Non-randomised comparison of efficacy and side effects of bicalutamide compared with LHRH analogues in combination with radiotherapy in the xxxxxx trial.

Alison Tree MD(Res) , Clare Griffin MSc , Isabel Syndikus MD , Alison Birtle MD , Ananya Choudhury PhD , John Graham FRCR , Catherine Ferguson FRCR , Vincent Khoo MD , Zafar Malik FRCR , Joe O'Sullivan MD , Miguel Panades LMS MRCR , Chris Parker MD , Yvonne Rimmer MD , Christopher Scrase FRCR , John Staffurth MD , David Dearnaley FRCR , Emma Hall PhD , on behalf of the CHHiP Investigators

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Title:
Non-randomised comparison of efficacy and side effects of bicalutamide compared with LHRH analogues in combination with radiotherapy in the CHHiP trial.

Short Running Title:
Bicalutamide compared with LHRHa in the CHHiP trial

Alison Tree MD(Res)* [1,2], Clare Griffin MSc*[2], Isabel Syndikus MD[3], Alison Birtle MD[4], Ananya Choudhury PhD[5], John Graham FRCR[6], Catherine Ferguson FRCR[7], Vincent Khoo MD[2,1], Zafar Malik FRCR[8], Joe O'Sullivan MD[9], Miguel Panades LMS MRCR[10], Chris Parker MD[1,2], Yvonne Rimmer MD[11], Christopher Scrase FRCR[12], John Staffurth MD[13], David Dearnaley FRCR^[2], Emma Hall PhD^[2] on behalf of the CHHiP Investigators
*joint first authors
^ joint last authors

[1] The Royal Marsden NHS Foundation Trust, London, UK
[2] Institute of Cancer Research, London, UK
[3] Clatterbridge Cancer Centre, Wirral, UK
[4] Royal Preston Hospital, UK
[5] University of Manchester, Manchester, UK
[6] Beatson Oncology Centre, Glasgow, UK
[7] Weston Park Hospital, Sheffield, UK
[8] Whiston Hospital, Merseyside, UK
[9] Patrick G. Johnston Centre for Cancer Research, Queen's University Belfast.
[10] Lincoln County Hospital, UK
[11] Addenbrooke's Hospital, Cambridge, UK
[12] Ipswich Hospital, Ipswich, UK
[13] Cardiff University/Velindre Cancer Centre, Cardiff, UK

Corresponding Author Name & Email Address:
Alison Tree
Alison.tree@icr.ac.uk

Author Responsible for Statistical Analysis Name & Email Address
Clare Griffin
Clare.griffin@icr.ac.uk

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Data Availability Statement for this Work

Research data are stored in an institutional repository and will be shared upon request to the corresponding author."

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Abstract

Background: XXXXX is a randomised trial evaluating moderately hypofractionated radiotherapy for treatment of localised prostate cancer. 97% of participants had concurrent short course hormone therapy (HT), either Luteinising Hormone Releasing Hormone analogues (LHRHa) or bicalutamide 150mg daily. This exploratory analysis compares efficacy and side effects in a non-randomised comparison.

Methods: 2700 pts received LHRHa, 403 bicalutamide. The primary endpoint was biochemical/clinical failure (BCF). Groups were compared with Cox regression adjusted for various prognostic factors and stratified by radiotherapy dose. A key secondary endpoint was erectile dysfunction (ED) assessed by clinicians (LENT-SOM subjective erectile function for vaginal penetration) and patients (single items within UCLA-PCI and EPIC-50 questionnaires) at 2 years and compared between HT regimens by chi square trend test.

Results: Bicalutamide patients were significantly younger (median 67 vs 69 years LHRHa). Median follow-up is 9.3 years. There was no difference in BCF with adjusted hazard ratio 0.97 (95%CI 0.77-1.23; p=0.8). At 2 years, grade≥2 LENT-SOM ED was reported in significantly more LHRHa patients 313/590 (53%) versus 17/68 (25%) bicalutamide

(p<0.0001). There were no differences in ED seen with UCLA-PCI and EPIC-50 questionnaires.

Conclusions: In this non-randomised comparison, there was no evidence of a difference in efficacy according to type of HT received. Bicalutamide preserved clinician assessed (LENT-SOM) erectile function at 2 years but patient reported outcomes were similar between groups.

Keywords

Prostate cancer, radiotherapy, androgen suppression, erectile dysfunction

Introduction

Neoadjuvant or adjuvant hormone therapy (HT) given with radiotherapy improves both biochemical progression-free survival and overall survival for men with localised prostate cancer[1–3]. Most trials have used luteinising hormone-releasing hormone analogues (LHRHa) to achieve this effect. Bicalutamide is an oral non-steroidal anti-androgen which acts as a competitive antagonist at the androgen receptor. Bicalutamide is sometimes preferred to LHRHa due to perceived reduced cardiovascular risk or the patient's wish to preserve sexual function.

In the metastatic disease setting, bicalutamide results in inferior overall and progression-free survival compared to LHRHa although there is a suggestion that side-effects might be reduced[4,5]. However for patients with non-metastatic disease, older studies showed no

difference in overall survival or clinical progression in those receiving anti-androgens versus LHRH or orchidectomy[6,7]. In the salvage radiotherapy setting, bicalutamide has been shown to reduce overall mortality [8].

To the best of our knowledge, there are no large randomised studies which have compared bicalutamide with LHRHa combined with radiotherapy. It is not known whether bicalutamide has equivalent efficacy to LHRHa and whether it preserves sexual function after curative radiotherapy.

The XXXXX trial is a multicentre, randomised, phase 3, non-inferiority trial comparing 2 gray (Gy) per fraction (74 Gy in 37 fractions (f)) with 3 Gy per fraction (either 60 Gy in 20 f or 57 Gy in 19 f) in men with localised prostate cancer. The trial showed non-inferiority of 60 Gy in 20 f compared with 74 Gy in 37 f [9]. The trial protocol permitted bicalutamide monotherapy or LHRHa. In these exploratory analyses we compare the efficacy, clinician-reported and patient-reported outcomes of men receiving bicalutamide with those receiving LHRHa.

Materials and Methods

Trial Design

The XXXXX trial design has been described elsewhere[9]. Briefly, men with histologically proven, T1b-T3a N0M0 prostate cancer with a maximum Gleason score of 7 were eligible. Men were randomised (1:1:1) to receive 74 Gy/37 f over 7.4 weeks or 60 Gy/20 f over 4 weeks or 57 Gy/19 f over 3.8 weeks. Randomisation was stratified by National

Comprehensive Cancer Network (NCCN) risk classification and treatment centre. HT was non-randomised.

The trial was registered (XXXXX), approved by the XXXXX Multicentre Research Ethics Committee (04/MRE02/10), and conducted in accordance with principles of good clinical practice.

