Title page

Manuscript title:

Medium-term oncologic outcomes for extended versus saturation biopsy and transrectal versus transperineal biopsy in active surveillance for prostate cancer.

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Abstract:

Purpose:

- In AS for low risk PCa, we assessed whether saturation or transperineal biopsy altered medium-term oncologic outcomes compared with standard transrectal biopsy.

Materials and methods:

- Retrospective analysis of prospectively collected data from two cohorts with localised PCa (1998-2012) undergoing AS.
- PCa-specific, metastasis-free and treatment-free survival, unfavourable disease and significant cancer at RP were compared for standard (6-12 core, median 10) versus saturation (>12 core, median 16), and transrectal versus transperineal biopsy, using multivariate analysis.

Results:

- 650 men analysed; Median (mean) follow-up of 55 (67) months.
- PCa-specific, metastasis-free and BCR-free survival were 100%, 100% and 99% respectively. Radical treatment-free survival at 5 and 10 years were 57% and 45% respectively (median time to treatment 7.5 years).
- On KM analysis, saturation biopsy was associated with increased objective biopsy progression requiring treatment (Log Rank x^2=5.87, p=0.01). On multivariate PH analysis, saturation biopsy (HR=1.68, p<0.01) but not transperineal approach (p=0.89) was associated with increased objective biopsy progression requiring treatment.
- On logistic regression analysis of 179 men who underwent RP for objective progression,

transperineal biopsy was associated with lower likelihood of unfavourable RP pathology (OR=0.42, p=0.03) but saturation biopsy did not alter the likelihood (p=0.25).

- Neither transperineal or saturation biopsy altered the likelihood of significant versus insignificant cancer at RP (p=0.19 and p=0.41 respectively).

Conclusions:

- Active surveillance achieved satisfactory oncologic outcomes.
- Saturation biopsy increased progression to treatment on AS; longer follow-up is needed to determine if this represents beneficial earlier detection of significant disease or over-treatment.
- Transperineal biopsy reduced the likelihood of unfavourable disease at RP, possibly due to earlier detection of anterior tumours.

Main manuscript

Introduction

Prostate cancer is the most common non-cutaneous cancer in men and second leading cause of cancer death 1, constituting a global public health challenge 2. PSA screening and extended biopsy templates have reduced PCa mortality by 40% 3 at the cost of 42-57% over-detection rates of insignificant PCa 4. To improve PSA screening, reducing over-treatment through increased AS is needed.

Early AS eligibility criteria based on pre-PSA era studies and sextant biopsy templates proposed 0.5-0.7cc as the volume threshold for significance 5, 6, but contemporary data supports a higher threshold of 1.3cc for pT2 Gleason 6 tumours 7. A study analysing 15,000 RPs found no nodal

metastases in Gleason 6 PCa, suggesting negligible metastatic risk without prior progression to higher-grade disease 8. Medium-term outcomes from cohorts using broader eligibility criteria 9-11 are similar to those of cohorts using strict criteria 12. Therefore current eligibility criteria may be overly restrictive.

On the other hand, current AS eligibility criteria have been criticised for high rates of Gleason upgrading and unfavourable disease at RP 13-15. Furthermore, it is unclear how to apply eligibility criteria based on 6-12 cores to men undergoing saturation biopsy , which may improve grade and volume estimation but increase over-detection, although there is little evidence that baseline saturation biopsy improves AS selection or survival 16, 17. Transperineal biopsy has been advocated based on studies suggesting improved detection of 'evasive' anterior cancers 18 but evidence for superiority over transrectal biopsy in AS is limited 19.

The objective of our study was to determine, in men undergoing AS for low risk PCa, whether saturation or transperineal biopsy altered oncologic outcomes, compared to standard transrectal biopsy.

Methods

A retrospective analysis of prospectively collected data from observational surveillance cohorts at two institutions was performed. All men diagnosed with localised PCa in the last 15 years (1998-2012) who were initially managed with AS and with life expectancy >10 years were included. Standard eligibility criteria were used to select men with low risk features suitable for AS (Text Box 1). Men with no high risk features were recommended AS over radical therapy; men with one or two high risk features had AS discussed as a management option, but were counselled regarding higher risks of AS failure, as practised at other leading institutions 9, 10 11.

Biopsy protocol

During the study period, one urologist (PS) performed transperineal biopsies under general anaesthesia as day surgery, using a floor-mounted brachytherapy grid-template, performing 10-12 cores prior to 2003 then a saturation protocol (14-30 cores depending on prostate volume); the other (MF) performed biopsies via the transrectal route, usually 10-12 cores until 2005, then 14-30 cores; both standard and saturation transrectal biopsies were performed under intravenous sedation in operating theatres as day surgery.

