Five-year follow-up of active surveillance for prostate cancer: A Canadian community-based urological experience

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Abstract

Introduction: We assessed oncological outcomes of active surveillance (AS) using a community database and identified factors associated with disease reclassification on surveillance biopsy.
Methods: A retrospective review was performed on 200 men on AS. Prostate-specific antigen (PSA) was measured every 3 to 6 months. Prostate biopsies were performed every 1 to 4 years, and at the individual physician's discretion. Disease reclassification was defined as clinical T1 to cT2 progression, or histologically as >2 cores positive, Gleason score >6, or >50% core involvement on surveillance biopsy. Multivariate Cox regression analysis evaluated factors associated with disease reclassification. Kaplan-Meier survival curves were plotted.
Results: We assessed a heterogeneous cohort of 86 patients, with a median age 67.2 years, who received ≥1 surveillance biopsies. The median follow-up was 5.2 years. The median times to first and second surveillance biopsies were 730 and 763 days, respectively. Overall, 47% of patients were reclassified on surveillance biopsy after a median 2.1 years. Factors associated with disease reclassification were PSA density >0.20 ($p < 0.0001$, hazard ratio [HR] 4.55, 95% confidence interval [CI] 2.116–9.782) and ≥3 positive cores ($p = 0.0152$, HR 3.956, 95% CI 1.304–12.003) at diagnosis, and number of positive cores on surveillance biopsy. In total, 25 (29%) patients received delayed intervention, with a median time to intervention of 2.6 years. The median time on AS was 4.4 years, with an overall survival of 95% and prostate-specific survival of 100%.
Conclusions: Our community study supports AS to reduce overtreatment of prostate cancer. PSA density >0.20 and ≥3 cores positive are associated with disease reclassification on surveillance biopsy.

Introduction

The percentage of prostate cancer with low-risk characteristics has increased since the mid-1990s largely due to widespread prostate-specific antigen (PSA) screening.[1] Over a similar period, the percentage of prostate cancer mortalities has reduced by more than 40%.[2] There is now growing evidence that men with low-risk prostate cancer may not benefit from radical treatment.[3] This has created controversy regarding PSA screening practices and the treatment of low-risk prostate cancer due to concerns of overdiagnosis and overtreatment.[4,5]

Active surveillance (AS) is an accepted alternative to immediate intervention for favourable-risk prostate cancer and it has shown promise in reducing overtreatment. Several large institutions have reported favourable experiences with AS.[6,7] However, these select patient cohorts may differ from that of clinical practice, as patients may periodically delay immediate therapy and choose AS despite disease characteristics outside contemporary AS inclusion criteria. We present our experience with AS of a heterogeneous population and report the oncological outcomes following retrospective analysis of a community database with a median 5-year follow-up.

Methods

Following institutional ethics board approval, we identified men diagnosed with prostate cancer between January 1, 1998 and June 28, 2013 from a local prospectively collected database of prostatic biopsies. Retrospective chart review identified 200 patients on AS and a cohort of 86 with at least one surveillance biopsy. Patients assigned to upfront watchful waiting and those who received treatment prior to initiation of AS or within 6 months of diagnosis were excluded.

AS was offered to men with clinical T1 or cT2a tumours, PSA ≤10 ng/mL, Gleason score ≤6, ≤2 cores positive, and ≤50% maximum core involvement. Some men proceeded with AS despite disease characteristics outside these criteria and were included in the present study. All transrectal ultrasound (TRUS) prostatic biopsies underwent review by a panel of in-house pathologists. Patients had 8 to 14 core

biopsies performed according to the Vienna nomogram. Digital rectal examinations (DREs) and PSA measurements were performed every 3 to 6 months. Surveillance biopsies were performed every 1 to 4 years, and at the individual physician's discretion following change on DRE or increasing PSA.

Disease reclassification was defined as cT1 to cT2 reclassification based on the development of a palpable nodule or by histological criteria on surveillance biopsy including: Gleason score >6, >50% maximum core involvement, and >2 cores positive. Histological reclassification triggered a recommendation for therapeutic intervention due to concerns of disease progression.