Procedures

HT was mandated in men with NCCN intermediate and high-risk disease. HT was given using monthly depot injections of LHRH agonists with initial cyproterone acetate to prevent 'flare' phenomenon or alternatively bicalutamide 150mg daily if preferred by the patient and physician. The duration of HT was at least three months (maximum six months) prior to start of radiotherapy and continued until the end of radiotherapy. The last monthly depot injection was to be given within 1 week of the start or during radiotherapy. Bicalutamide was continued for 2 months after the end of radiotherapy to mimic the duration of action of monthly depot LHRHa injections[10].

PSA concentrations were recorded pre-HT, pre-radiotherapy and then at weeks 10, 18, and 26 after start of radiotherapy and then at 6-monthly intervals for 5 years, thereafter annually. Acute and late toxicity was assessed using clinician-reported outcome (CRO) grading systems and patient-reported outcome (PRO) questionnaires. Sexual function assessments were conducted pre-HT, pre-radiotherapy and then at 6, 12, 18, 24, 36, 48 and 60 months and were graded according to the Late Effects on Normal Tissues: Subjective/Objective/Management (LENT-SOM)[11] and XXXXX (XXX)[12] scoring systems. Men

participating in a PRO substudy received questionnaires at baseline if they had not yet started ADT and all men received questionnaires pre-radiotherapy and at 10 weeks and 6, 12, 18 and 24 months after the start of radiotherapy, thereafter annually until 5 years. Full details of the PRO substudy have been published previously[13]. Initially the University of California Los Angeles Prostate Cancer Index (UCLA-PCI)[14] including Short Form 36 (SF-36) and Functional Assessment of Cancer Therapy-Prostate (FACT-P)[15] were used but following a protocol amendment in 2009 the Expanded Prostate Cancer Index Composite (EPIC)[16,17] and Short Form 12 (SF-12)[18] were used instead. The Radiation Therapy Oncology Group (RTOG) system[19] was used to score late bladder and bowel toxicity.

Outcomes

Efficacy was the primary endpoint, evaluated as biochemical or clinical failure (BCF) and overall survival. The Phoenix consensus definition[20] of a PSA > nadir +2ng/ml was used to define biochemical failure; clinical failure events included recommencement of HT, local recurrence, lymph node or pelvic recurrence and distant metastases. Key secondary endpoints for this analysis were: the proportion of patients with LENT-SOM grade ≥2 erectile dysfunction (ED) for vaginal penetration at 2 years; erectile functioning over time assessed by clinician assessed LENT-SOM and XXX scales (Supplementary Appendix 1); individual patient reported sexual functioning scores (EPIC questionnaire); general quality of life measures including hot flushes, fatigue, breast tenderness, low mood and general health scores; testosterone levels pre-HT and at 12 months; RTOG bladder and bowel toxicity. Disease-free survival and recommencement of hormone therapy are reported as exploratory endpoints.

Statistical considerations

All analyses presented are exploratory in nature, however a statistical analysis plan was written prior to conducting the analyses. As this was a non-randomised comparison of LHRHa with bicalutamide, statistical comparisons were made for the baseline demographic data by HT group (t-tests, Mann-Whitney, chi-square and chi-square trend tests were used as appropriate). Kaplan-Meier methods were used to analyse time-to-event data stratified by treatment regimen. Comparisons of HT groups were made using the log-rank test. An adjusted Cox model included age (continuous), NCCN risk group (low v intermediate v high), Gleason score (≤6 v 7/8), Clinical T-stage (T1 vs T2 vs T3a), pre-hormone PSA (<10 vs 10-20 vs >20 ng/ml) and the proportion of core biopsies which were positive (≤50 v >50%)[21,22,23]. Stratified log-rank tests were used to compare HT groups for baseline variables that were imbalanced. The proportional hazards assumption held for all time-to-event analyses. Hazard ratios (HR) less than 1 favoured bicalutamide. Competing risks analysis was conducted for BCF with death from any cause as the competing event.

Analysis for the sexual functioning secondary endpoints was restricted to patients with preserved sexual function pre-HT. For the XXX scale, data were analysed separately for patients with normal erections (grade 0) and decreased erections (grade 1) pre-HT. Chi-square trend tests were used to compare hormone groups at 2 years. Due to the non-randomised comparisons being made, multivariable logistic models were used for analysis of some secondary endpoints. Binary variables were created for grade≥2 (poor/very poor for PRO endpoints) at 2 years and models were adjusted for age, pre-ADT symptom score and pre-ADT testosterone level.

To account for multiple testing, a significance level of 0.5% was used for the primary endpoints of efficacy and key secondary endpoints (LENT-SOM erectile function for vaginal penetration and UCLA/EPIC question on ability to have an erection). For all other secondary endpoints, a significance level of 0.1% was used. Analyses were based on a data snapshot taken on 09/10/2019 for the efficacy and clinician assessments (median follow-up 9.3 (IQR 8.2-11.0) years) and on 26/08/2016 for the patient reported outcomes data (final data set, follow-up completed at 5 years for PRO). All analyses were undertaken with STATA v15.1.

Results

Baseline demographics

Baseline demographics for patients in the LHRHa (n=2700) and bicalutamide (n=403) groups are shown in Table 1. All but 29 patients had started hormones prior to randomisation. HT was omitted in 3% of men who are excluded from all analyses. Patients receiving bicalutamide were younger with median age 67 years (IQR 63-72) compared to 69 years (IQR 65-73) for LHRHa. Men receiving bicalutamide had a shorter time between diagnosis and randomisation and a lower burden of core involvement (Table 1). Patients treated with LHRHa received HT for a median of 5.3 (IQR 4.5-6.2) months (measured from date of first monthly injection to last injection plus 4 weeks) and bicalutamide patients for a median 6.3 (IQR 5.7-7.1) months.

Efficacy

There was no evidence of a difference in BCF between the two HT groups with an unadjusted HR 0.97 (95%CI 0.77-1.23, p=0.8) (Figure 1A). In the LHRHa group, the 5 year BCF-free rate was 88% (95% CI: 87-89) and 86% (95% CI: 82-89) in the bicalutamide group.

In view of the imbalances in baseline characteristics we performed log-rank tests stratified for age (≤69 v >69) and proportion of positive core biopsies (≤50 v >50%). These indicated no difference between HT groups for BCF. The adjusted HR was 0.98 (95%CI 0.70-1.36; p=0.9) (Supplementary Appendix 2). Competing risks analysis indicated no evidence of a difference between HT groups (Gray's test p=0.9, Supplementary Appendix 3). An exploratory analysis restricted to unfavourable intermediate and high risk patients (as defined by Zumsteg et al [21]) gave similar results (Supplementary Appendix 4). There was no evidence of a difference in overall survival between HT groups with an adjusted HR 0.87 (95%CI 0.60-1.26; p=0.5). (Figure 1B). Time to recommencement of hormone therapy and disease free survival also showed no evidence of a difference between the HT groups (Figure 1C, 1D and Supplementary Appendix 2).