Active surveillance management protocol

Both urologists adhered to the AS management protocol outlined in Text Box 1.

The two surgeons both recommended treatment using the standard criteria above, weighting biopsy criteria over PSA and DRE criteria alone. PSA and DRE were rarely used alone to justify treatment in the absence of biopsy-proven progression (see results Tables 2a-b). Tables 1-2 demonstrate that groups had similar characteristics at baseline and at time of progression to RP, suggesting consistency in application of AS selection and treatment criteria across the two surgeons. Minor measured differences at baseline and time of treatment were adjusted for in multivariate analysis. BCR was defined as PSA ≥0.2ng/mL and increasing following RP, and PSA nadir +0.4ng/mL following radiotherapy.

Outcome measures and statistical methods

The primary endpoint was radical treatment-free survival. Secondary endpoints included PCa-specific, metastasis-free, BCR-free survival, unfavourable disease (pG8-10, pT3, PSM or pN1) and significant PCa (pG6 >1.3cc, pG7 >0.7cc or G8-10) at RP. Baseline and outcome variables were analysed by biopsy approach (transrectal vs transperineal) and number of cores collected at

diagnosis (6-12 vs >12), then differences compared using Wilcoxon, chi-squared and Fisher's exact tests. Kaplan-Meier analysis was performed (stratified by biopsy approach, number of cores collected and AS eligibility) using the Log-Rank test for differences between groups. Multivariate PH analysis modelled treatment-free survival against biopsy approach (transrectal vs transperineal) and number of cores collected. Explanatory covariates included NCCN risk category, PSA, age, family history of PCa, clinical T-stage, prostate volume, PSA density, year of diagnosis, percentage of cores positive, maximum cancer length, biopsy Gleason sum, mean number of cores per biopsy and Charlson score. In secondary endpoint analysis, we performed multivariate logistic regression to assess predictors of unfavourable disease and significant cancer at RP. Analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC).

Results

796 men underwent initial observation for localised PCa. 759 had adequate data for inclusion in the analysis, of whom 650 were managed with AS (see Supplementary Table 1). Mean and median follow-up were 67 and 55 months respectively (range 6 to 252 months). Baseline characteristics stratified by number of cores collected and biopsy approach at diagnosis are summarised in Tables 1a-b, and outcomes are summarised in Tables 2a-b. Baseline characteristics were generally similar between groups, however some variables differed significantly according to number of cores collected (PSA, PSA density, biopsy approach, percentage of cores positive, follow-up duration and cores per AS biopsy; see Table 1a) and biopsy approach (cT-stage, number of cores collected, percentage of cores positive, max cancer per core, follow-up duration and cores per AS biopsy; see Table 1b); multivariate analysis adjusted for these differences.

38% of men progressed from AS to radical treatment, 88% for objective disease progression. Median time to radical treatment was 90 months (95%CI 63-146 months). At 1, 3, 5, 7, 10 and 15

years, treatment-free survival rates were 92%, 68%, 57%, 50%, 45% and 42% respectively. PCa-specific, metastasis-free and BCR-free survival rates at median follow-up were 100%, 100% and 99% respectively. Of 245 men who underwent radical treatment, 2.9% experienced asymptomatic BCR and 2.0% received salvage ADT/ XRT. The overall BCR rate in the cohort (n=650) was 1.1%. BCR rates for transperineal vs transrectal biopsy were 0% vs 1.5% (not significant, Log Rank x^2=2.37, p=0.12). Findings were similar for saturation vs standard biopsy, with BCR rates of 0.2% vs 2.9% (Log Rank x^2 = 1.74, p=0.19). Despite a trend towards lower BCR rates for saturation and transperineal biopsy, differences were not significant (p>0.05).

Radical-treatment free survival

The KM treatment-free survival curve is shown in Figure 1a. The curves were similar when stratified by NCCN eligibility (Figure 1b, LR x^2=1.76, p=0.18) and biopsy approach (Figure 1c, LR x^2=1.48, p=0.22), but a higher treatment-free survival for standard versus saturation biopsy was observed (Figure 1d, LR x^2=5.87, p=0.01).