All patients were assessed at baseline relative to the Prostate Cancer Research International: Active Surveillance (PRIAS) or Epstein inclusion criteria. Baseline characteristics (diagnostic age, family history of prostate cancer, PSA, PSA density [PSAD], prostate volume, clinical stage, Gleason score, D'Amico risk classification, number of biopsy cores, number of positive cores, maximum percent of core involvement) were included in a multivariate Cox regression analysis to assess factors associated with disease reclassification on surveillance biopsy. Times to disease reclassification and intervention were calculated from the date of diagnosis. Multivariate Cox regression analysis and Kaplan-Meier survival curves evaluated overall-survival, prostate cancer-specific survival, and progression-free survival. Separate analysis was performed on a modified cohort after exclusion of patients with intermediate- or high-risk characteristics at baseline (defined as PSA >10, Gleason score >6, or stage >cT2a). Calculations were performed using SAS statistical analysis (SAS Institute, Cary, NC). All statistical analyses were two-sided, with statistical significance set at $p < 0.05$.

Results

The cohort consisted of 86 patients, with a median age 67.2 years and a median follow-up 5.18 years (Table 1). The median baseline PSA was 5.9 ng/mL; however, one individual with PSA 21.4 ng/mL, small foci Gleason 6 (3+3), and negative workup for metastatic disease choose to proceed with AS. Overall, 71% of patients met the PRIAS inclusion criteria and 53% met the Epstein criteria. Most patients (86%) were part of the D'Amico low-risk classification and all but 1 patient had an initial Gleason score of ≤6. Four patients had fewer than 8 cores at diagnostic biopsy. The median times to first and second surveillance biopsies were 730 days and 763 days, respectively.

Three patients died during the study period because of metastatic sarcoma, cardiac arrest, and metastatic melanoma. Overall survival was 95%, and prostate cancer-specific survival was 100%. Seven patients were lost to urological follow-up, but all were confirmed alive at the end of the study based on medical records. Six patients (7%) were transitioned to watchful waiting.

Overall, 40 (47%) patients experienced signs of disease progression and were offered definitive intervention (Table 2). The median time to overall reclassification was

Table 1. Demographics and baseline characteristics of study patients

Parameter	Entire cohort, N = 86
Age, year, median	67.2 (47.7–77.6)
PSA, ng/mL, median	5.9 (1.1–21.4)
PSA density, median	0.12 (0.02–0.30)
≤0.20, %	74 (86.0)
>0.20, %	12 (14.0)
Prostate volume, cc, median	46 (19–228)
DRE	
Normal, %	30 (39.0)
BPH, %	22 (28.6)
Firm/irregular, %	13 (16.9)
Nodule, %	12 (15.6)
Clinical stage	
T1a, %	1 (1.2)
T1c, %	65 (76.5)
T2a, %	17 (20.0)
T2c, %	2 (2.4)
Gleason	
<6, %	3 (3.5)
6, %	82 (95.4)
7 (3+4), %	1 (1.2)
Risk	
Low, %	74 (86.0)
Intermediate, %	9 (10.5)
High, %	3 (3.5)
Family history of prostate cancer, %	27 (31.4)
No. surveillance biopsies, mean	1.48 ± 0.07
No. cores initial biopsy, median	10 (3–14)
No. positive cores initial biopsy, median	1 (1–4)
<3 cores positive, %	77 (89.5)
≥3 cores positive, %	9 (10.5)

PSA: prostate-specific antigen; DRE: digital rectal examination; BPH: benign prostatic hyperplasia.

Table 2. Type and median time to reclassification on surveillance biopsy

Type of reclassification	Entire cohort, N = 86
Overall, %	40 (46.5)
T1/T2 reclassification, %	10 (11.6)
Gleason reclassification, %	20 (23.3)
Volume/core reclassification, %	30 (35.3)
Median time to reclassification	
Time to overall reclassification, years	2.12 (0.53–5.75)
Time to T1/T2 reclassification, years	2.23 (1.72–4.47)
Time to Gleason reclassification, years	2.22 (0.53–5.43)
Time to volume/core reclassification, years	2.23 (0.77–5.75)

Table 3. Type of delayed intervention

Type of intervention	Entire cohort, N = 86 (%)
Overall	25 (29.1)
Radical prostatectomy	9 (10.5)
Radiation therapy	8 (9.3)
Radiation therapy + ADT	5 (5.8)
ADT alone	3 (3.5)

ADT: androgen deprivation therapy.