Clinician reported sexual functioning – LENT-SOM & XXX

Prior to starting HT, 607/786 (77%) LHRHa and 73/89 (82%) bicalutamide patients had preserved erectile function (LENT-SOM grade≤2) and were included in subsequent analyses (Supplementary Appendix 5). At 2 years, grade≥2 LENT-SOM ED (intermittently insufficient for vaginal penetration or worse) was reported in significantly more LHRHa patients 313/590 (53%) compared to 17/68 (25%) bicalutamide patients (p<0.0001). At 2 years, grade 3-4 ED (erections not sufficient for penetration or impotent) was reported in 220/585 (38%) LHRHa patients and 14/68 (21%) bicalutamide patients. A similar pattern was seen throughout follow-up with fewer bicalutamide patients assessed as having severe symptoms according to the LENT-SOM sexual dysfunction scale (Figure 2A, 2B, 2C and 2D). A multivariable logistic model including pre-ADT erectile function score, age and pre-ADT

testosterone level also indicated reduced erectile dysfunction in the bicalutamide patients (OR=0.30, 99%CI 0.10-0.90, p=0.005, Supplementary Appendix 6).

Using the XXX scale pre-hormones 378/761 (50%), 44/80 (55%) reported normal erections and 259/761 (34%), 23/80 (29%) reported decreased erections in the LHRHa and bicalutamide groups respectively (Supplementary Appendix 5). Of those with preserved sexual function at baseline, a lower proportion of the patients receiving bicalutamide developed ED defined using the XXX scale, but this did not reach statistical significance. At 2 years, there was no evidence of a difference between HT groups for either patients with normal erections (p=0.1) or decreased erections (p=0.6) pre-hormones (Supplementary Appendix 7).

Patient reported sexual functioning – UCLA/PCI

Prior to starting hormones, 215/553 (39%) and 17/49 (34%) of LHRHa and bicalutamide patients reported very poor or poor ability to have an erection (Supplementary Appendix 5). At 2 years, there was no evidence of a difference between HT groups for ability to have an erection (p>0.9). Multivariable models also indicate no difference between hormone treatments (OR=0.77, 99%CI 0.15-3.85, p=0.676, Supplementary Appendix 8). Patients reported worst erectile function at 10 weeks from the start of radiotherapy (Figure 3A). UCLA/EPIC sexual function scores appeared better in bicalutamide patients prior to starting radiotherapy and at the week 10 and month 6 assessments (no statistical comparisons made). From 12 months onwards the distribution of scores remained similar for each HT group (Supplementary Appendix 9). This pattern was also seen when all patients were

included in the analysis, including those without erectile function documented pre-hormonal therapy (Supplementary Appendix 10)

Patient reported general items

Hot flushes were worse in the LHRHa group up to 6 months but untroublesome thereafter (Figure 4A) with no difference between HT groups at 2 years (p=0.4). Lack of energy was reported similarly between HT groups and there was little improvement in scores over time (Figure 4B) with no evidence of difference at 2 years (p=0.3). Breast tenderness was reported more often in patients receiving bicalutamide across all time points assessed (Figure 4C). At week 10 moderate or worse breast tenderness was seen in 10/39 (26%) patients on bicalutamide and 6/214 (2.8%) on LHRHa. More bicalutamide patients (3/40 (7.5%) remained with moderate or big problems with breast tenderness at 2 years than the LHRHa group 2/299 (0.7%) (p=0.002). General health assessments were similar in the HT groups HT over time (Figure 4D with no difference at 2 years; p=0.5). Reported levels of depression were low and there was no difference between HT groups at 2 years (p=0.6) (Supplementary Appendix 11).

Prior to starting HT there was no difference in the testosterone levels between patients receiving LHRHa or bicalutamide with median values of 12.6 and 11.9 nmol/L respectively (p>0.9) (Figure 5 and Supplementary Appendix 12). By 12 months, the majority of patients had testosterone levels within the normal range (>8 nmol/L) 1170/1553 (75%) of LHRHa and 181/213 (85%) of bicalutamide patients (Supplementary Appendix 12).

Late RTOG bladder toxicity was reported by very few patients, with similar distributions for those receiving LHRHa or bicalutamide (Supplementary Appendix 13). Small numbers of patients had predominantly grade 1 RTOG bowel toxicity which was similar for both HT groups (Supplementary Appendix 13).

Discussion

This non-randomised comparison of short course bicalutamide and LHRHa with prostate radiotherapy showed similar efficacy with a median follow-up over 8 years. Initially sexual function declined less pre-radiotherapy using bicalutamide with some evidence of reduced ED 2 years after treatment. Hot flushes were reduced using bicalutamide. Gynaecomastia and breast discomfort were more common in the bicalutamide group (25.6% at 6 months) but less marked that in other studies which have reported rates of about 70%[24], likely due to the protocol recommendation to use tamoxifen if gynaecomastia developed and the shorter course of bicalutamide[25]. Prophylactic use of Tamoxifen may be more effective. By 12 months testosterone levels had recovered in most patients in both groups but there was no difference in levels of ongoing fatigue. Interventions using structured exercise might be of value[26,27].

HT using LHRHa with radiotherapy is well established for the treatment of localised prostate cancer[2,3,28,29]. Bicalutamide has compared favourably with placebo in locally advanced and recurrent disease[30,8] but no phase 3 comparisons with LHRHa have been performed. Single centre series[31,32], albeit with short follow-up, have reported similar efficacy between

bicalutamide and LHRHa. However concerns about the efficacy of bicalutamide monotherapy have persisted. One randomised trial did not show the expected improvement in biochemical control with bicalutamide compared with radiotherapy alone [33] and, for earlier disease, overall survival with bicalutamide appeared to be worse than watchful waiting in another study [34].

Because bicalutamide is less effective in metastatic disease [4,5], standard practice is to offer LHRHa concomitantly with radiotherapy, and our data does not change that. There is some concern relating to cardiovascular side effects with LHRHa and a suggestion that anti-androgens may have a more favourable profile although this remains controversial [35] and higher cardiac events were noted in the bicalutamide arm of the RTOG 9601 study [36]. For men wishing to minimize the chance of erectile dysfunction, our analysis suggests that bicalutamide is a safe option but any advantages are modest.

