Supplementary Appendix

Appendix 1: LENTSOM Sexual Dysfunction Scale and Royal Marsden Hospital (RMH) Erectile Potency Scale

LENTSOM SEXUAL DYSFUNCTION – MALE

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Erectile function for vaginal penetration	Occasionally insufficient	Intermittently insufficient	Not sufficient	Impotent
Dryness	Occasional	Intermittent	Persistent	Refractory
Desire	Occasional	Intermittent	Seldom	Never
Satisfaction	Occasional	Intermittent	Seldom	Never
Objective				
Frequency		Decreased from normal	Rare	Never
Orgasm	Occasional	Intermittent	Seldom	Never
Management				
Impotence	-	Medical intervention	Surgical intervention	-

RMH ERECTILE POTENCY

	Grade 0	Grade 1	Grade 2
Erectile potency	Normal erection	Decreased erection	Absent erection

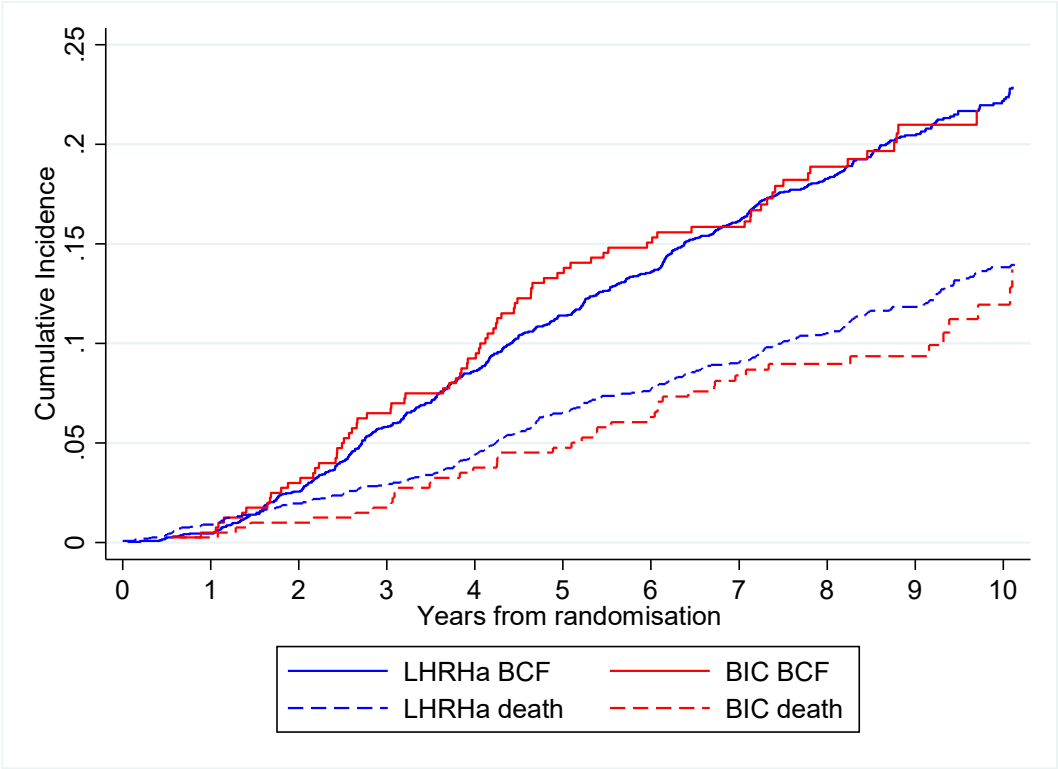
Appendix 2: Multivariable Cox regression models for efficacy outcomes – Hazard Ratios (HR), 95% confidence intervals and p-values (Wald tests)