2.12 years, and similar among subgroup analysis. Twenty-five (29%) patients received therapeutic intervention (Table 3) after a median time of 2.55 years. At the end of the study, 53 (62%) patients remained on AS, with a median time on AS of 4.40 years for the entire cohort.

Final pathological details were available for all 9 patients who received radical prostatectomy. Three patients had non-organ confined disease; 2 with pT3a, and 1 with pT3b. Overall, 3 patients had Gleason 7 (3+4) and 2 patients had Gleason 7 (4+3).

Multivariate analysis indicated that the PSAD >0.20 at diagnosis was associated with future disease reclassification ($p < 0.0001$, HR 4.55, 95% CI 2.116–9.782) (Table 4), Gleason reclassification ($p < 0.0001$, HR 9.55, 95% CI 3.253–28.053) and volume/core reclassification ($p = 0.0029$, HR 4.30, 95% CI 1.646–11.243). Kaplan-Meier curves are shown in Figure 1.

The presence of ≥3 positive cores on initial biopsy was associated with future Gleason reclassification ($p = 0.0152$, HR 3.956, 95% CI 1.304–12.003). Kaplan-Meier curves are shown in Figure 2. Disease reclassification on first and second surveillance biopsy correlated with the number of positive cores (Table 4).

Multivariate analysis of the modified cohort, following the removal of 12 patients with intermediate- or high-risk characteristics, revealed similar findings, except that clinical stage was no longer associated with reclassification at the time of second surveillance biopsy (Table 4).

Discussion

We present a community urological perspective on the use of AS. Our median follow-up of 5.2 years surpasses many other studies with shorter follow-up of oncological outcomes for AS.[6]

Our cohort was heterogeneous, and many patients included in the present study would have been excluded from contemporary AS protocols.[6] Indeed, 71% of patients met PRIAS criteria[8] and 53% met Epstein criteria.[9,10] Following the removal of 12 patients with initial D'Amico intermediate- or high-risk classification, 78% and 55% met the PRIAS and Epstein criteria, respectively. Thus, the present study illustrates a difference between cohorts of clinical research and that of clinical practice, as some patients may choose AS despite the higher risk of disease progression and traditional recommendation for immediate intervention. As most AS series also have been performed retrospectively, patients included in individual studies may also have not met the most conservative inclusion criteria of contemporary protocols.

In total, 86% of patients in the present study met the D'Amico low-risk criteria. The remainder had PSA >10, or Gleason score >6, or cT2c. All patients elected to proceed with AS with therapeutic intervention to begin at further signs of disease progression. Despite the inclusion of 14% intermediate- and high-risk patients, we reported 100% prostate cancer-specific survival, and 95% overall survival. This compares favourably with previous reports indicating 97% to 100% prostate cancer-specific survival after short- to intermediate-term follow-up of variable AS protocols.[6,7] Overall, 29% of patients proceeded with definitive therapy, comparable to previous systematic review indicating that up to 33% of patients received further therapy after a median 2.5 years.[6] The median time to intervention was 2.6 years, and similar to reports ranging from 1.3 to 3.5 years.[6]

In our cohort, 47% of patients experienced overall disease reclassification, including 12% with cT1-cT2 reclassification. In contemporary studies, disease reclassification is often taken as a sign of disease progression, and defined as upgrading or upstaging at the time of repeat biopsy.[6] Early upgrading following repeat biopsy is concerning for initial sampling error, whereas later upgrading may represent true dedifferentiation of prostate cancer.[11] To increase the precision of risk assignment, most centres now recommend a confirmatory biopsy or an extended-template biopsy before initiating AS.[12] Unfortunately, due to the retrospective nature of this study most patients did not receive a confirmatory biopsy.