Long term ED benefit for bicalutamide was apparent using the LENT-SOM assessment but not with the XXX scoring system nor the PRO. We speculate that this might be because patients selecting bicalutamide had higher expectations of retaining sexual function and were consequently more bothered by ED. With both HT options, ED remains a major concern; a combination of radiotherapy and increasing age appear responsible. It has been suggested that dose to the penile bulb may be important [37]. The use of image-guided radiotherapy facilitates small margins, sparing these structures in most patients [38]. In addition, pre-habilitation or early treatment with PDE5 after radiotherapy may be beneficial.

Limitations of our work are that it is a non-randomised comparison, albeit from a large phase 3 trial. Only 13 % of the patient population had HT with bicalutamide. In consequence there are imbalances in some presenting features; bicalutamide treated patients were younger with some more favourable pathological parameters although adjusted analyses continued to show similar efficacy between groups. Most patients had started HT prior to collection of baseline data and randomisation (Supplementary Appendix 14) limiting the number of patients with both baseline and two year data for comparison. However, when data for all patients was analysed (Appendix 10) similar patterns were seen. Additionally PRO data collection decreased over time limiting the robustness of data interrogation.

Whilst acknowledging the problems inherent with non-randomised data our analysis should reassure oncologists considering prescribing short-course bicalutamide with radiotherapy and assist appropriate discussion with patients. Bicalutamide may be preferred in patients wishing to maintain sexual function, although the evidence presented here shows no guarantee of avoiding ED. Bicalutamide may also be preferred in patients who experience significant hot flushes, especially if this limits compliance with LHRHa, although this may be achieved at the cost of some breast symptoms, unless prophylactic tamoxifen is given.

Conclusion

In a non-randomised analysis within the XXXXX trial, patients receiving HT with bicalutamide had similar 5 year biochemical or clinical failure compared to those receiving LHRHa. There was some evidence that bicalutamide reduced ED, although this was not seen on all outcome scales. Bicalutamide also reduced hot flushes but global quality of life was

unaffected. With appropriate patient counselling about risks and benefits, Bicalutamide can be considered as an option for men wishing to preserve sexual function or for those who have severe hot flushes.

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Table and Figure titles

Table 1 Baseline demographics by hormone therapy received

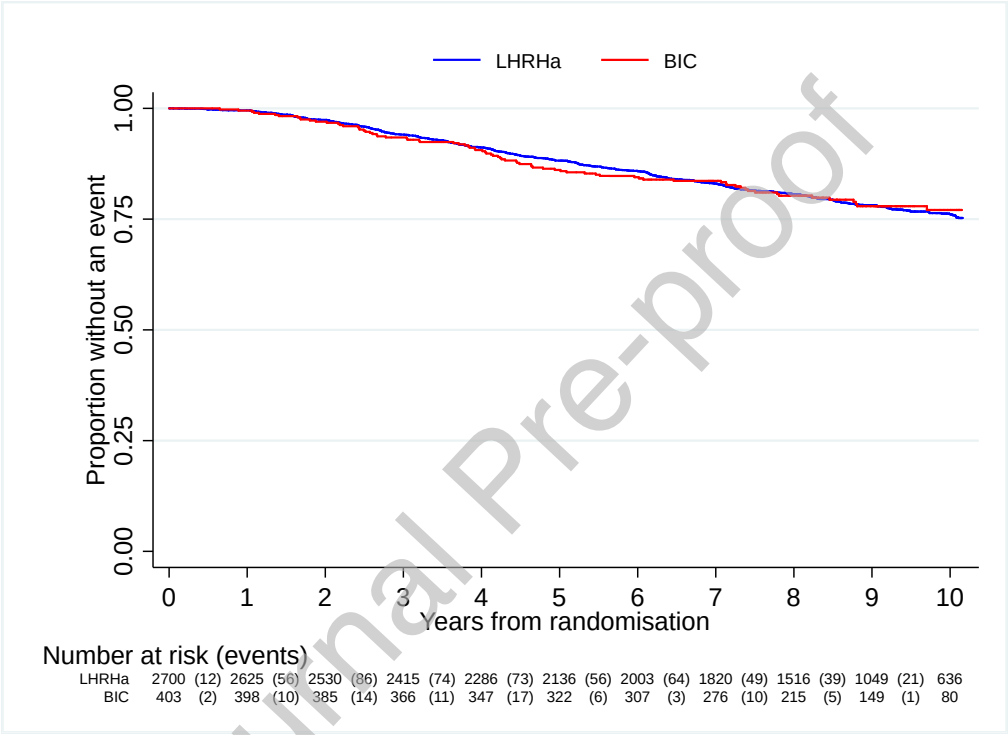
	LHRHa (N=2700)		Bicalutamide (N=403)		P-value
	No.	%	No.	%	
Treatment group					
74Gy/37f	881	33	144	36	0.4[a]
60Gy/20f	910	34	133	33	
57Gy/19f	909	33	126	31	
NCCN risk group					
High Risk	332	12	50	12	0.4[b]
Intermediate Risk	2006	74	308	76	
Low Risk	362	13	45	11	
Age (years)					
Median (IQR)	69 (65-73)		67 (63-72)		<0.001[c]
Range	44-85		50-83		
Age category					
≤69 years	1445 (54)		256 (64)		
≥70 years	1225 (47)		147 (36)		<0.001[a]
Gleason score					0.040[b]
≤6	918	34	114	28	
3+4	1179	44	189	47	
4+3	515	19	89	22	
8	87	3	11	3	
Clinical T stage					
T1	945	35	158	39	0.4[d]
T2	1520	56	203	50	
T3	232	9	42	11	
TX	1	<1	0	0	
MRI T stage					
T1	158	8	51	16	0.044[d]
T2	1235	66	184	59	
T3	445	24	75	24	
TX	44	2	4	1	
Months from histological confirmation of PCa to randomisation					<0.001[c]
N	2697		403		
Median (IQR)	5 (3-6)		4 (3-5)		
Range	0-177		1-102		

Pre-hormone PSA (ng/ml)			
N	2676	401	0.8c[e]
Median (IQR)	10.3 (7.2, 14.6)	10.0 (7.2, 14.6)	
Range	0.2, 33.6	1.3, 28.8	
Number of core biopsies taken[f]			
N	2006	261	
Median (IQR)	11 (10-12)	11 (8-13)	
Range	2-20	3-20	0.3[c]
Number of positive core biopsies[e]			
N	1892	247	
Median (IQR)	4 (3-7)	4 (2-6)	<0.001[c]
Range	0-16	0-12	
Proportion of positive core biopsies[e]			
N	1862	234	
<50%	973 (52)	150 (64)	
≥50%	889 (48)	84 (36)	0.001[a]
Maximum length of core involvement (%)			
N	1426	259	
Median (IQR)	40 (16-70)	30 (10-60)	
Range	1-100	1-100	0.001[c]
Maximum length of core involvement[f] (mm)			
N	383	79	
Median (IQR)	10 (5-16)	6 (3-9)	<0.001[c]
Range	0.4-20)	0.7-20	