Adjusted Cox model	HR (95% CI)	P value
Biochemical and/or clinical failure		
LHRHa	1.00	-
Bicalutamide	0.98 (0.70-1.36)	0.889
Age (continuous)	0.99 (0.97-1.01)	0.382
Low risk	1.00	-
Intermediate risk	0.77 (0.44-1.36)	0.372
High risk	1.59 (0.79-3.21)	0.193
Gleason ≤6	1.00	-
Gleason 7/8	1.74 (1.28-2.36)	<0.001
Clinical stage T1	1.00	-
Clinical stage T2	1.30 (1.01-1.67)	0.042
Clinical stage T3	1.03 (0.59-1.80)	0.908
Pre-hormone PSA <10ng/ml	1.00	-
Pre-hormone PSA 10-20ng/ml	1.86 (1.47-2.35)	<0.001
Pre-hormone PSA >20ng/ml	1.37 (0.76-2.47)	0.288
Proportion of positive biopsies ≤50%	1.00	-
Proportion of positive biopsies >50%	1.55 (1.25-1.93)	<0.001
Overall survival		
LHRHa	1.00	-
Bicalutamide	0.87 (0.60-1.26)	0.465
Age (continuous)	1.10 (1.08-1.12)	<0.001
Low risk	1.00	-
Intermediate risk	0.62 (0.38-1.02)	0.058
High risk	0.95 (0.48-1.86)	0.876
Gleason ≤6	1.00	-
Gleason 7/8	1.21 (0.90-1.64)	0.210
Clinical stage T1	1.00	-
Clinical stage T2	1.18 (0.92-1.52)	0.194
Clinical stage T3	1.09 (0.60-2.00)	0.772
Pre-hormone PSA <10ng/ml	1.00	-
Pre-hormone PSA 10-20ng/ml	1.23 (0.96-1.58)	0.107
Pre-hormone PSA >20ng/ml	0.95 (0.51-1.76)	0.859
Proportion of positive biopsies ≤50%	1.00	-
Proportion of positive biopsies >50%	1.03 (0.82-1.28)	0.820
Disease free survival		
LHRHa	1.00	-
Bicalutamide	0.94 (0.72-1.22)	0.630
Age (continuous)	1.04 (1.02-1.05)	<0.001
Low risk	1.00	-
Intermediate risk	0.68 (0.46-0.99)	0.047
High risk	1.18 (0.71-1.97)	0.532
Gleason ≤6	1.00	-
Gleason 7/8	1.42 (1.14-1.78)	0.002
Clinical stage T1	1.00	-
Clinical stage T2	1.23 (1.02-1.49)	0.029
Clinical stage T3	1.11 (0.72-1.73)	0.632
Pre-hormone PSA <10ng/ml	1.00	-
Pre-hormone PSA 10-20ng/ml	1.54 (1.28-1.85)	<0.001
Pre-hormone PSA >20ng/ml	1.17 (0.74-1.85)	0.503

Proportion of positive biopsies ≤50%	1.00	-
Proportion of positive biopsies >50%	1.25 (1.06-1.48)	0.007
Recommencing hormones		
LHRHa	1.00	-
Bicalutamide	0.80 (0.50-1.29)	0.368
Age (continuous)	0.99 (0.97-1.02)	0.672
Low risk	1.00	-
Intermediate risk	1.87 (0.70-4.98)	0.214
High risk	4.21 (1.40-12.67)	0.011
Gleason ≤6	1.00	-
Gleason 7/8	1.51 (1.02-2.24)	0.039
Clinical stage T1	1.00	-
Clinical stage T2	1.37 (0.97-1.94)	0.070
Clinical stage T3	1.02 (0.51-2.04)	0.960
Pre-hormone PSA <10ng/ml	1.00	-
Pre-hormone PSA 10-20ng/ml	1.68 (1.24-2.29)	0.001
Pre-hormone PSA >20ng/ml	1.22 (0.59-2.53)	0.598
Proportion of positive biopsies ≤50%	1.00	-
Proportion of positive biopsies >50%	1.82 (1.35-2.44)	<0.001

Appendix 3: Competing risks analysis

A competing risk analysis has been performed for biochemical/clinical failure (BCF) with death from any cause treated as a competing event. The adjusted subhazard ratio for BCF was 1.00 (95% CI 0.71-1.40) with HR<1 favouring the bicalutamide group. The p-value from Gray's test was p=0.870. The cumulative incidence curves for BCF and death are presented below by hormone group

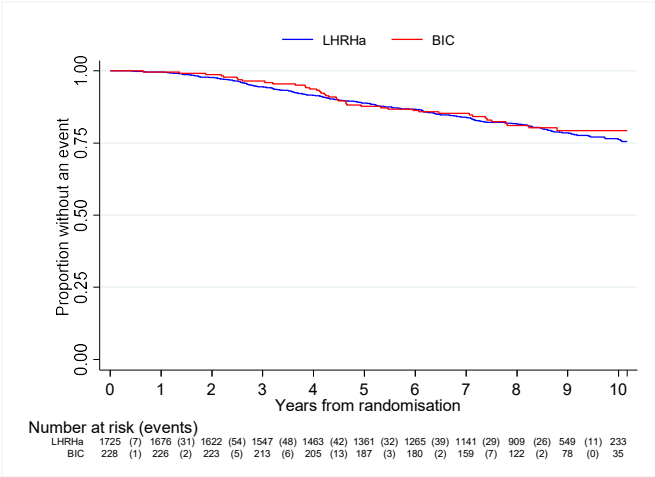


Appendix 4: Biochemical and/or clinical failure analysis restricted to unfavourable intermediate and high risk patients only

