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Original Article

Active surveillance for intermediate risk prostate cancer: the Manitoba Prostate Center experience

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Objectives

To report long-term oncological outcomes of men with intermediate-risk prostate cancer managed with active surveillance at a single centre.

Subjects/Patients and Methods

We retrospectively analysed a prospectively maintained Manitoba Prostate Centre active surveillance database. Included were men with disease classed per National Comprehensive Cancer Network risk categories: very low-, low-, favourable intermediate-, and unfavourable intermediate-risk prostate cancer managed with surveillance (2004–2023). Active surveillance involved serial prostate-specific antigen testing, digital rectal exam, and confirmatory/surveillance biopsies. Outcomes were treatment-free survival, metastasis-free survival, prostate cancer–specific survival, overall survival, and biopsy grade progression. Kaplan–Meier estimated survival; Cox regression evaluated variables associated with outcomes.

Results

Among 561 men, the median age was 65 years (interquartile range 59–69) and the median follow-up was 4.4 years. Overall, 256 men (45.6%) transitioned to definitive treatment. Five-year treatment-free survival declined stepwise by risk group: 84.8% in very low-risk, 61.4% in low-risk, 50.0% in favourable intermediate-risk, and 21.4% in unfavourable intermediate-risk disease ($P < 0.001$). On multivariable analysis, older age, higher prostate-specific antigen density, and grade group ≥2 were independently associated with earlier treatment. Metastatic progression and prostate cancer–specific mortality were rare across the cohort, with higher event rates observed among patients with unfavourable intermediate-risk disease.

Conclusions

In this real-world active surveillance cohort, the likelihood of remaining on surveillance differed substantially by baseline risk, with unfavourable intermediate-risk disease associated with earlier transition to treatment and higher risks of disease progression. Older age, higher prostate-specific antigen density, and grade group ≥2 were independently associated with discontinuation of active surveillance. Despite less intensive surveillance protocols, rates of metastatic progression and prostate cancer–specific mortality remained low, particularly among patients with low-risk and favourable intermediate-risk disease, supporting active surveillance as a viable management strategy in carefully selected men beyond low-risk disease.

Keywords

prostatic neoplasms, survival analysis, active surveillance, intermediate-risk prostate cancer, risk stratification, treatment-free survival

Introduction

Prostate cancer (PCa) is among the most diagnosed malignancies in men, exhibiting a wide spectrum of disease ranging from indolent, localized tumours to aggressive, life-threatening disease [1]. Because definitive treatment can carry functional morbidity, and many tumours will likely never affect patient survival, active surveillance (AS) has emerged as the preferred management strategy for men with very low-risk (VLR) and low-risk (LR) PCa, allowing deferral

of curative treatment while maintaining excellent long-term oncologic outcomes and preserving quality of life [1–4].

Current National Comprehensive Cancer Network (NCCN), European Association of Urology, and American Urological Association guidelines also consider AS for select men with favourable intermediate-risk (FIR) PCa [5,6]. However, intermediate-risk (IR) disease encompasses a broad and clinically heterogeneous group, including men with limited Gleason pattern 4 (GP4) disease, prostate-specific antigen (PSA) values between 10 and 20 ng/mL, or higher-volume biopsy involvement. Further, although some patients may share favourable characteristics with LR disease, others may exhibit features more akin to high-risk cancer [7–9].

Randomized trials comparing AS against radical treatment, such as ProtecT and PIVOT, have largely excluded or underrepresented patients with IR disease [10,11]. As a result, current evidence relies on observational studies that have varied in inclusion criteria, definitions, and surveillance protocols. As such, much uncertainty remains with regards to which patients with IR disease can safely pursue AS and what long-term outcomes to expect.

In this context, we present our institution's 18-year experience with AS for localized PCa, including a large cohort of men with FIR and unfavourable intermediate-risk (UIR) disease. Our aim is to provide real-world intermediate-term outcomes compared across the widely used NCCN PCa risk categories [6].

Subjects/Patients and Methods

Study Design and Population

A prospective institutional database was established in January 2004 to capture data from men with localized PCa managed with AS at the Manitoba Prostate Center. The present study represents a retrospective analysis of this prospectively maintained cohort, with a data cutoff of 31 December 2023. Approval for the study was obtained from the University and Cancer Center Research Ethics Board (HS25977).

Patients were classified based on NCCN risk categories, including VLR, LR, FIR, and UIR disease, according to the clinical T stage, grade group (GG), PSA level, PSA density, and extent of core involvement [6]. To ensure accurate classification and improve cohort specificity, we retrospectively reviewed all patients enrolled in the AS database.

Patients were excluded if they were managed with watchful waiting without confirmatory biopsy, underwent definitive treatment within 6 months of diagnosis, or had high-risk disease at presentation.

Surveillance Protocol

AS was offered to patients with LR disease and, in more recent years, to select patients with IR disease who prioritized quality of life despite a higher risk of progression. Patients were considered to be on AS after the initial positive diagnostic biopsy.