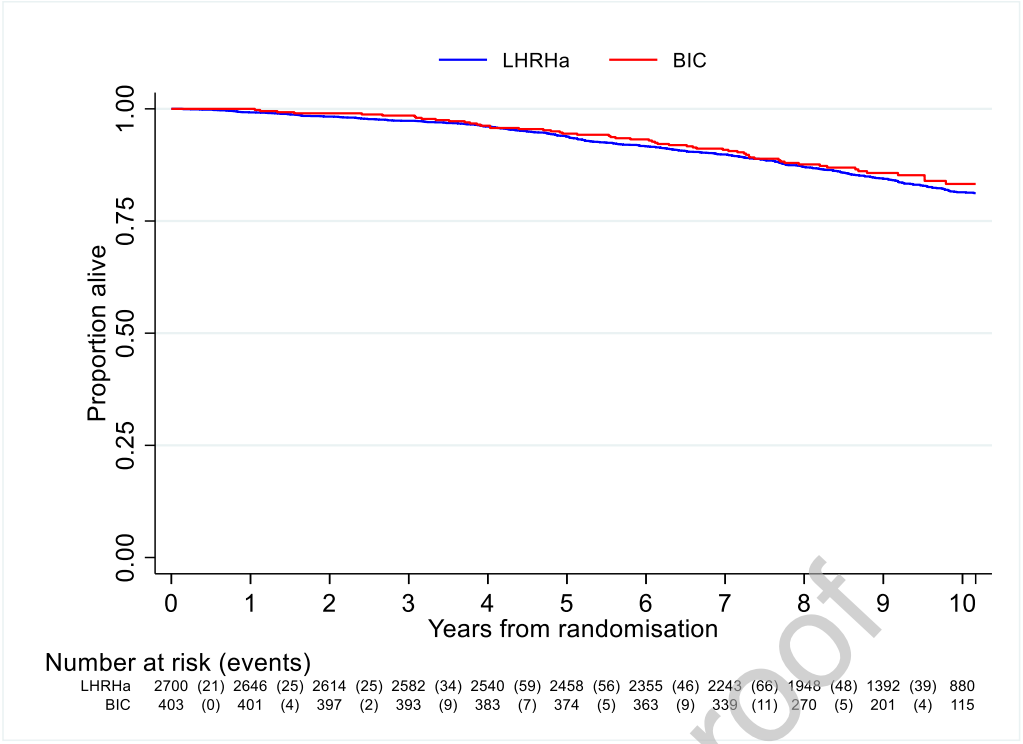
[a] chi-square;
[b]test for trend;
[c]Mann-Whitney;
[d]test for trend excluding TX;
[e]Number of core biopsies taken/positive was capped at 20 as part of central data cleaning with values >20 discarded as errors/implausible in an era when template biopsies were not used
[f]maximum length of core involvement capped at 20mm as part of central data cleaning with values >20 discarded as errors/implausible given cutting length of biopsy needle.

Figure 1. Kaplan Meier curves for (A) biochemical and/orclinical failure, (B) overall survival, (C) recommencing hormone treatment, (D) disease free survival by hormone therapy received