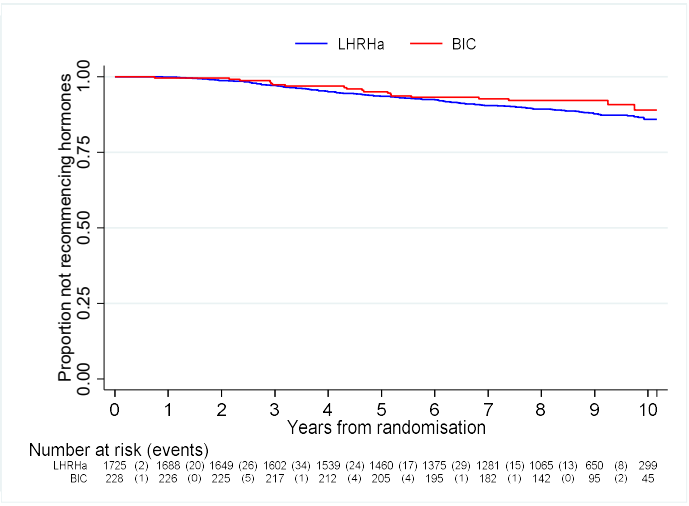
Intermediate risk patients were divided into favourable and unfavourable intermediate risk patients as per Zumsteg et al. (2013). Data on the proportion of positive core biopsies were only available on 1571/2314 intermediate risk patients thus it was not possible to categorise all the intermediate patients. Patients were only included in this subgroup analysis if their proportion of positive core biopsies was known. An exploratory subgroup analysis only including unfavourable intermediate and high risk patients was conducted (n=1953).

Unfavourable intermediate & high risk patients (n=1953)	HR (95% CI)	P value
Biochemical/clinical failure free	0.98 (0.70-1.38)	0.604
Recommencement of hormones	0.82 (0.51-1.32)	0.220
Disease free survival	0.91 (0.70-1.20)	0.523
Overall survival	0.83 (0.56-1.23)	0.132

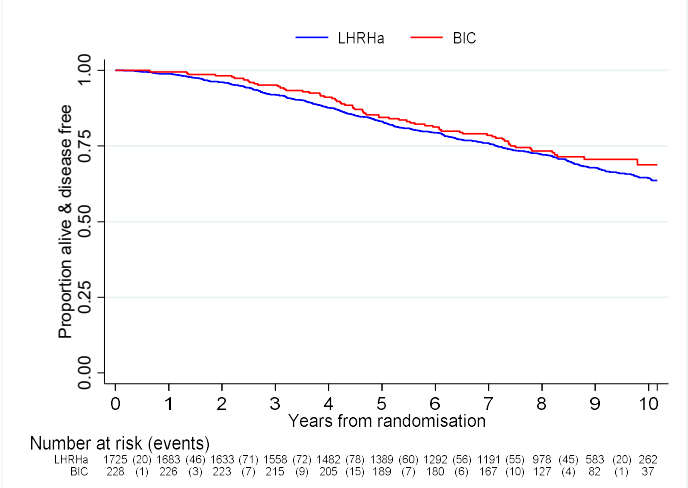
Biochemical and/orclinical failure



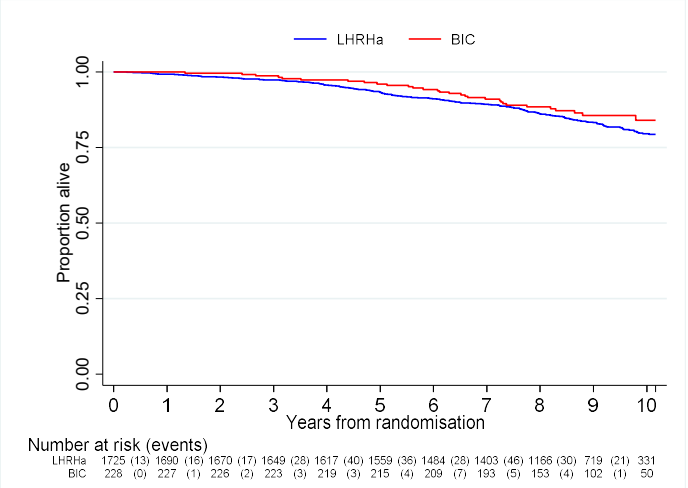
Recommencement of hormones



Disease free survival



Overall survival



Appendix 5: Pre-hormone assessment of sexual function assessed by LENTSOM, RMH and UCLA/PCI

	LHRHa n (%)	Bicalutamide n (%)
LENTSOM Subjective:		
Erectile function for vaginal penetration	N=786	N=89
Grade 0	461 (59)	54 (60)
Grade 1	66 (8)	16 (18)
Grade 2	80 (10)	3 (3)
Grade 3	*73 (9)*	*4 (4)*
Grade 4	*106 (14)*	*12 (13)*
RMH erectile potency	N=761	N=80
Normal erection (Grade 0)	378 (50)	44 (55)
Decreased (Grade 1)	259 (34)	23 (29)
Absent (Grade 2)	*124 (16)*	*13 (16)*
UCLA/PCI Ability to have an erection	N=553	N=49
Very poor	*113 (20)*	*11 (22)*
Poor	*102 (18)*	*6 (12)*
Fair	172 (31)	12 (25)
Good	113 (20)	16 (33)
Very good	53 (10)	4 (8)