Current National Comprehensive Cancer Network guidelines consider AS an option for healthy men with very low-risk or low-risk prostate cancer and at least a 10-year life expectancy.[13] However, there is limited consensus in defining optimal candidates, surveillance protocols, or triggers for delayed intervention. In agreement with the recent PRIAS

Table 4a. Multivariate analysis of baseline characteristics for possible predictors of reclassification on repeat biopsy

	Entire cohort, N = 86		Modified cohort, N = 74	
	p value	HR (95% CI)	*p* value	HR (95% CI)
PSA density ≤0.20	ref	ref	ref	ref
PSA density >0.20	0.0001	4.550 (2.116–9.782)	0.0006	4.338 (1.818–10.206)

PSA: prostate-specific antigen; HR: hazard ratio; CI: confidence interval.

Table 4b. Multivariate analysis of first surveillance biopsy characteristics for possible predictors of reclassification on repeat biopsy

	Entire cohort, N = 86		Modified cohort, N = 74	
	p value	HR (95% CI)	*p* value	HR (95% CI)
Age	0.1937	–	0.0400	0.946 (0.898–0.997)
PSA	0.0984	0.913 (0.819–1.101)	0.4586	-
DRE nodule	0.9139	1.051 (0.425–2.601)	0.7049	1.217 (0.441–3.355)
No. positive cores	<0.0001	2.083 (1.598–2.716)	<0.0001	2.070 (1.574–2.721)

PSA: prostate-specific antigen; DRE: digital rectal examination; HR: hazard ratio; CI: confidence interval.

study,[8] we found PSAD >0.20 to be strongly associated with disease reclassification. We identified PSAD >0.20 as a strong independent risk factor associated with overall disease reclassification, Gleason reclassification, and volume/core reclassification. This suggests a potential clinical utility of PSAD as a selection criterion for candidacy in AS protocols.

At the time of diagnosis, having ≥3 positive cores was strongly associated with future Gleason reclassification (HR 4.369). The number of positive cores at the time of first and second surveillance biopsy was also associated with overall disease reclassification. While the number of positive cores is variable among inclusion criteria of current AS protocols,[6] our data support an appropriate cutoff of ≤2 cores positive.

Sixty-two percent of patients remained on AS at the end of the study, with a median time on AS of 4.40 years for the entire cohort, and 4.35 years for the modified cohort. This is lower than previous reports indicating 72% remained on AS at 5 years and 62% at 10 years.[7] This discrepancy may be explained by individual differences in respective cohorts, differences in follow-up protocols, and inclusion of cT1 to cT2 reclassification in the present study. In addition, the lack of a confirmatory biopsy may have allowed higher rates of disease reclassification on surveillance biopsy secondary to initial sampling error.

Despite a recent report suggesting men with very low-risk prostate cancer were at lower risk for adverse pathological findings at radical prostatectomy than low-risk patients,[14] we believe many low-risk patients remain good candidates for AS. A previous comparison of AS protocols for detection of insignificant prostate cancer identified the PRIAS and University of Miami criteria as the best balance of sensitivity and specificity, and both protocols include cT2a lesions that are excluded from very low-risk criteria.[15] Furthermore, minor changes in grade or stage may not translate into unfavourable oncologic outcomes, as Xia and colleagues illustrated that only 2.8% of men with low-risk disease on AS versus 1.6% with low-risk disease undergoing immediate radical prostatectomy would die from prostate cancer in 20 years.[16] Thus, AS was predicted to produce only a modest decline in prostate cancer-specific survival among low-risk patients. These men would also remain free of treatment for an additional 6.4 years and spared adverse effects related to immediate intervention.

