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RAPID COMMUNICATION

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Comparison of outcomes of different biopsy schedules among men on active surveillance for prostate cancer: An analysis of the G.A.P.3 global consortium database

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Abstract

Background: The optimal interval for repeat biopsy during active surveillance (AS) for prostate cancer is yet to be defined. This study examined whether risk of upgrading (to grade group ≥ 2) or risk of converting to treatment varied according to intensity of repeat biopsy using data from the GAP3 consortium's global AS database.

Materials and Methods: Intensity of surveillance biopsy schedules was categorized according to centers' protocols: (a) Prostate Cancer Research International Active Surveillance project (PRIAS) protocols with biopsies at years 1, 4, and 7 (10 centers; 7532 men); (b) biennial biopsies, that is, every other year (8 centers; 4365 men); and (c) annual biopsy schedules (4 centers; 1602 men). Multivariable Cox regression was used to compare outcomes according to biopsy intensity.

Results: Out of the 13,508 eligible participants, 56% were managed according to PRIAS protocols (biopsies at years 1, 4, and 7), 32% via biennial biopsy, and 12% via annual biopsy. After adjusting for baseline characteristics, risk of converting to

treatment was greater for those on annual compared with PRIAS biopsy schedules (hazard ratio [HR] = 1.66; 95% confidence interval [CI] = 1.51–1.83; $p < 0.001$), while risk of upgrading did not differ (HR = 0.96; 95% CI = 0.84–1.10).

Conclusion: Results suggest more frequent biopsy schedules may deter some men from continuing AS despite no evidence of grade progression.

KEYWORDS

active surveillance, biopsy schedule, prostate cancer, treatment, upgrading

1 | INTRODUCTION

Active surveillance (AS) is the preferred treatment option for men with low-risk prostate cancer (PCa). However, there is a lack of consistency between institutions and across guidelines on recommended protocols for monitoring disease progression.[1,2] Although evidence from long-standing cohorts confirm the safety of AS,[3,4] a substantial proportion of men (2%–38%[2]) discontinue AS without evidence of disease progression. The need for repeated biopsies may be a potential deterrent to continuing AS.[5] Despite the increasing use of magnetic resonance imaging (MRI) and targeted biopsy in AS,[6] uncertainty remains about whether they can replace repeat systematic biopsies.[7] Most guidelines still recommend repeat biopsy at various intervals.

2 | METHODS

To determine whether risk of upgrading (to grade Group II or higher) and risk of transitioning to treatment (i.e., prostatectomy, radiotherapy, and hormone therapy) among men on AS differed according to biopsy schedule intensity we interrogated the Global Action Plan Active Surveillance Prostate Cancer (GAP3) database,[8] the largest international database on AS for PCa (21,000 men, 27 centers, 15 countries [v3.2, November 2019]). Eligible participants included men aged ≤80 years with characteristics consistent with AS inclusion (Grade Group [GG] I, cT1–2, prostate-specific antigen [PSA] < 20 ng/ml) and ≥9 months follow-up or ≥1 follow-up biopsy. Men managed at centers with MRI-based biopsy protocols (2 centers/450 men) or centers where no biopsy data were provided (3 centers/2997 men) were excluded. 13,508 men from 22 centers were eligible. Centers were categorized into three groups according to the intensity of their biopsy schedule as per their institution's AS protocol: (a) centers who followed the Prostate Cancer Research International Active Surveillance project (PRIAS) protocols with biopsies scheduled at years 1, 4, and 7 (10 centers; 7532 men); (b) those with biennial (i.e., every other year) repeat biopsies (8 centers; 4365 men); and (c) those with annual repeat biopsy schedules (4 centers; 1602 men). Kaplan–Meier methods were used to determine the observed average annual rates of biopsy and PSA testing, and to estimate treatment-free and upgrade-free proportions at 5 years. Multivariable Cox proportional hazards regression was used to assess risk of conversion to treatment and risk of upgrading according to biopsy schedule intensity, with PRIAS schedules as the reference. Models were adjusted for baseline characteristics: age (5 years categories), diagnostic period (5 years categories), PSA concentration (5 ng/ml categories); clinical T-stage (cT1 vs. cT2); number of cores sampled (continuous), number of positive cores (continuous), prostate volume (continuous per 5cc) and intensity of PSA testing schedule (grouped according to centers' protocols as either 6 monthly, 3–6 monthly, or 3 monthly). Time to conversion (or upgrading) was calculated from diagnosis date to date of conversion/upgrading, with censoring at the last known date of follow-up. Sensitivity analyses were also undertaken (1) including men with GG2 who were otherwise eligible, assessing risk of transitioning to treatment and risk of any upgrading; (2) including men with less than 9 months follow-up and no biopsy, assessing risk of transitioning to treatment only; and (3) excluding men who underwent confirmatory biopsy within 9 months, assessing transitioning and upgrading. Missing data for covariates were imputed using multiple imputation by chained equations. Analyses were undertaken using Stata v15.1. Ethical approval to contribute data to the GAP3 platform was obtained by each individual participating center.