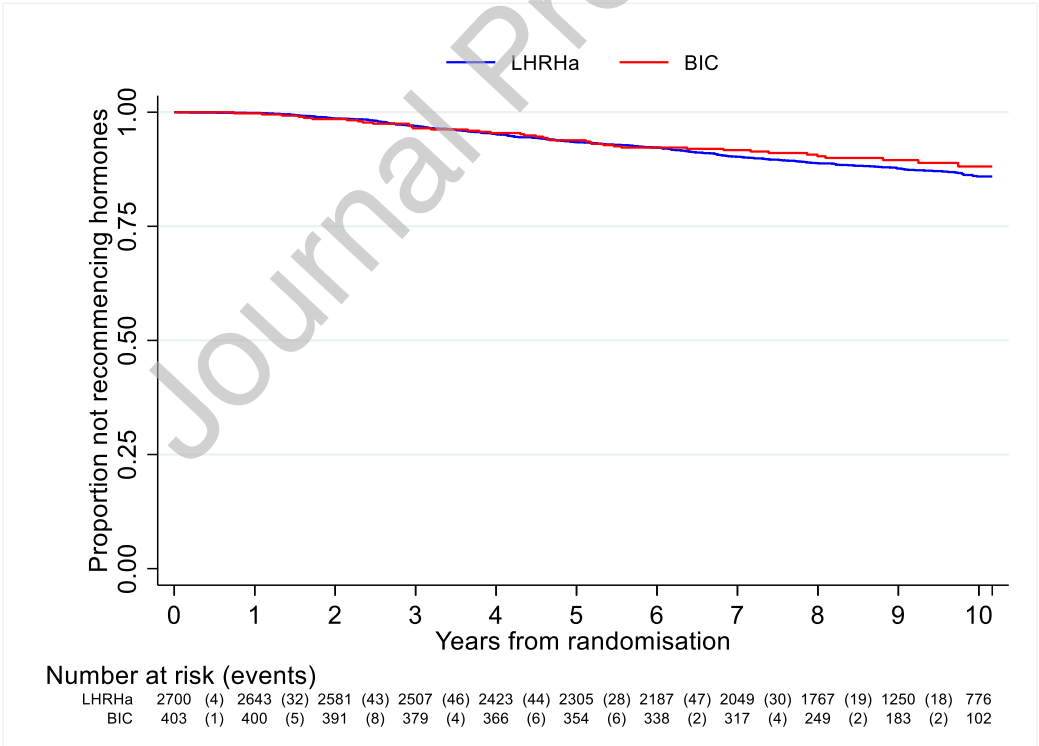
(A) Biochemical and/or clinical failure



(B) Overall survival



(C) Recommencing hormone treatment



(D) Disease free survival

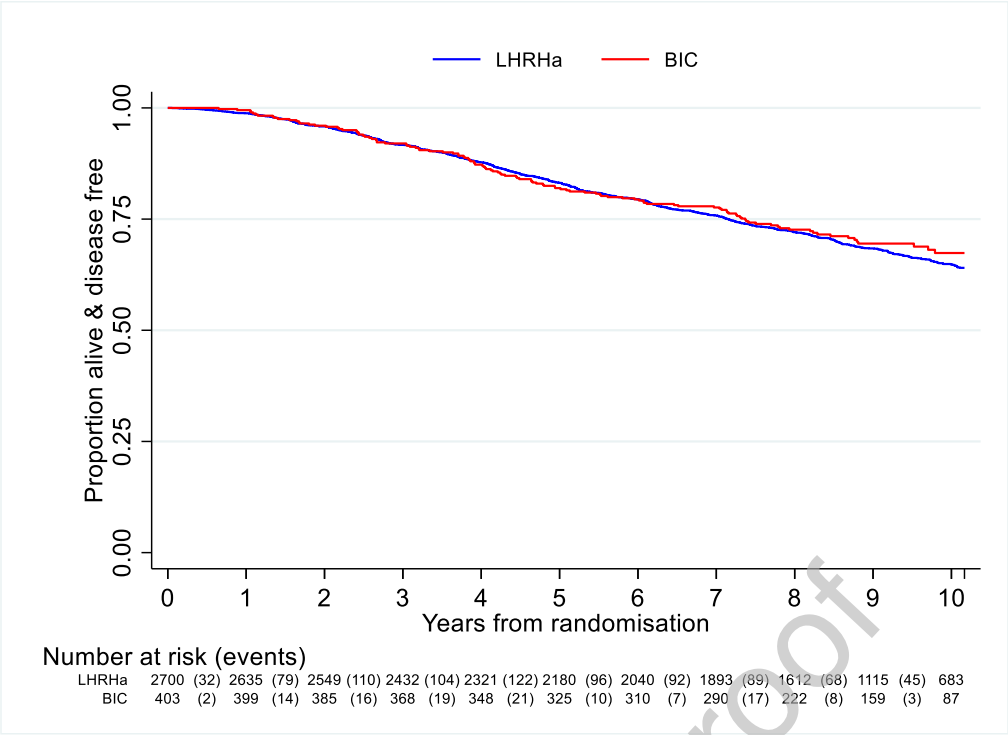
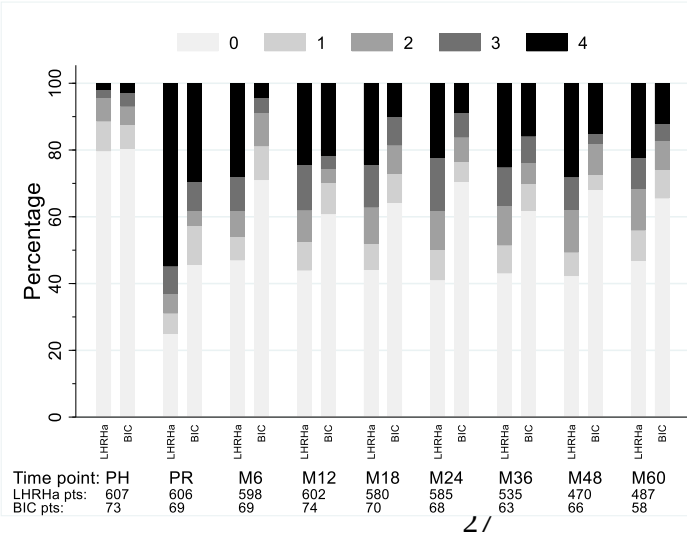
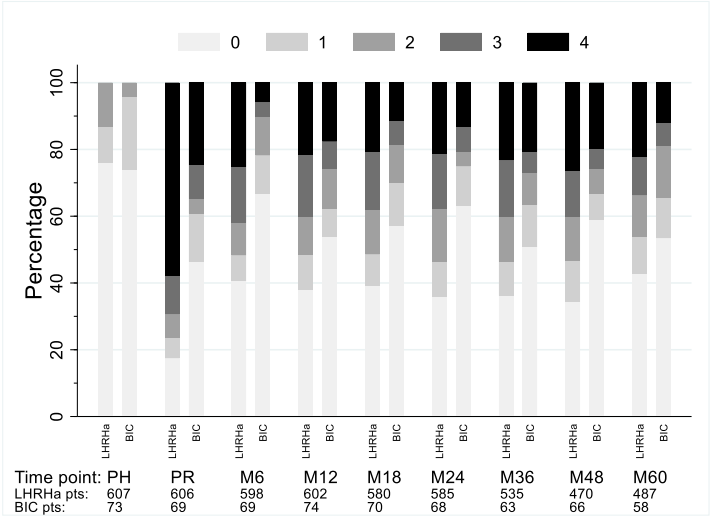


Figure 1. Kaplan Meier curves for (A) biochemical and/or clinical failure, (B) overall survival, (C) recommencing hormone treatment, (D) disease free survival by hormone therapy received

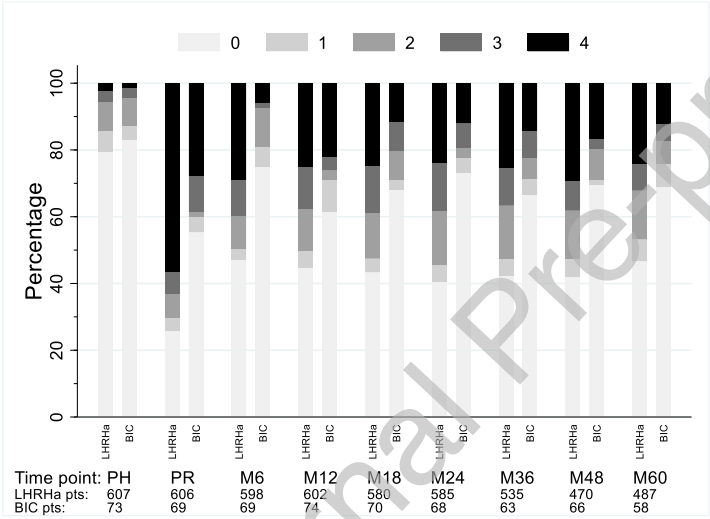
Figure 2 LENTSOM sexual dysfunction items – distribution of grade at each time point assessed by hormone therapy received (A) Subjective: Erectile function for vaginal penetration, (B) Subjective worse grade (C) Objective worse grade (D) Management worse grade. PH=pre-hormone treatment, PR = pre-radiotherapy

(A) Subjective: Erectile function for vaginal penetration (B) Subjective worse grade