Previous reports indicate few men with low-risk disease would die from prostate cancer during intermediate term follow-up, and the most common cause of death in these patients was cardiovascular disease.[17] The rate of prostate cancer mortality in our cohort may increase with longer follow-up; however, the ratio of non-prostate cancer to prostate cancer mortality on AS has been reported as 18.6 to 1 at 10 years.[7]

Limitations to the present study include its retrospective nature and small sample size. Patients were followed for a median 5.2 years, which is relatively long for community practice, but still short in the natural history of prostate cancer. Screening trials indicate that even 10 years is too short to evaluate oncologic outcomes and thus longer follow-up is necessary. Important differences between the present study and contemporary AS protocols include its heterogeneous population and inconsistent follow-up, as median time to serial surveillance biopsies were ≥730 days. These discrepancies should be considered when comparing our findings to previous AS series with more frequent follow-up. Although men were assessed relative to Epstein and PRIAS active surveillance criteria at baseline, missing data precluded full assessment in some patients who elected to proceed with AS.

Table 4c. Multivariate analysis of second surveillance biopsy characteristics for possible predictors of reclassification on repeat biopsy

	Entire cohort, N = 86		Modified cohort, N = 74	
	p value	HR (95% CI)	*p* value	HR (95% CI)
Clinical stage T1	ref	ref	ref	ref
Clinical stage T2	0.0475	4.164 (1.016–17.062)	0.0680	3.738 (0.907–15.399)
No. positive cores	0.0001	1.956 (1.386–2.762)	0.0003	1.894 (1.337–2.683)

HR: hazard ratio; CI: confidence interval.

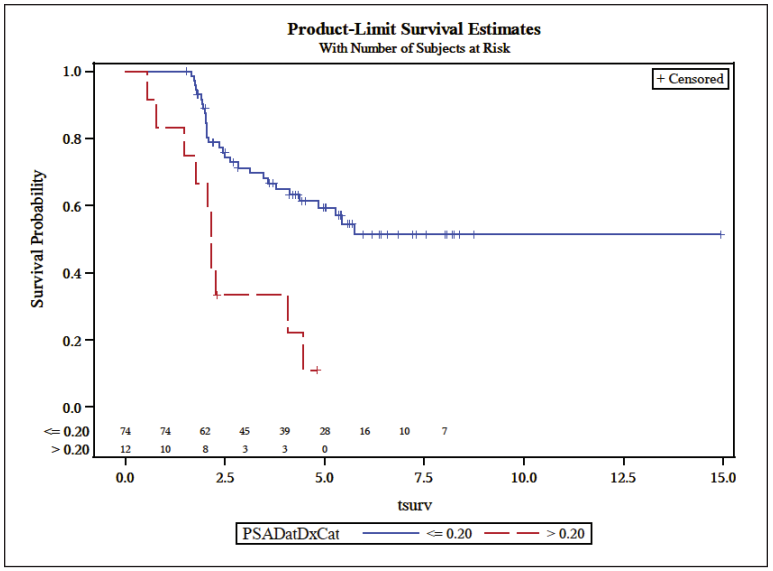

Fig. 1a. Kaplan-Meier estimated progression-free survival* for overall reclassification as predicted by prostate-specific antigen density at diagnosis ($p = 0.0004$, hazard ratio 3.759, 95% confidence interval 1.797–7.859). *Reclassification was considered sign of disease progression.