3 | RESULTS

Most men (56%) were managed in centers that followed PRIAS protocols, 32% in centers with biennial biopsy schedules, and 12% in centers with annual biopsy schedules. The observed annual biopsy rates confirmed differences in the actual frequency of repeat biopsy between groups (Table 1). The proportions remaining on AS at 5 years were 65%, 59%, and 54% for the PRIAS, biennial, and annual biopsy groups, respectively (log-rank test $p < 0.001$). Similar proportions of men were upgraded during follow-up across groups. In adjusted models, risk of converting to treatment was greater among men managed at centers with annual compared with PRIAS biopsy schedules (hazard ratio [HR] = 1.66; 95% confidence interval [CI] = 1.51–1.83) while no

TABLE 1 Characteristics at diagnosis and follow-up events, according to biopsy schedule groupings

	Biopsy intensity		
	Years 1, 4, and 7	Biennial	Annual
Number of centers	10 centers	8 centers	4 centers
Number of men (% of total)	7532 (56)	4365 (32)	1611 (12)
Diagnostic characteristics			
Age – Median years (IQR)	65 (60–70)	65 (59–69)	66 (62–70)
cT2 – No. (%)	920 (12)	512 (12)	315 (19)
PSA – Median ng/ml (IQR)	5.6 (4.4–7.1)	5.3 (4.0–7.0)	4.9 (3.7–6.4)
No. Cores samples – Median (IQR)	12 (10–13)	12 (12–13)	12 (10–12)
No. Cores positive – Median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)
Prostate volume – Median cc (IQR)	46 (36–59)	45 (35–59)	45 (35–58)
Follow-up			
Median follow-up years (IQR)	3.1 (1.4–6.0)	2.5 (1.3–4.3)	3.1 (1.4–5.6)
Biopsy rate per year (95% CI)	0.35 (0.34–0.35)	0.45 (0.43–0.46)	0.62 (0.60–0.64)
PSA testing rate per year (95% CI)	2.5 (2.4–2.5)	2.1 (2.1–2.2)	1.8 (1.7–1.8)
Treatment free at 5 years, % (95% CI)	65 (63–66)	59 (57–60)	55 (52–59)
Risk of upgrading ≥3 + 4, % (95% CI)	26 (25–28)	27 (25–29)	22 (19–24)

Abbreviations: AS, active surveillance; IQR, interquartile range; PSA, prostate-specific antigen.

difference was seen in risk of upgrading (Table 2). Results of sensitivity analyses gave similar results to our original analysis, except that risk of transitioning to treatment was also slightly elevated in the biennial compared with PRIAS biopsy schedule group when those with <9 months follow-up were included in the regression model (see Supporting Information).

4 | DISCUSSION

These findings suggest that men undergoing intense biopsy surveillance may, over time, choose to convert to active treatment despite a lack of progression in preference to the burden of annual biopsy. While reasons for withdrawing from AS without progression are multi-faceted, qualitative evidence indicates that requirement for repeat biopsies, and associated levels of anxiety and uncertainty, can deter some men from continuing on AS.[5,9] However, some caution is warranted in drawing this conclusion, given upgrading is not the only indicator of disease progression that can trigger a decision switch to active treatment. An increase in proportion of positive cores, maximum cancer length, or PSA density, may also influence clinical decisions to recommend treatment. Conversely, upgrading to grade Group II may not necessarily signal the need to transition to treatment if other disease characteristics are favorable. Furthermore, since reclassification criteria for transitioning to treatment vary considerably between and within regions, it is possible that observed differences are due to systematic differences in other triggers for treatment between biopsy schedule groups. Possible explanations for the increase in upgrading and transitioning to treatment in recent calendar years include: improved biopsy methods; increasing use of other surveillance methods not reported to GAP3 (e.g., mp-MRI with targeted biopsy); changes in grading systems; and inclusion of younger AS cohorts in which thresholds for risk of progression are (informally) lower.