Results of multivariate PH analysis are summarized in Supplementary Table 2. Higher number of cores collected at diagnostic biopsy was associated with radical treatment on multivariate analysis (HR=1.05 for each core >6, 95%CI 1.02-1.07, p<0.01; HR=1.68 for >12 cores vs 6-12 cores, 95%CI 1.22-2.30, p<0.01), as were family history of PCa (HR=1.89, 95%CI 1.33-2.71, p<0.01) and higher PSA density (HR=1.01 per 0.01 increase, 95%CI 1.00-1.03, p=0.040). Biopsy approach was not associated with radical treatment (p=0.22 and p=0.89 on univariate and multivariate analyses).

Predictors of unfavourable pathology and significant cancer at RP

Logistic regression modelled predictors of unfavourable histopathologic findings and significant cancer in 179 men who underwent RP for objective disease progression (Supplementary Table 3).

Transperineal biopsy approach was associated with a lower risk of unfavourable pathology than transrectal approach on univariate analysis (OR=0.42, 95%CI 0.19-0.93, p=0.03); on multivariate analysis adjusting for number of cores collected, the risk of unfavourable pathology with transperineal biopsy remained significantly lower (OR=0.29, 95%CI 0.09-0.94, p = 0.04); the OR was unchanged when restricting the analysis to saturation transperineal vs saturation transrectal biopsy, although significance became borderline due to reduced sample size (OR=0.20, 95%CI 0.04-1.02, p=0.05).

Biopsy approach and abnormal DRE were predictors of significant cancer at RP on univariate analysis; number of cores collected, age and PSA density were borderline (p>0.05, Supplementary Table 3). Higher PSA density (OR = 1.05 per 0.01 increase, 95%CI 1.01-1.10, p=0.04) and abnormal DRE (OR = 4.34, 95%CI 1.82-10.38, p<0.01) were predictors of significant cancer on multivariate analysis; biopsy approach (p=0.41) and number of cores collected (p=0.19) were not.

Discussion

In this cohort of men enrolled on AS for low risk PCa, surveillance was a safe management strategy: half of men remained free from radical treatment at 7.5 years, with no PCa-related deaths or metastases, low BCR rates (1.1%) and comparable rates of unfavourable features at RP to primary RP studies (34% in this series, including a 19% PSM rate). This is the first report of medium-term outcomes comparing saturation versus standard and transperineal versus transrectal biopsy, and the first report of medium-term AS outcomes from Australasia, complementing reports from North American 20 21 and European cohorts 22 9.

This study did not have restrictive criteria for determining eligibility for inclusion in the analysis; all men enrolled on AS were included, regardless of AS 'eligibility'. Only 6% of men were 'very low risk' by NCCN criteria, with 64% classified as 'low risk' and 30% as 'intermediate risk'. Despite being a higher-risk cohort, outcomes were similar to cohorts with strict eligibility criteria 21 20, and 'NCCN eligibility' for AS was not associated with progression to treatment, significant cancer or unfavourable disease at RP on multivariate analysis. These results complement satisfactory medium-term oncologic outcomes in other cohorts using broader eligibility criteria 9 23 10.

This study analyzed the impact of biopsy approach and number of cores collected on outcomes. Increasing the number of cores collected at diagnostic biopsy was associated with a *higher* risk of radical treatment (HR=1.05 for each additional core above 6,), as was saturation biopsy (HR=1.68) compared to standard biopsy. Given that higher number of cores collected at diagnostic biopsy was associated with a higher number of cores being collected at subsequent surveillance biopsies, increased sensitivity for 'significant' cancer with saturation biopsy is a likely explanation for the increased treatment rates. This hypothesis is supported by the analysis of men who underwent RP,

which demonstrated similar pre-RP biopsy characteristics, proportions with significant cancer using RP criteria and proportions with unfavourable disease at RP for standard and saturation biopsy groups. Therefore men whounderwent RP in both groups had similar disease at diagnosis and at RP, but those undergoing saturation biopsy were upgraded to significant cancerin a higher proportion during AS. It remains unknown whether the increased reclassification/ upgrading rates in the saturation biopsy group were beneficial – due to earlier detection of significant cancers – or detrimental – due to increasing over-detection and thus over-treatment of insignificant cancers. Given that the rate of significant cancer at RP was similar between groups, and BCR rates were lower (although non-significant) in the saturation group, the increased progression rates appear beneficial howeverfollow-up of 10-15 years is required to determine whether this will translate to lower long-term metastasis and mortality rates.

Following randomized trials in which the benefits of PSA screening and RP were offset by over-treatment, AS has gained support as a strategy to reduce over-treatment 24, 25. Given that in this study, 50% of men progressed to treatment by 7.5 years and only 61% had significant cancer at RP, over-treatment remains an issue even in AS cohorts, perhaps due to current treatment criteria being too strict, especially when applied to saturation biopsy. Given extremely low rates of BCR, metastasis and PCa-related death with current AS protocols reported consistently across AS cohorts 26, perhaps the thresholds to trigger treatment on AS should be increased when saturation biopsy is used.. Long-term studies reporting metastasis and mortality outcomes are needed, however, before criteria can be relaxed.