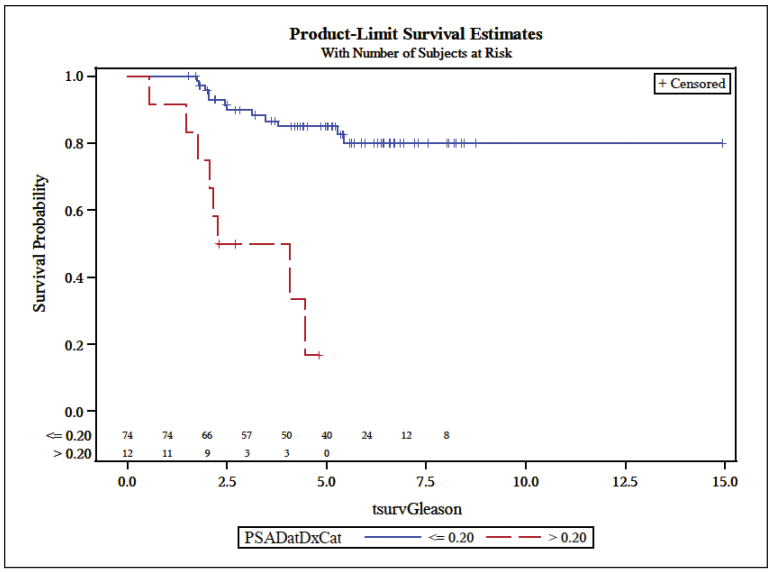

Fig. 1b. Kaplan-Meier estimated progression-free survival* for Gleason reclassification as predicted by prostate-specific antigen density at diagnosis ($p < 0.0001$, hazard ratio 8.128, 95% confidence interval 3.141–21.033). *Reclassification was considered sign of disease progression.

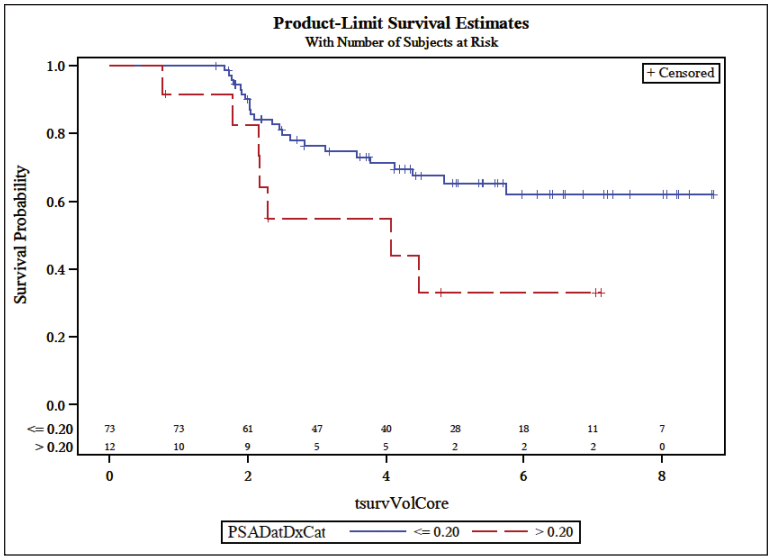

Fig. 1c. Kaplan-Meier estimated progression-free survival* for volume/core reclassification as predicted by prostate-specific antigen density at diagnosis ($p = 0.0392$, hazard ratio 2.443, 95% confidence interval 1.045–5.710). *Reclassification was considered sign of disease progression.

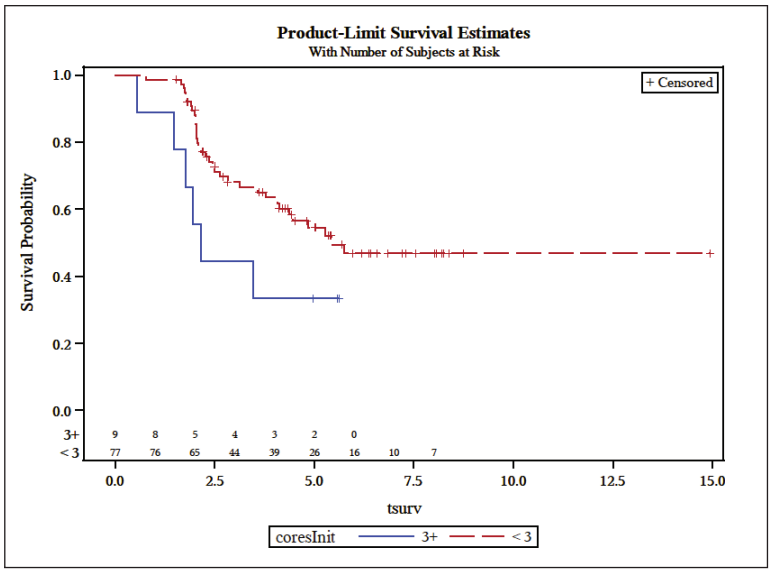

Fig. 2a. Kaplan-Meier estimated progression-free survival* for overall Reclassification as predicted by number of positive cores at diagnosis ($p = 0.1014$, hazard ratio 2.070, 95% confidence interval 0.867–4.945).*Reclassification was considered sign of disease progression.