(C) Objective worse grade



(D) Management grade

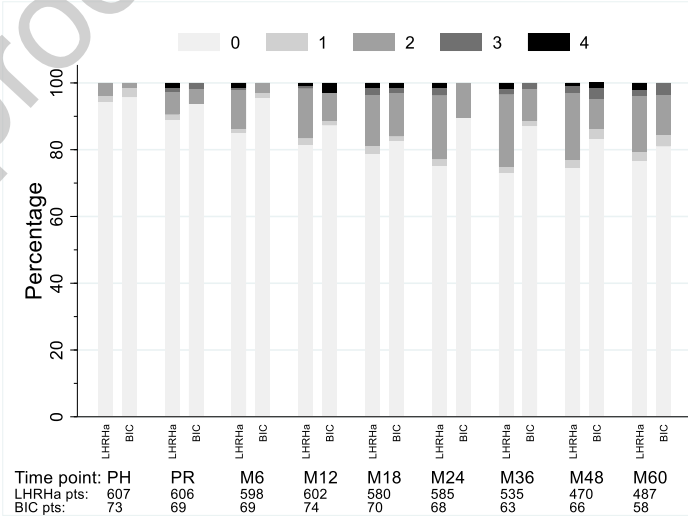


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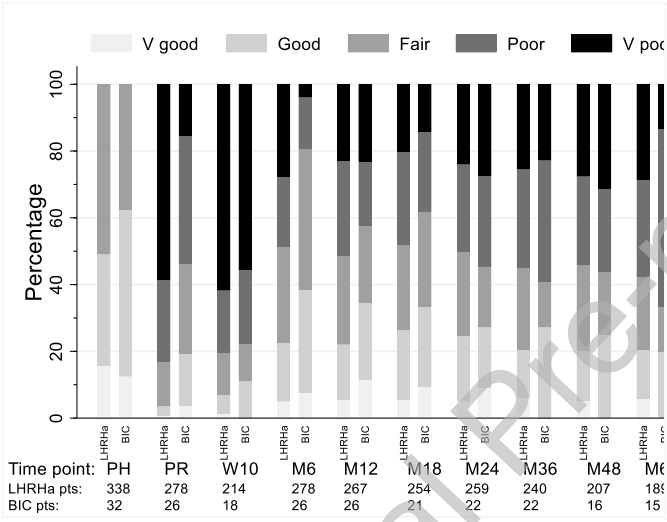
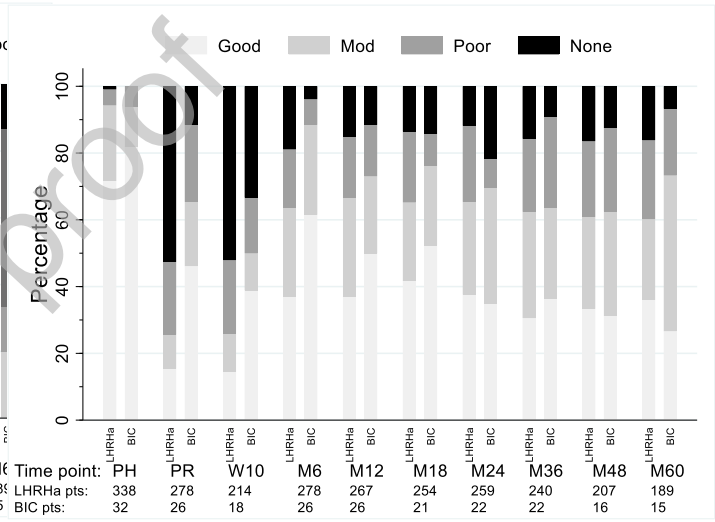
Figure 3 Patient reported outcomes of sexual function assessed using UCLA/EPIC questionnaires – distribution of grade at each time point assessed by hormone therapy received (A) Rate your ability to have an erection, (B) Usual quality of erections (C) Rate your ability to function sexually (D) How big a problem has sexual function been (sexual bother). PH=pre-hormones, PR=pre-radiotherapy.

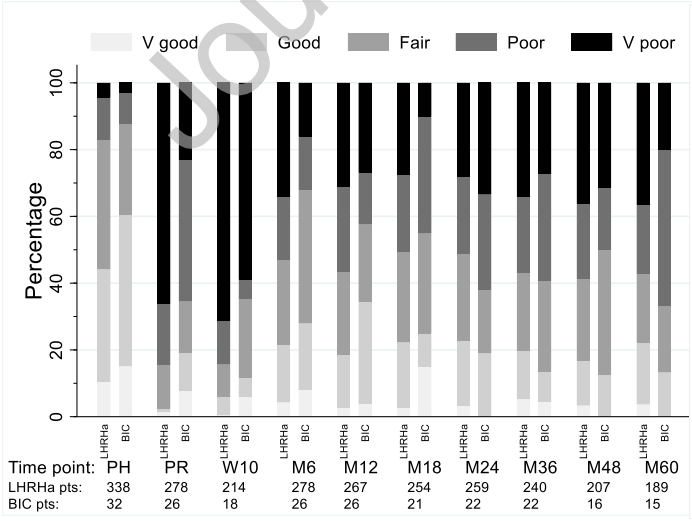
(A) Rate your ability to have an erection