Patients generally underwent PSA testing and digital rectal examinations every 6 months. A confirmatory transrectal ultrasound-guided biopsy was recommended within 24 months of diagnosis. Subsequent surveillance biopsies were typically performed at intervals of 3–5 years or earlier if clinically indicated by rising PSA, changes on digital rectal exam, or concerning multiparametric magnetic resonance imaging (mpMRI) findings. Notably, through shared decision-making, some patients with stable PSA levels deferred subsequent surveillance biopsies and continued follow-up with semi-annual PSA testing and digital rectal examinations.

This biopsy schedule reflects real-world surveillance practices during the early years of cohort enrolment, when routine mpMRI was not yet widely available and biopsy intensity was largely determined by the patient's PSA. From approximately 2016 onward, mpMRI and MRI-targeted fusion biopsy were increasingly incorporated into surveillance and risk stratification at the discretion of the treating physician. However, most patients in this long-term cohort were enrolled and followed during the pre-MRI era and therefore did not undergo routine mpMRI as part of their surveillance.

Triggers for Treatment and Discontinuation of Active Surveillance

Recommendations for discontinuation of AS and initiation of definitive treatment differed by baseline risk group and were made through shared decision-making between patients and treating physicians.

For patients with VLR and LR disease, definitive treatment was recommended after biopsy reclassification/progression to GG ≥2. In the earlier years of the cohort, biopsy tumour volume progression (e.g., percentage of positive cores) was also used as a trigger for treatment, primarily among patients enrolled under Epstein criteria.

For patients with FIR disease, treatment was generally recommended upon upgrading to GG ≥3 or with the development of increasing tumour volume of GG 2 cores. Selected patients with FIR disease with limited GG 2 disease elected to remain on AS following shared decision-making.

For patients with UIR disease, definitive treatment was often recommended even in the absence of biopsy upgrading, reflecting the higher baseline oncologic risk; however, some patients elected to continue AS to preserve quality of life.

Outcomes and Definitions

The primary endpoint was treatment-free survival (TFS), defined as the time from enrolment on AS to the initiation of any PCa-directed therapy. AS enrolment was defined as the date of the initial positive biopsy. Secondary endpoints included overall survival (OS), PCa–specific survival (PCSS), and metastasis-free survival (MFS). Biopsy reclassification was defined as either (1) any increase in GG on a subsequent biopsy compared with the initial diagnostic biopsy ('grade reclassification') or (2) an increase in cancer volume, defined by a higher proportion of positive biopsy cores ('volume reclassification').

Statistical Analysis

All analyses were conducted in R version 4.3.1 using the EZR package. Baseline characteristics were summarized by NCCN risk group as medians (interquartile ranges [IQRs]) for continuous variables and counts (percentages) for categorical variables. Follow-up began at the diagnostic biopsy (time point 0). Patients who remained event-free or were lost to follow-up were censored at their last recorded visit.

Survival estimates were determined using Kaplan–Meier curves, and groups were compared using the global log-rank test. PCSS was analysed with cumulative incidence treating non-PCa death as a competing risk, with Grey's test for comparisons. We report 5-year event estimates with 95% confidence intervals (CIs).

Multivariable Cox proportional hazards models were used for each endpoint to estimate adjusted hazard ratios (HRs). Covariates were assessed at the diagnostic biopsy and selected to reflect NCCN risk components with strong prognostic value: age, PSA density, percent positive cores, and maximum core involvement. To avoid collinearity and overadjustment, NCCN risk group and GG were not included in these models. Biopsy grade was entered as GG 1 vs GG ≥2 to conserve events per variable and maintain model consistency. Raw PSA values were excluded because of collinearity with PSA density. Pairwise log-rank and Grey's tests were adjusted for multiple comparisons using the Holm method. All tests were two-sided, with P-values <0.05 considered statistically significant. Follow-up intensity was summarized descriptively, including observed biopsy frequency during follow-up by baseline risk group (Table S1).

Results

Study Cohort

Overall, 704 patients enrolled in the AS database, and 143 were excluded from analysis (Fig. S1). The final cohort included 227 patients with IR PCa and 334 with VLR or LR PCa (Table 1). Among patients with IR disease, 215 (95%) had GG ≥2 disease at diagnosis, including 190 with GG 2 and 25 with GG 3. Median age at diagnosis was 66 years (IQR 61–71) for IR disease and 64 years (IQR 58–68) for LR and VLR disease, and median follow-up duration was 4.4 years (IQR 2.5–9.6) for IR disease and 6.2 years (IQR 2.8–11.0) for LR and VLR disease. The median time to confirmatory biopsy was 13.1 months (IQR 11.5–19.2), and the median interval until surveillance biopsy was 25.5 months (IQR 14.0–39.3). A total of 261 patients were followed for at least 5 years and 128 for at least 10 years.