NB. Italics indicates patients excluded from assessment of sexual function post-hormones starting as they are not considered to have preserved sexual function

Appendix 6: Multivariable logistic models for LENTSOM sexual functioning

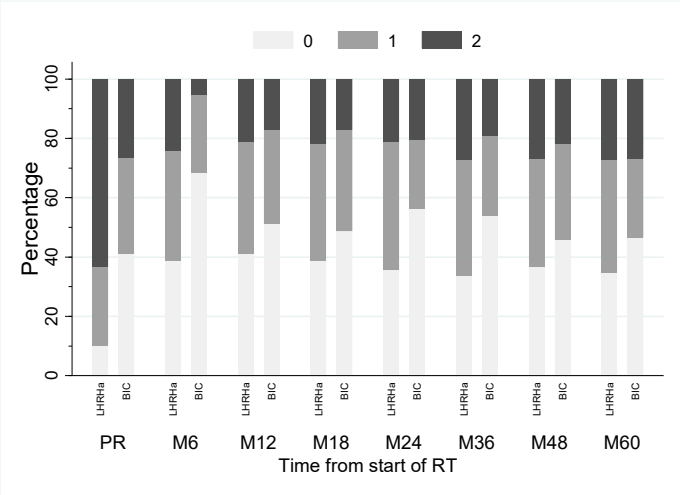
Binary variables have been created for LENTSOM sexual functioning scores at two years. An event is a patient with grade 2 or greater LENTSOM score at 2 years. An odds ratio <1 indicates a decrease in the odds of having a grade≥2 event at 2 years. Multivariable logistic regression models included hormone group, pre-hormone LENTSOM score, age and pre-hormone testosterone level.

	OR (99% CI)	P-value
LENTSOM erectile function for vaginal penetration (n=404)		
Hormone		
LHRHa	1.00	-
Bicalutamide	0.30 (0.10-0.90)	0.005
Pre-ADT erectile function for penetration		
G0	1.00	-
G1	3.07 (1.10-8.53)	0.005
G2	3.93 (1.54-10.04)	<0.001
Age		
<=69	1.00	-
70+	2.53 (1.41-4.53)	<0.001
Pre-ADT testosterone	0.97 (0.95-1.00)	0.003
LENTSOM sexual dysfunction subjective score (n=394)		
Hormone		
LHRHa	1.00	-
Bicalutamide	0.28 (0.09-0.90)	0.005
Pre-ADT subjective score		
G0	1.00	-
G1	3.39 (1.16-9.93)	0.003
G2	6.59 (1.50-29.06)	0.001
G3	4.04 (0.78-21.03)	0.029
G4	4.99 (0.58-43.09)	0.055
Age		
<=69	1.00	-
70+	2.17 (1.20-3.89)	0.001
Pre-ADT testosterone	0.97 (0.94-0.99)	<0.001
LENTSOM sexual dysfunction objective score (n=392)		
Hormone		
LHRHa	1.00	-
Bicalutamide	0.25 (0.08-0.79)	0.002
Pre-ADT objective score		
G0	1.00	-
G1	2.11 (0.60-7.39)	0.124
G2	4.78 (1.48-15.49)	0.001
G3	3.62 (0.59-22.38)	0.069
G4	5.32 (0.62-45.54)	0.045
Age		

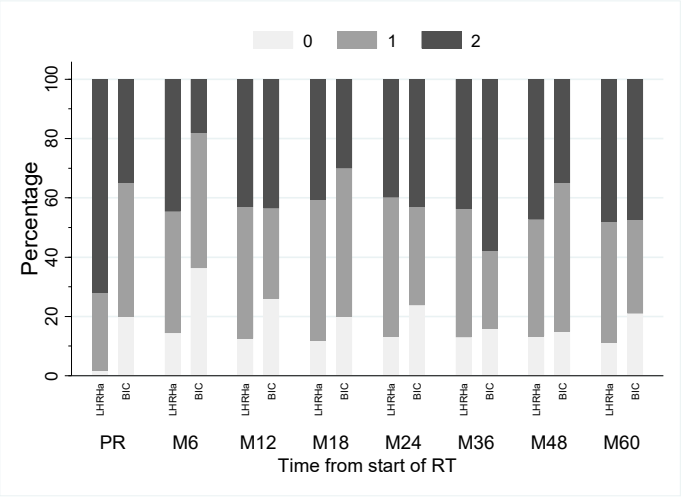
<=69	1.00	-
70+	2.50 (1.38-4.53)	<0.001
Pre-ADT testosterone	0.98 (0.95-1.00)	0.019
LENTSOM management (n=384)		
Hormone		
LHRHa	1.00	-
Bicalutamide	0.29 (0.06-1.43)	0.046
Pre-ADT sexual bother		
G0	1.00	-
G1	5.07 (0.60-42.75)	0.050
G2	3.02 (0.80-11.48)	0.033
Age		
<=69	1.00	-
70+	0.59 (0.29-1.21)	0.059
Pre-ADT testosterone	0.92 (0.90-0.95)	<0.001

