2 years for all trial end points (personal communication from MRC RT01 Trial) so 58 men will be recruited to cohorts 5. 23 patients in cohort 3 had radiologically positive nodes; 14 of whom received a boosted dose to the pathological node of 5Gy. These 14 patients will be analysed as part of the node positive cohort for the purposes of the primary endpoint, ie late RTOG grade II toxicity.

G. RADIOTHERAPY PLANNING

i. Scanning and Outlining

Patients have a planning CT scan in the treatment position. The following structures are outlined on the planning computer:

Targets: CTV_1 = Prostate and any involved seminal vesicle

CTV_2 = Uninvolved seminal vesicle and pelvic lymph nodes

CTV_3 = Radiologically or pathologically involved lymph nodes.

The pelvic lymph node target volume (CTV_2) will be outlined as described in Staffurth et al 2005 (24)

Normal Tissue: Rectum

Bladder

Bowel (small bowel to sigmoid colon)

Femoral heads

ii. **Margins**

CTV_1 is grown by 8 mm posteriorly and 10 mm in all directions to create PTV_1.

CTV_2 is grown by 5 mm uniformly to create PTV_2.

CTV_3 is grown by 5 mm uniformly to create PTV_3.

iii. **Inverse Planning**

Patients will be inverse planned to deliver the following **median** target doses. For dose escalation protocol see below.

	PTV_1	PTV_2	PTV_3
Cohort 1	70 Gy 35F	50 Gy	55 Gy
Cohort 2	70 Gy 35F	55 Gy	60 Gy
Cohort 3	70 Gy 35F	60 Gy	65 Gy
Cohort 4	60 Gy 20F	47 Gy	51 Gy
Cohort 5	74Gy 37F	60Gy	65Gy

For post-prostatectomy patients in cohorts 1-2, the prostate bed dose will be 64Gy in 32 fractions. In cohort 3, the dose is 65Gy in 35 fractions and in cohort 4, the prostate bed will receive 55Gy in 20 fractions.

The post-prostatectomy dose in cohort 5 will be 64Gy in 32 fractions.

H. TREATMENT PLANNING AND DELIVERY

Treatment planning and delivery will be performed with the systems currently available and most suitable for purpose at the Sutton and Chelsea branches of the RMH. At Sutton, the NOMOS Corvus system was initially used to plan dynamic IMRT delivery; subsequently Helax-TMS and Pinnacle planning systems will be used to deliver "step and shoot" IMRT. Treatment delivery is given with ELEKTA linear accelerators. At Chelsea, initially the CADPLAN and subsequently ECLIPSE and HELIOS planning systems were used. Dynamic treatment delivery on a VARIAN 2100CD linear accelerator. All of the planning methods use a simultaneous boost technique treating the prostate and pelvis together. 5 coplanar beams are used delivering treatment from posterior, 2 anterior oblique and 2 posterior oblique fields.

I. TREATMENT VERIFICATION

i. Pre-treatment

For the first 5-10 patients, the treatment plan will be delivered to a phantom, and dosimetry verified using radiographic film in 2 and 3 dimensions. Thereafter, the phantom studies will be continued on patients where there is any concern regarding the delivery of the planned dose distribution.

ii. On-treatment

For all patients, portal images of each treatment field will be taken using radiographic film to verify the correct dose intensity map is delivered from each beam direction, and exit portal images will be used to check that the patient is correctly positioned. Current levels of treatment set-up accuracy and protocols for patient movement will be applied. i.e. If a field set-up error of greater than 3mm is detected on three consecutive days, then the patients position will be adjusted accordingly.

iii. Verification techniques will be developed and adopted during the trials progress to take advantage of new technological developments in IMRT planning and dosimetry.

J. SYSTEMIC MANAGEMENT

All patients will be advised to receive a minimum of six months of hormonal therapy prior to definitive radiotherapy . Additional adjuvant therapy for a total of 3 years will be considered for patients particularly those with high grade (Gleason score ≥8) or NCCN very high risk disease.

L. ADVERSE EVENTS (AE) / SERIOUS ADVERSE EVENTS (SAE)

Definition of an Adverse Event

An 'adverse event' is any untoward medical occurrence in a patient administered a research procedure; where the events do not necessarily have a causal relationship with the procedure.

For the purpose of this trial, any detrimental change in the patient's condition subsequent to the start of the trial (i.e. registration) and during the follow-up period, which is not unequivocally due to progression of disease (prostate cancer), should be considered as an AE.

Whenever one or more signs and/or symptoms correspond to a disease or well-defined syndrome only the main disease/syndrome should be reported.

For each sign/symptom the highest grade observed since the last visit should be reported.

Definition of Serious Adverse Events

A serious adverse event is any untoward occurrence, that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity or
- consists of a congenital anomaly or birth defect

- additionally RTOG Grade≥4 acute or late radiation side effects i.e. related to study treatment, will be regarded as an SAE

A related adverse event is one for which the Principal Investigator and/or Chief Investigator (or nominated representative), assesses as resulting from administration of any of the research procedures.

An unexpected adverse event is any type of event not listed in the protocol as an expected occurrence.

Reporting of Adverse Events

Adverse events will be collected from the time of randomisation to the end of the follow-up period. Adverse events should be recorded in the appropriate section of the CRF.

Due acknowledgement has to be given to likely co-morbidity and co-morbid events in an elderly and ageing male population, many of whom will die from diseases unrelated to prostate cancer and its treatment.

The following are possible anticipated treatment related SAEs (i.e. expected occurrences) which are not subject to expedited reporting but should be reported in the appropriate section of the CRF.

Bone fractures

Bowel strictures

Second Malignancies

Ureteric obstruction

Expedited reporting of SAEs

All SAEs occurring within 30 days of study treatment (i.e. intensity modulated radiotherapy) being administered and not listed above, are subject to expedited reporting. In addition RTOG grades ≥4 acute or late radiation side effects occurring within 5 years of radiotherapy treatment are subject to expedited reporting.

All SAEs must be reported within 24 hours using the SAE form. The form must be sent by FAX to the Bob Champion Unit on **020 8643 1725**. It must be completed, signed and dated by the Principal Investigator or nominated representative.

The Bob Champion Unit (BCU) will send the SAE to the Chief Investigator (or nominated representative) for review of causality and expectedness.

Reporting related and unexpected SAEs

If an SAE is assessed as related and unexpected, the Bob Champion Unit will report this to the main REC within 15 days from the date the Bob Champion Unit became aware of the event.

SAE follow up

For each SAE, the subject must be followed-up until clinical recovery is complete and laboratory tests have returned to normal, or until the condition has stabilised. Information on final diagnosis and outcome of SAEs which may not be available at the time the SAE is initially reported should be forwarded to the ICR-CTSU in the timeframe requested.

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NCCN : National Comprehensive Cancer Network

www.nccn.org V.2.2005

Recurrence risk

Low:	T1/T2a and Gleason 2-6 and PSA<10
Intermediate:	T2b/c or Gleason 7 or PSA 10 - 20
High:	T3a or Gleason 8-10 or PSA >20
Very High:	T3b/T4