Simply relaxing criteria for eligibility and treatment is unlikely to improve oncologic outcomes because under-treatment rates in AS cohorts are also high. In this study 39% had insignificant cancer at RP, however another 34% were found to have unfavourable disease – thus potentially

having missed their 'window of curability'. These findings are similar to recent studies reporting unfavourable disease at RP in 22-34% of men in AS cohorts with medium-term follow-up 13 9. Over- and under-treatment thus cannot be overcome simply by refining criteria based on PSA, DRE and biopsy, because these tests sub-optimally discriminate between biologically aggressive and indolent tumours. In our study, higher PSA density and abnormal DRE predicted significant cancer at RP, but with limited accuracy, just as increased number of positive cores 22 and increased percentage of cancer in positive cores 13 have been reported previously to provide weak incremental improvements in predictive accuracy. The finding that PSA density improved prediction of both AS outcomes and significant PCa at RP is significant, supporting its role in AS protocols such as PRIAS, however the incremental benefit was small (HR 1.01 per 0.01 increase) and statistical significance was marginal (p=0.05). Novel diagnostic tools are needed to improve the prediction of significant cancer; promising tools include multi-parametric magnetic resonance imaging 27 28, serum/ urinary biomarkers 29 and genetic/ tissue markers 30, however prospective studies are needed to determine their utility.

One other finding from this study isimportant. Transperineal biopsy independently predicted unfavourable disease at RP, demonstrating a lower risk than transrectal biopsy on univariate (HR = 0.42) and multivariate analysis (OR = 0.29). The most likely explanation is that transperineal biopsy identified men with significant anterior tumours at an earlier stage than transrectal biopsy, as recognized previously as the *prostatic evasive anterior tumour syndrome (PEATS)* 31, 18. This finding complements a cohort study of 101 men diagnosed on standard transrectal biopsy who then underwent transperineal saturation surveillance biopsy, of which 34% had significant cancers detected, 44% being predominately anterior 19.

Our study is subject to limitations. Firstly, this is a community cohort study without strict,

prospective inclusion criteria, thus creating heterogeneity in disease characteristics at baseline that may confound outcomes. There was limited heterogeneity between groups at baseline, and multivariate analysis adjusted for differences; nevertheless, the potential for unmeasured and residual confounding remains. Secondly, this was a retrospectively conducted analysis of prospectively collected data , with potential for selection and measurement biases. However, the endpoints and statistical methods were prospectively defined prior to extracting the dataset. Thirdly, the majority of men had only medium-term follow-up data; longer follow-up is needed to assess the risk of metastasis and PCa-specific mortality. Fourthly, the study spans a time period of 15 years; interpretation of Gleason grade has changedover that time, which may confound results. Year of diagnosis was not a predictor of outcomes on multivariate analysis, however, suggesting that changes in Gleason grading over time did not confound outcomes. Finally, data on biopsy complication rates was not collected; possible increased complication rates must be weighed against the benefits of saturation/ transperineal biopsy.

Conclusions

AS was associated with excellent medium-term oncologic outcomes in this cohort, despite broad inclusion criteria. Saturation biopsy reduced treatment-free survival, with similar rates of significant cancer and unfavourable disease at RP; longer follow-up is needed to determine whether the higher treatment rates will translate to lower mortality/ metastasis rates. T ransperineal biopsy was associated with a lower risk of unfavourable disease in RP following AS.