Appendix 7: RMH score for erectile potency - distribution of scores at each time point assessed by hormone group for (A) patients with normal erection at pre-hormone assessment and (B) patients with decreased erections at pre hormone assessment. PR=pre-radiotherapy

(A) Normal erections pre-hormones



(B) Decreased erections pre-hormones



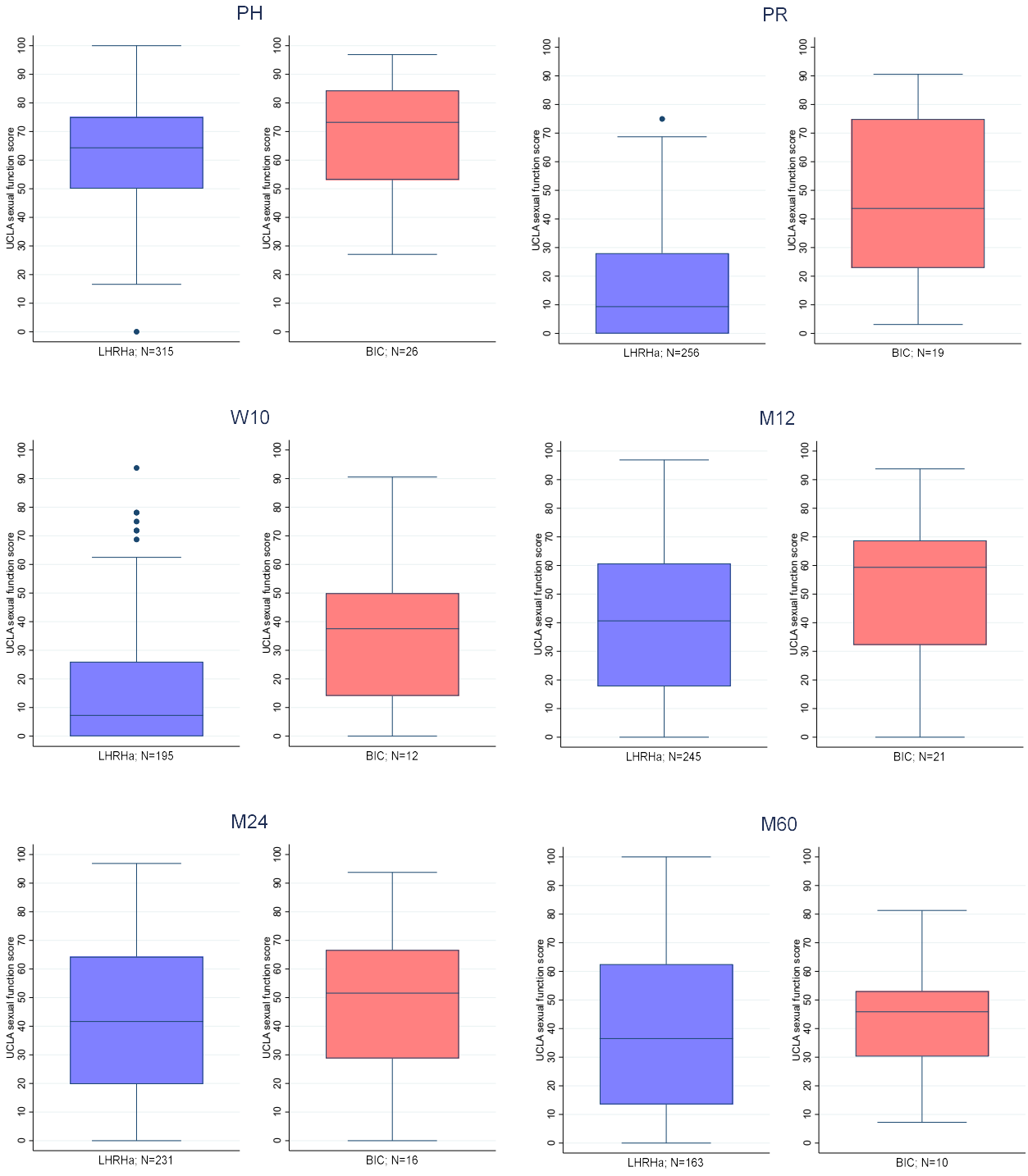
Appendix 8: Multivariable logistic models for UCLA/PCI sexual functioning at 2 years

Binary variables have been created for UCLA/PCI sexual functioning scores at two years. An event is a patient with poor or very poor UCLA/PCI score at 2 years. An odds ratio <1 indicates a decrease in the odds of having poor/very poor sexual functioning at 2 years. Multivariable logistic regression models included hormone group, pre-hormone UCLA/PCI score, age and pre-hormone testosterone level.