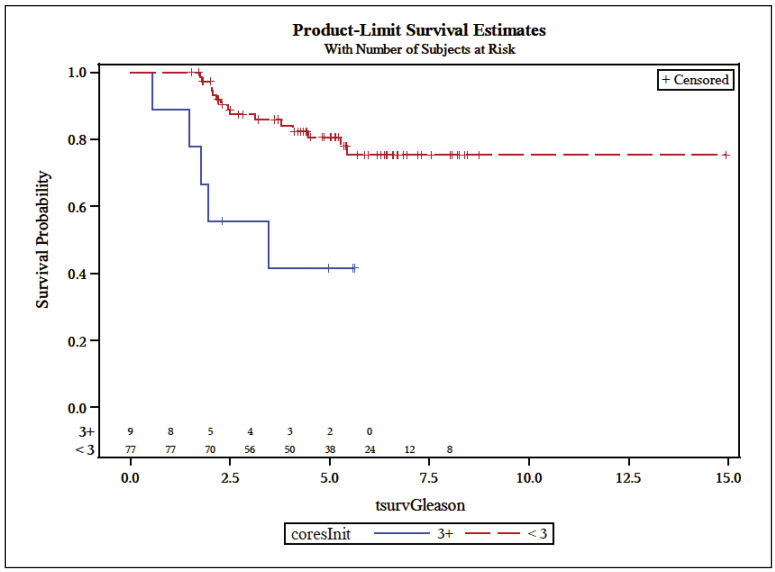

Fig. 2b. Kaplan-Meier estimated progression-free survival* for Gleason reclassification as predicted by number of positive cores at diagnosis ($p = 0.0044$, hazard ratio 4.369, 95% confidence interval 1.583–12.060). *Reclassification was considered sign of disease progression.

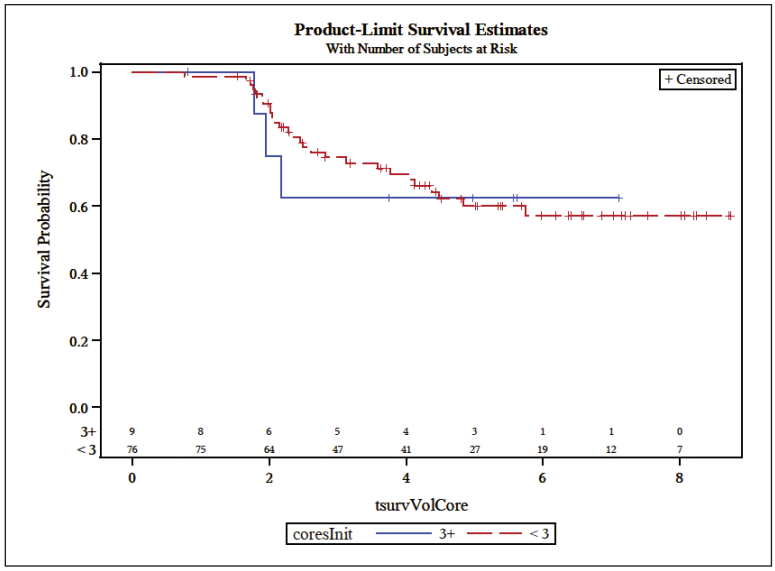

Fig. 2c. Kaplan-Meier estimated progression-free survival* for volume/core reclassification as predicted by number of positive cores at diagnosis ($p = 0.8917$, hazard ratio 1.087, 95% confidence interval 0.329–3.586). *Reclassification was considered sign of disease progression.

Conclusion

Our community urological data support AS to reduce over-treatment of prostate cancer. PSAD >0.20 and ≥3 cores positive were associated with disease reclassification on surveillance biopsy.

Competing interests: Dr. Andrews, Dr. Ashfield, Dr. Morse and Dr. Whelan all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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