Clinical implications are not straightforward. Where prostatic MRI is available, the current findings might allow for more dependency on aspects of lesion detection and alteration, with subsequently targeted biopsies to avoid follow-up biopsies. In clinics without MRI, these findings may justify a more relaxed biopsy scheme, for example, PRIAS protocols. Adopting personalized risk-based biopsy schedules may be another alternative to reduce the burden of frequent biopsies.[10]

Strengths of this study include the diversity of AS protocols across participating centers within GAP3 which allow the impact of different follow-up schedules on outcomes to be assessed; the large size of the cohort providing sufficient statistical power; and detailed baseline, follow-up, and outcome data to assess disease progression and conversion over time. Limitations include the lack of data on MRI and targeted biopsies from most participating centers, preventing analysis of imaging-based surveillance and outcomes. The relatively short follow-up time in GAP3 also limited longer-term outcome assessment. Given our study population comprised mostly men with relatively low volume (GG1) disease, our findings may not be generalizable to AS cohorts that include high proportions of men with favorable intermediate-risk PCa or >2 positive cores.

In conclusion, this study found that more intense biopsy schedules correlated with more frequent conversion to active treatment but not risk of upgrading. While the decision to switch to active

TABLE 2 Risk of converting to treatment and risk of upgrading among men with low-risk prostate cancer on active surveillance

	Conversion to treatment		Upgrade ≥ 3 + 4	
	HR	95% CI	HR	95% CI
Biopsy schedule				
Years 1, 4, and 7	1.00	Reference	1.00	Reference
Biennial	1.03	0.96–1.11	1.01	0.92–1.11
Annual	1.67	1.51–1.83	0.96	0.84–1.10
PSA test schedule				
6 monthly	1.00	Reference	1.00	Reference
3–6 monthly	1.26	1.17–1.36	1.04	0.95–1.14
3 monthly	1.47	1.32–1.64	0.74	0.62–0.88
Age group – years				
<55	1.00	Reference	1.00	Reference
55–59	1.14	1.00–1.31	1.03	0.87–1.22
60–64	1.27	1.12–1.44	1.15	0.98–1.35
65–69	1.33	1.18–1.50	1.30	1.11–1.52
70–74	1.36	1.20–1.55	1.42	1.21–1.67
75+	1.27	1.09–1.49	1.30	1.07–1.57
Diagnosis period				
1995–2002	1.00	Reference	1.00	Reference
2003–2007	0.86	0.76–0.97	0.95	0.80–1.14
2008–2012	1.08	0.96–1.22	1.27	1.07–1.50
2013–2018	1.19	1.04–1.36	1.52	1.27–1.83
Baseline PSA – ng/ml				
<5	1.00	Reference	1.00	Reference
5–9.9	1.36	1.28–1.45	1.31	1.20–1.42
10–14.9	1.22	1.04–1.42	1.28	1.06–1.55
15–19.9	1.36	1.01–1.82	1.46	1.02–2.09
Clinical stage (cT2 vs. cT1)	1.12	1.03–1.21	1.15	1.04–1.28
No. cores sampled	0.98	0.98–0.99	0.98	0.98–0.99
No. cores positive at diagnosis	1.10	1.07–1.12	1.12	1.09–1.15
Prostate volume – per 5cc	0.95	0.94–0.95	0.96	0.95–0.97

Abbreviations: 95% CI, 95% confidence interval; cc, cubic centimeters; HR, hazard ratios derived from Cox regression models; PSA, prostate-specific antigen.

treatment is based on a mix of biological and personal factors, the requirement for frequent biopsies may also be influential. In slow-growing tumors like low-risk PCa, it remains to be seen which surveillance protocol is optimal in the long term, and whether individualized protocols can be offered.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used in the current study are available via the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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