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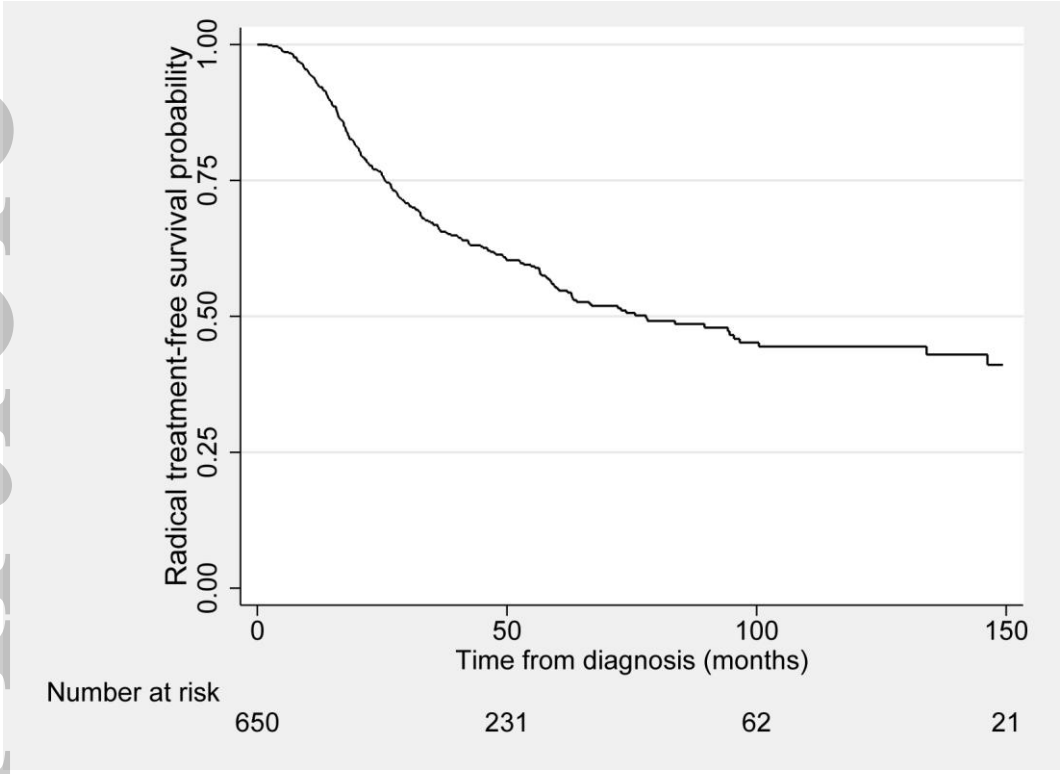

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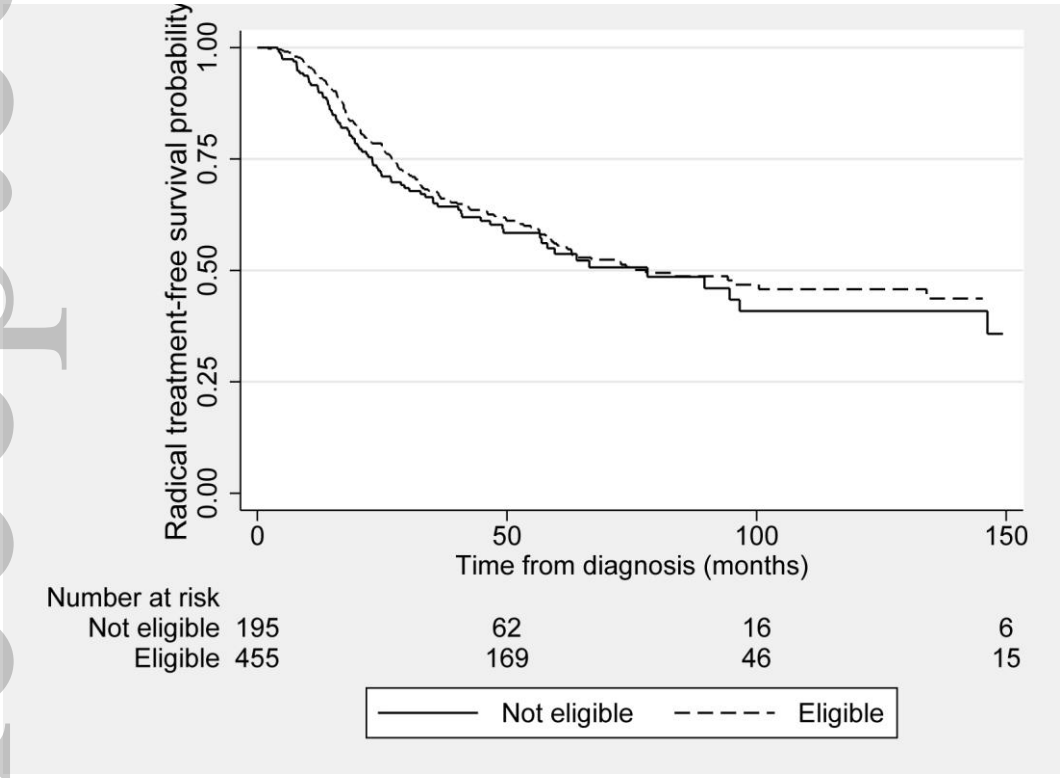