	OR (99% CI)	P-value
Rate your ability to have an erection (n=215)		
Hormone		
LHRHa	1.00	-
Bicalutamide	0.77 (0.15-3.85)	0.676
Pre-ADT ability to have an erection score		
Fair	1.00	-
Good	0.25 (0.11-0.56)	<0.001
Very good	0.17 (0.05-0.56)	<0.001
Age		
<=69	1.00	-
70+	1.87 (0.81-4.34)	0.055
Pre-ADT testosterone	1.04 (1.00-1.08)	0.022
Usual quality of erection (n=211)		
Hormone		
LHRHa	1.00	-
Bicalutamide	1.46 (0.32-6.66)	0.518
Pre-ADT quality of an erection		
None	1.00	-
Poor	5.18 (0.25-106.35)	0.161
Moderate	0.91 (0.27-3.07)	0.842
Good	0.47 (0.17-1.30)	0.057
Age		
<=69	1.00	-
70+	1.14 (0.46-2.80)	0.709
Pre-ADT testosterone	0.98 (0.92-1.05)	0.499
Ability to function sexually (n=221)		
Hormone		
LHRHa	1.00	-
Bicalutamide	1.32 (0.29-5.96)	0.637
Pre-ADT ability to function sexually		
Very poor	1.00	-
Poor	4.37 (0.88-21.68)	0.018
Fair	1.62 (0.58-4.51)	0.229

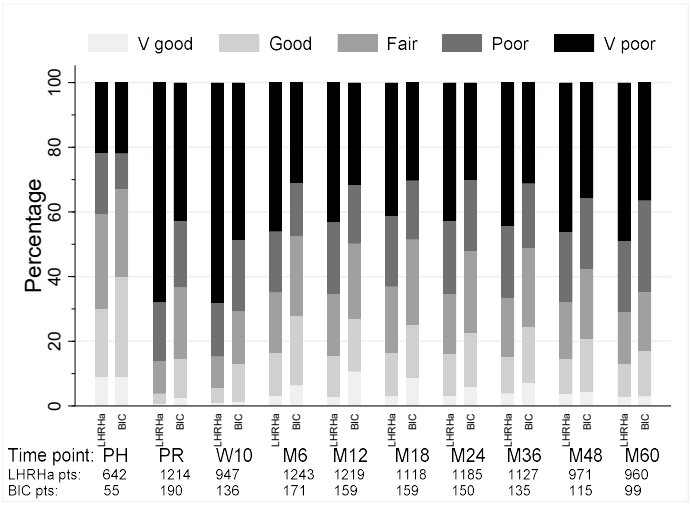
Good	0.46 (0.17-1.23)	0.043
Very good	0.31 (0.07-1.35)	0.041
Age		
<=69	1.00	-
70+	0.84 (0.36-1.96)	0.599
Pre-ADT testosterone	1.01 (0.95-1.07)	0.676
Sexual bother (n=219)		
Hormone		
LHRHa	1.00	-
Bicalutamide	1.03 (0.20-5.36)	0.963
Pre-ADT sexual bother		
No problem	1.00	-
Very small problem	0.94 (0.35-2.58)	0.882
Small	2.84 (1.04-7.76)	0.007
Moderate problem	12.91 (2.21-75.23)	<0.001
Big problem	7.95 (0.30-213.82)	0.105
Age		
<=69	1.00	-
70+	0.74 (0.30-1.82)	0.392
Pre-ADT testosterone	0.93 (0.89-0.97)	<0.001

Appendix 9: Box plots illustrating UCLA sexual function scores at each time point assessed by hormone group (PH=Pre-hormonal therapy, PR=Pre-radiotherapy, W10=week 10, Mx=scores at x months after treatment)

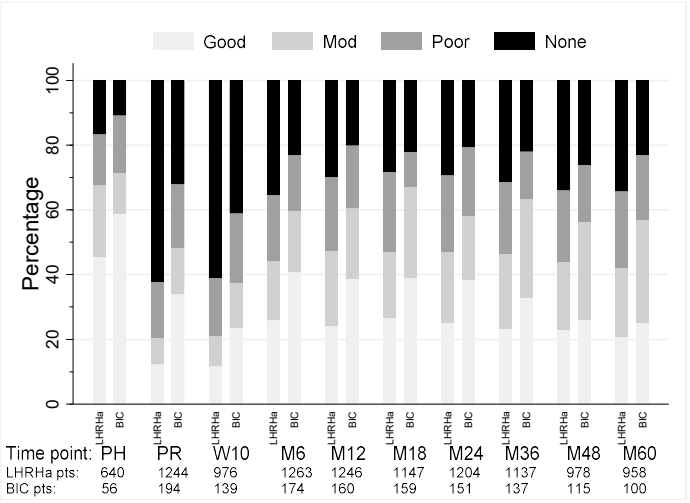


Appendix 10 Patient reported outcomes of sexual function assessed using UCLA/EPIC questionnaires using ALL received data – distribution of grade at each time point assessed by hormone therapy received. All received data is presented in these stacked barcharts with no restrictions based on availability of a pre-hormone assessment.