(B) Usual quality of erections



(C) Rate your ability to function sexually



(D) Sexual bother

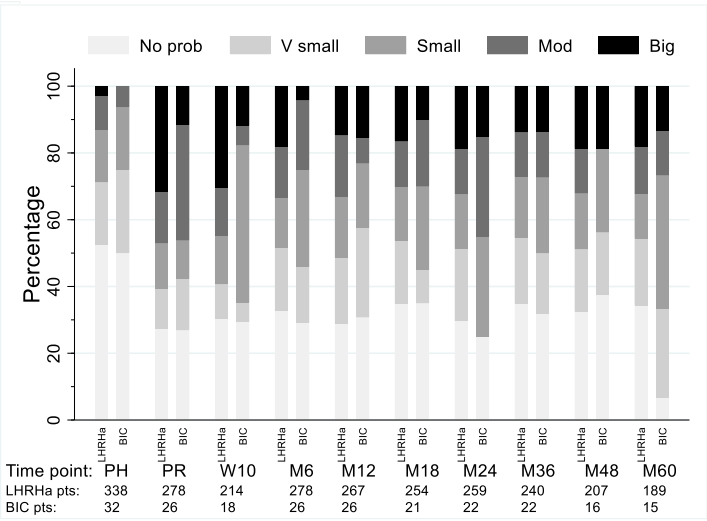


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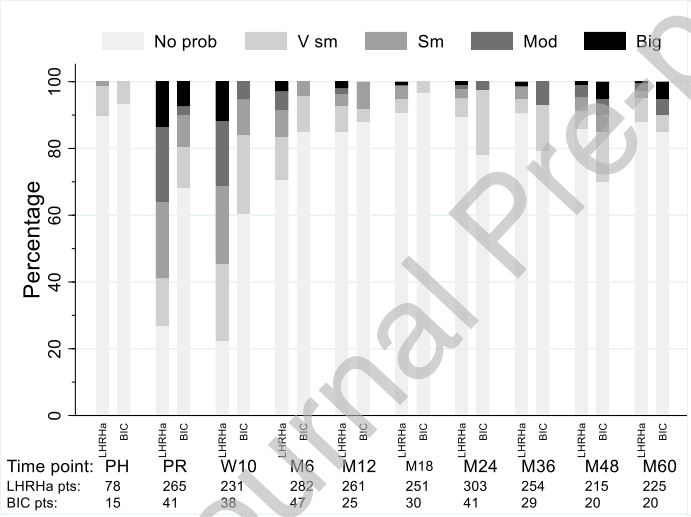
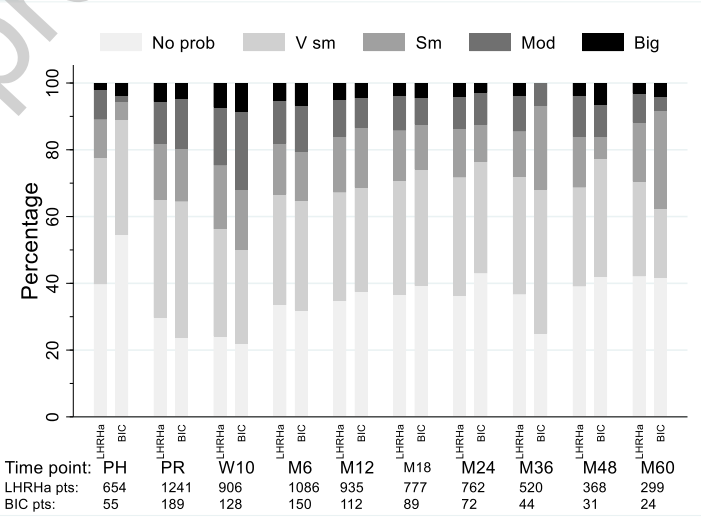
Figure 4 Patient reported outcomes of general quality of life items – distribution of scores at each time point assessed by hormone therapy received (A) Hot flushes, (B) Lack of energy (C) Breast tenderness (D) General health score. PH=pre-hormones, PR=pre-radiotherapy.

(A) Hot flushes



(B) Lack of energy a problem



(C) Breast tenderness a problem

(D) General health

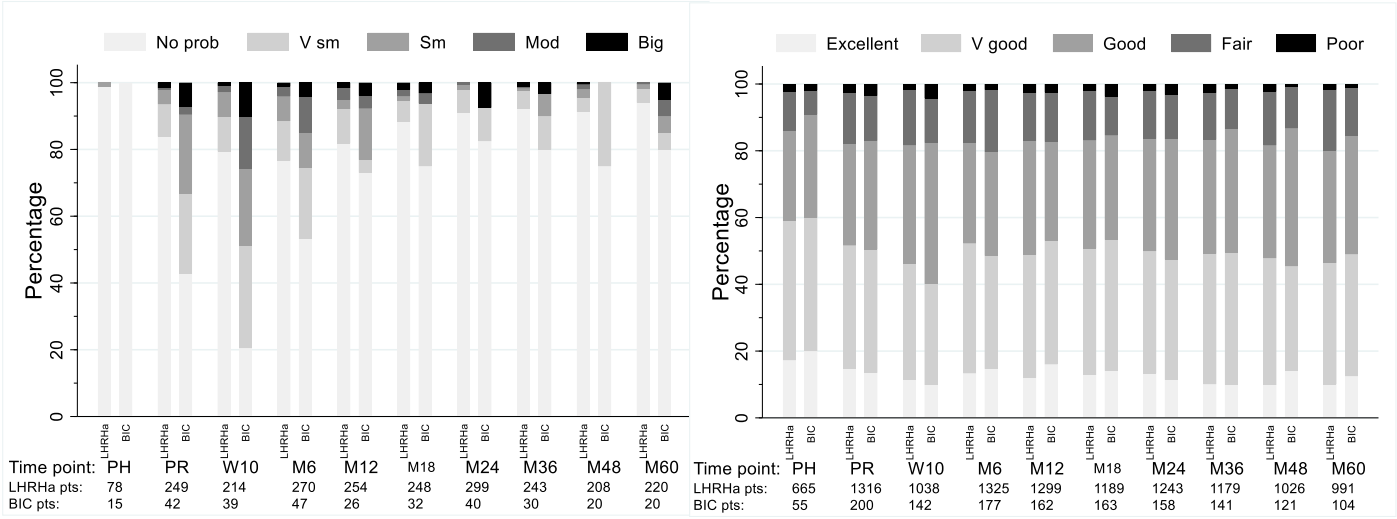


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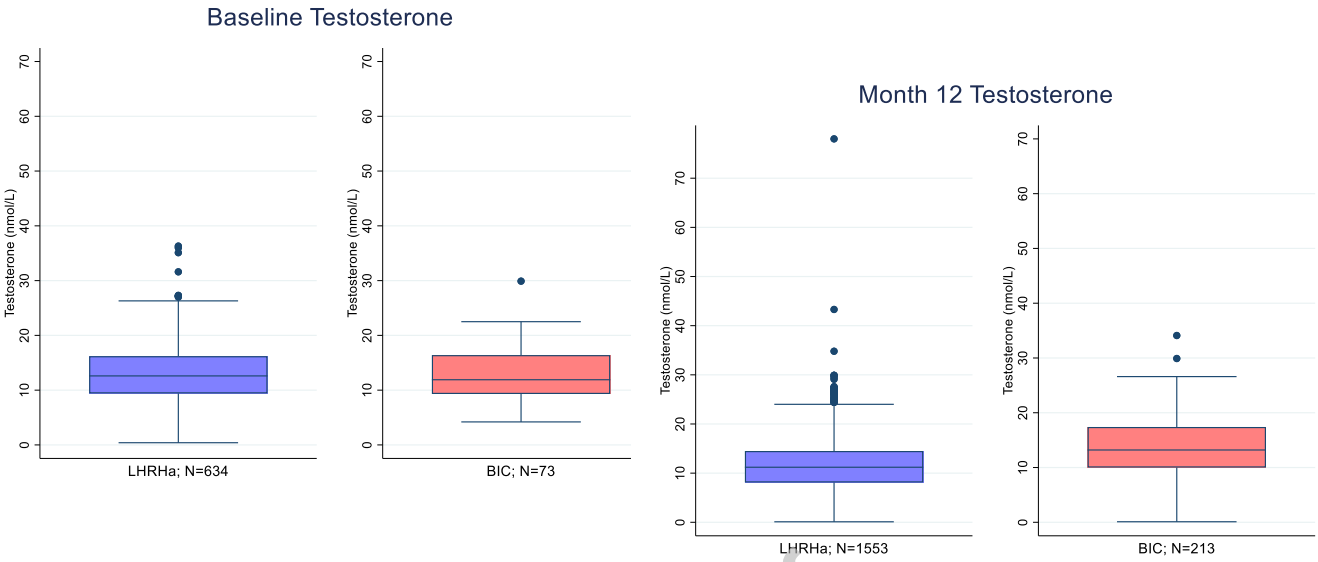
Figure 5 Boxplots illustrating testosterone levels at baseline and 12 months



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