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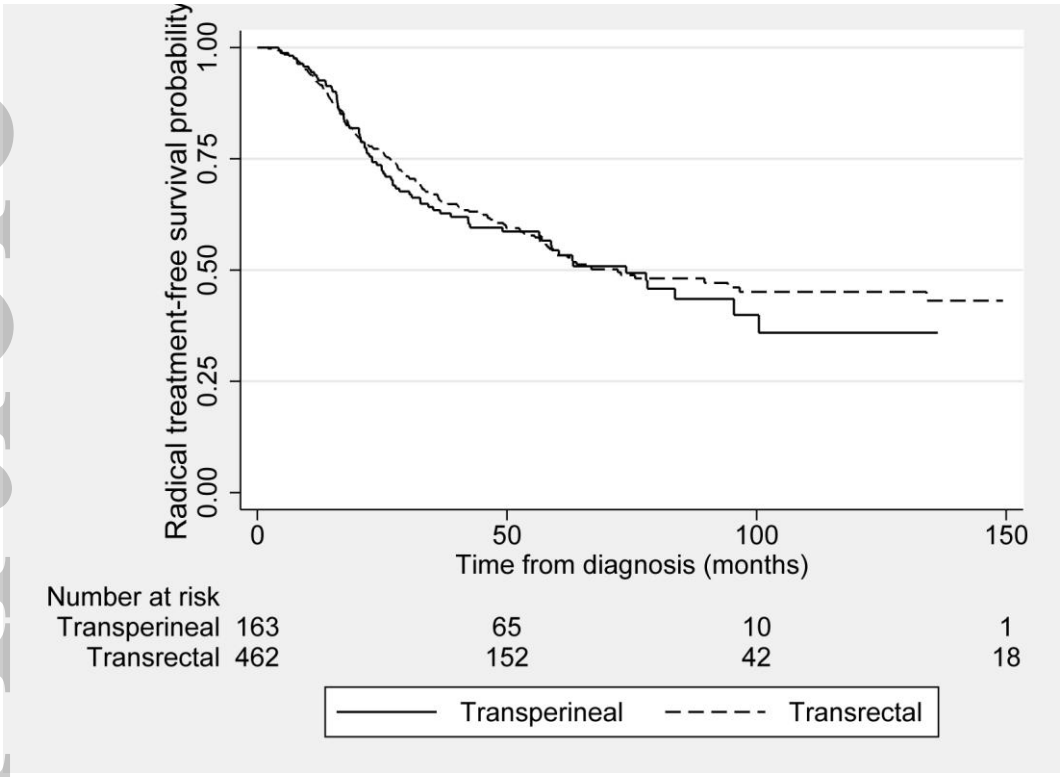

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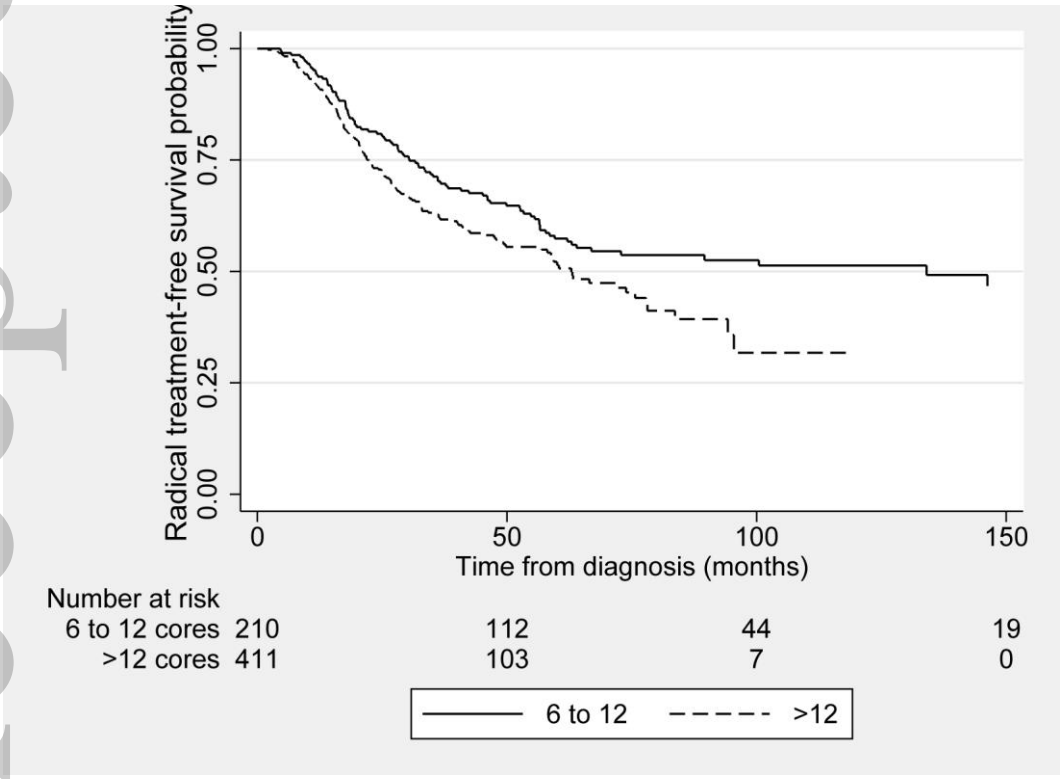