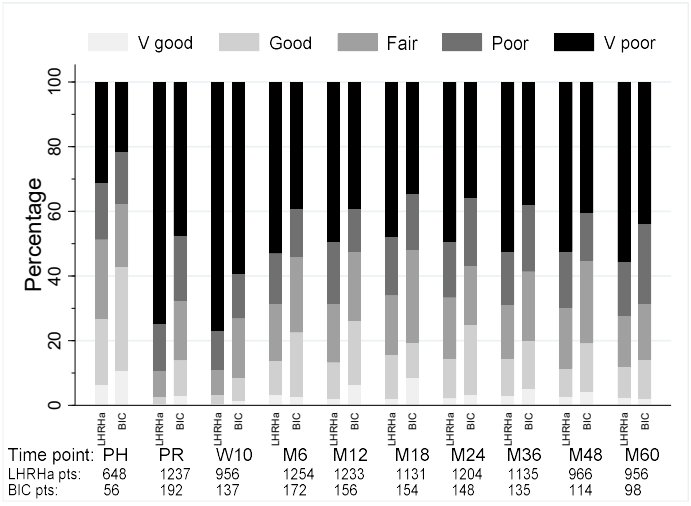
(A) Rate your ability to have an erection



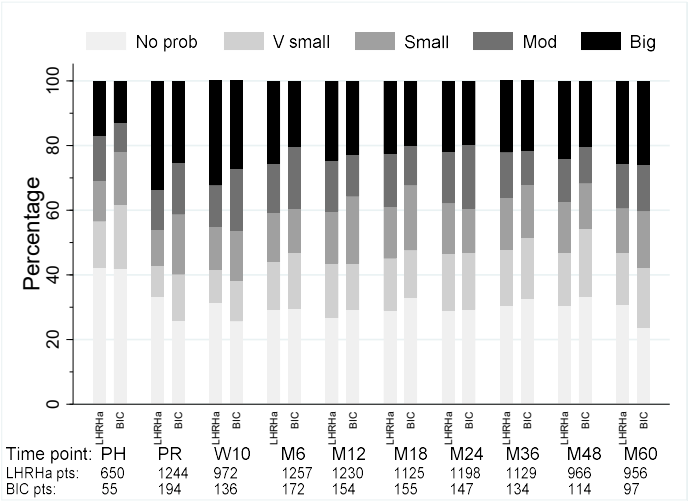
(B) Usual quality of erections



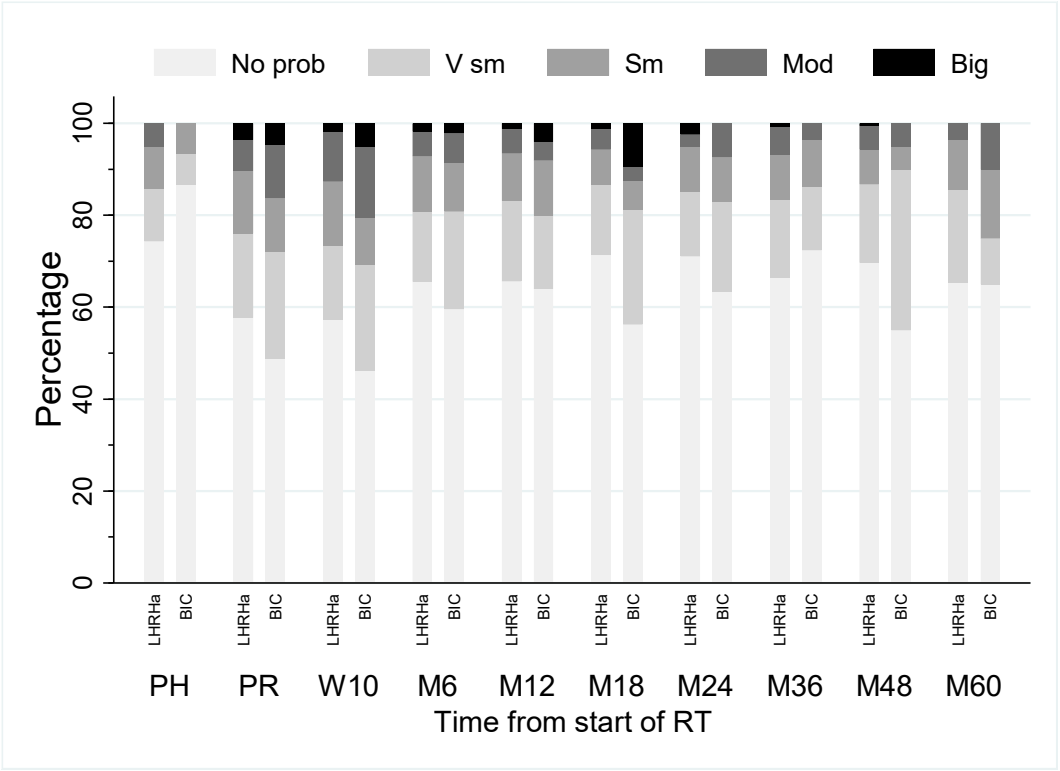
(C) Rate your ability to function sexually