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Selection criteria:

- PSA <10
- Clinical T-stage <T2b on DRE
- Gleason 3+3
- < 20% of cores with cancer and < 30%/6mm cancer in all positive cores

Note: men with 1-2 higher risk features (Age <55, PSA >10, cT-stage >T2a, small volume Gleason 3+4, >20% of cores positive, >30%/6mm cancer in any core) had AS discussed, but were counselled regarding higher risk of failure.

Monitoring protocol:

- PSA 3-monthly for 3 years, then 6-monthly;
- Review and DRE 6-monthly for 3 years, then annually;
- Biopsies at 12 months, 12-24 months later, then every 3-5 years;
- Switched to WW once age >75 years/ life expectancy <7 years.

Criteria triggering radical treatment:

- PSA kinetics (PSADT <3 years/ PSA Velocity >0.75ng/mL);
- DRE progression (cT-stage ≥2b);
- Grade progression (Gleason ≥ 7/ increasing proportion of grade 4);
- Volume progression (>20% of cores positive or >8mm in any core).

Table 1a: Baseline characteristics stratified by number of cores collected at diagnostic biopsy (≤12 vs >12) in men undergoing AS

Baseline Characteristics	12 or less cores	More than 12 cores	p-value for difference*
Number of men (total n=650)	239	411	-
Median age (years)	63	63	0.66
Median PSA (ng/mL)	6.2	6.1	0.04
Clinical T-stage at diagnosis (%)			0.34
- T1c	75	71	
- T2a	19	22	
- T2b	6	7	
- T2c	0	<0.5	
- T3	0	0	
Median volume on TRUS (cc)	42	45	0.27
Median PSA density (ng/mL/cc)	0.14	0.13	0.02
Family History of Pca (%)	16	17	0.94
Biopsy approach (%)			<0.01
- Transrectal	84	64	
- Transperineal	16	36	
Median number of cores collected	10	16	<0.01
Median proportion of cores positive (%)	17	8	<0.01
Median max cancer in any core (mm)	1.6	1.3	0.07
Gleason Sum at diagnosis (%)			0.17
- 6	90%	84%	
- 7	10%	16%	
NCCN Risk category at diagnosis (%)			0.65
- Very low risk	7	5	
- low risk	65	64	
- intermediate risk	28	31	
Median followup duration (months)	71	44	<0.01
Median number of cores per AS biopsy	16	19	0.01

*Wilcoxon 2 sample t-test used for continuous variables due to non-parametric distribution; Chi-squared test and Fisher's exact test used for categorical variables.

Table 1b – Baseline characteristics stratified by diagnostic biopsy approach (transrectal vs transperineal) of men undergoing AS

Baseline Characteristics	Transrectal	Transperineal	p-value for difference*
Number of men	473	177	-
Median age (years)	63	63	0.28
Median PSA (ng/mL)	6.1	6.1	0.80
Clinical T-stage at diagnosis (%)			0.02
- T1c	70	81	
- T2a	23	18	
- T2b	6	1	
- T2c	0.4	-	
- T3	-	-	
Median volume on TRUS (cc)	45	41	0.16
Median PSA density (ng/mL/cc)	0.13	0.13	0.33
Family History of Pca (%)	16	20	0.21
Median number of cores collected	14	21	<0.01
Median proportion of cores positive (%)	13	6	<0.01
Median max cancer in any core (mm)	1.6	1.3	0.02
Gleason Sum at diagnosis (%)			0.89
- 3-6	87	86	
- 7	13	14	
NCCN Risk category at diagnosis (%)			0.05
- very low risk	6	4	
- low risk	64	72	
- intermediate risk	30	24	
Median followup duration (months)	48	57	0.01
Median no. cores collected on AS biopsy	16	24	<0.01

*Wilcoxon 2 sample t-test used for continuous variables due to non-parametric distribution; Chi-squared test and Fisher's exact test used for categorical variables.