(D) Sexual bother



Appendix 11: EPIC questionnaire item 'how big a problem has feeling depressed been' - distribution of scores at each time point assessed by hormone group. PH=pre-hormones, PR=pre-radiotherapy.

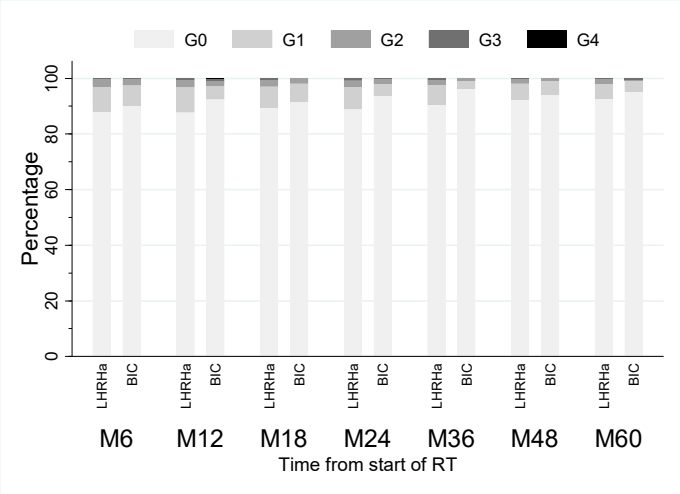


Appendix 12 Testosterone at pre-hormone and 12 month assessments

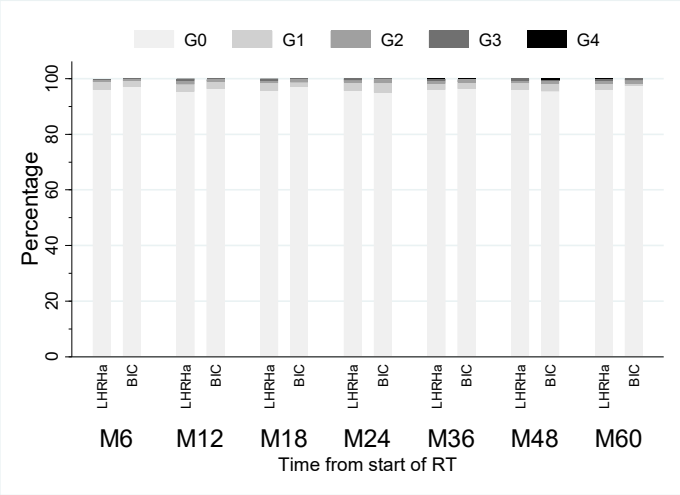
	Pre-hormone treatment assessment				12 month assessment			
	LHRHa (N=634)		Bicalutamide (N=73)		LHRHa (N=1553)		Bicalutamide (N=213)	
	N	%	N	%	N	%	N	%
Testosterone nmol/L								
0≤1.7	3	<1	0	0	43	3	1	<1
1.7≤8	93	15	11	15	340	22	31	15
>8	538	85	62	85	1170	75	181	85
Testosterone								
Median (IQR)	12.6 (9.4-16.2)		11.9 (9.3-16.4)		11.2 (8.1-14.5)		13.2 (10.0-17.4)	
Range	0.4-36.3		4.2-29.9		0.1-78.0		0.1-34.1	
Patients with paired pre-hormone and 12 month data								
	N=408		N=44		N=408		N=44	
Testosterone nmol/L								
0≤1.7	1	<1	0	0	8	2	0	0
1.7≤8	64	16	8	18	77	19	8	18
>8	343	84	36	82	323	79	36	82
Testosterone								
Median (IQR)	12.4 (9.2-15.8)		11.4 (9.4-16.9)		11.4 (8.7-14.7)		12.5 (9.5-17.8)	
Range	0.8-22.5		4.5-22.5		0.1-78.0		2.8-25.6	

Appendix 13: RTOG toxicity scale - distribution of scores at each time point assessed by hormone group for (A) bowel and (B) bladder symptoms

(A) Bowel



(B) Bladder



Appendix 14 Flow chart illustrating the PRO sexual functioning data available for analysis