Table 2a – Clinical and pathological outcomes for men on AS stratified by number of cores collected at diagnostic biopsy (</= 12 cores vs > 12 cores)

Outcome parameter	6-12 cores	> 12 cores	p-value for difference
Reason for change to radical treatment (%)			
- Patient preference	12	13	0.83
- Disease Progression	88	87	
Type of disease progression on AS (%)			
- PSA kinetics	13	9	0.07
- DRE progression	1	1	
- Biopsy progression	86	90	
Vital Status (%)			
- Still on AS	43.5	56.2	-
- Relapse free post-radical treatment	34.7	38.9	
- Asymptomatic BCR, not treated	0.8	0	
- Asymptomatic BCR with salvage Tx	1.7	0.2	
- Progression to metastasis	0	0	
- Dead from another cause	10	0.7	
- Dead from prostate cancer	0	0	
- Changed to WW, treatment-free	6.3	3.7	
- Changed to WW, ADT/ XRT initiated	2.5	0	
Pathologic outcomes in men who underwent RP (n = 179)			
- Number of men	58	121	-
Median characteristics on pre-RP biopsy			
- Number of cores taken	18	19	0.07
- Gleason Score 6 / 3+4/ 4+3/ 8/ 9 (%)	20/ 63/ 14/ 0/ 2	20/ 58/ 13/ 8/ 1	0.34
- Percentage of cores with cancer (%)	20	21	0.63
- Max core length of cancer (mm)	4.2	4.8	0.81
- Percentage high grade (%)	10	20	0.31
Pathologic T-stage (%)			
- pT2	70	77	0.30
- pT3/4	30	23	
pGleason sum (%)			0.59
- 6 / 3+4 / 4+3 / 8 / 9	21/ 58/ 14/ 4/ 4	17/ 61/ 19/ 2/ 1	
Median amount of high grade tumour (%)	18	20	0.67
Median tumour volume (cc)	1.2	0.9	0.97
Proportion with positive margin (%)	16	20	0.78
Proportion with positive lymph nodes (%)	5	2	0.45
Proportion with unfavourable findings (%)	36	33	0.67
Proportion with significant cancer at RP (%)	59	61	0.78

*Wilcoxon 2 sample t-test used for continuous variables due to non-parametric distribution; Chi-squared test and Fisher's exact test used for categorical variables.

Table 2b – Clinical and pathological outcomes for men on AS stratified by diagnostic biopsy approach (transrectal vs transperineal)

Outcome parameter	Transrectal	Transperineal	p-value for difference*
Vital Status (%)			
- Still on AS	54	43	
- Relapse free post-radical treatment	36	45	
- Asymptomatic BCR not treated	0.4	-	
- Asymptomatic BCR, on salvage therapy	1	-	
- Progressed to metastasis post-treatment	-	-	-
- Dead from an unrelated cause	4	2	
- Dead from a prostate cancer-related cause	-	-	
- Changed to WW, treatment-free	3	9	
- Changed to WW, on palliative therapy	1	1	
	0.2	0.2	
Reason for crossover to radical treatment (%)			
- Patient preference	13	11	0.72
- Disease Progression	87	89	
Type of disease progression on AS (%)			
- PSA kinetics	9	12	0.58
- DRE progression	2	0	
- Biopsy progression	89	88	
Path outcomes in men who underwent RP (n=167)			
Number of men	124	55	-
Median characteristics on last pre-RP biopsy			
- Number of cores taken (n)	17	24	<0.01
- Gleason Grade 6 /3+4/ 4+3/ 8-9	22/ 60/ 11/ 7	18/ 58/ 18/ 7	0.70
- Percentage of cores with cancer (%)	21	14	0.07
- Max core length of cancer (mm)	4	4	0.87
- Percentage high grade (%)	10	15	0.34
pT-stage (%)			
- pT2	69	87	0.01
- pT3/4	31	13	
pGleason sum (%)			
- 6	19	19	
- 3+4 (7)	58	66	0.57
- 4+3 (7)	19	15	
- 8/9	5	-	
Median proportion of high grade tumour (%)	20	10	0.57
Median tumour volume (cc)	1.1	0.6	<0.01
PSM %	23	11	0.08
Proportion with positive lymph nodes (%)	2	0	-
Proportion with unfavourable pathology (%)	40	22	**0.03**
Proportion with significant cancer (%)	72	52	**0.02**

*Wilcoxon 2 sample t-test used for continuous variables due to non-parametric distribution; Chi-square test and Fisher's exact test used for categorical variables.