Transition to Definitive Treatment

During follow-up, 256 patients (45.6%) transitioned from AS to definitive treatment, with a median time to treatment of 2.89 years (IQR 1.64–6.54) (Table 1). The 5-year cumulative incidence of definitive treatment was 15.2% in the VLR group, 38.6% in the LR group, 50.0% in the FIR group, and 78.6% in the UIR group (Fig. 1; Table 2). TFS differed significantly across NCCN risk groups (global log-rank $P < 0.001$): patients with UIR disease were most likely to discontinue AS. Longer 10-year estimates are to be interpreted cautiously given the decreasing numbers at risk (Table S2).

In total, 209 patients (81.6%) underwent definitive treatment because of pathologic progression on biopsy; 156 because of grade reclassification/progression and 53 because of volume reclassification/progression (Fig. 2). Among the 47 men who underwent definitive treatment without biopsy reclassification/progression, four (8.5%) had VLR disease, 12 (25.5%) had LR disease, and 31 (66.0%) had IR disease. Patients with IR disease underwent confirmatory biopsy earlier than those with VLR or LR disease (Table 1). Among patients transitioning to treatment, 75 (29.3%) initially underwent radical prostatectomy, 40 (15.6%) received initial radiation therapy (external beam or brachytherapy), and 140 (54.7%) initially received only androgen-deprivation therapy. Many patients received combination therapy.

Predictors of Definitive Treatment

On multivariable Cox regression analysis, older age (HR 1.02 per year; 95% CI 1.00–1.04; $P = 0.026$), higher PSA density (HR 1.78; 95% CI 1.48–2.14; $P < 0.001$), and GG ≥2 (HR 1.52; 95% CI 1.13–2.06; $P = 0.006$) remained independent predictors of time to treatment. (Table 3).

Survival Outcomes: Overall Survival, Cancer-Specific Mortality, and Metastatic Disease

Survival outcomes stratified by NCCN risk group are summarized in Table 2. During follow-up, 79 men died, at a

Table 1 Baseline demographic and clinical characteristics by prostate cancer risk group.

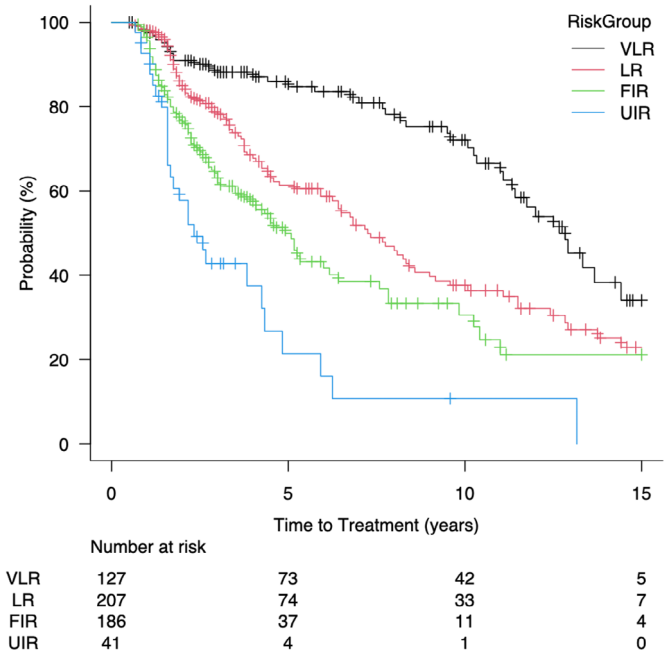
Characteristic	Initial risk group				Cohort (*n* = 561)
	Very low risk (*n* = 127)	Low risk (*n* = 207)	Intermediate-favourable (*n* = 186)	Intermediate-unfavourable (*n* = 41)	
Age at diagnosis, years	64 (58–68)	64 (58–68)	66 (60–71)	68 (65–73.5)	65 (59–69)
Year of diagnosis					
≤2016	94 (76.02)	122 (58.64)	60 (32.26)	12 (29.27)	288 (51.34)
≥2017	33 (25.98)	85 (41.06)	126 (67.02)	29 (70.73)	273 (48.66)
Grade group					
1	127 (100)	207 (100)	11 (5.91)	1 (2.44)	346 (61.68)
2	0 (0)	0 (0)	175 (94.09)	15 (36.59)	190 (33.87)
3	0 (0)	0 (0)	0 (0)	25 (60.98)	25 (4.46)
cT stage					
T1–T2a	48 (37.80)	82 (39.61)	9 (4.84)	3 (7.32)	142 (25.31)
T2b–T2c	0 (0)	0 (0)	4 (2.15)	1 (2.44)	5 (0.89)
PSA (ng/mL)	5.41 (3.55–7.16)	7.45 (6.11–8.53)	7.75 (5.71–10.57)	7.37 (5.58–9.00)	7.16 (5.33–8.88)
PSA density, ng/mL^2	0.091 (0.071–0.114)	0.194 (0.157–0.268)	0.197 (0.137–0.300)	0.186 (0.163–0.233)	0.167 (0.106–0.250)
Number of cores positive	1 (1–2)	2 (1–3)	2 (1–3)	6 (2–7)	2 (1–3)
Number of cores	12 (12–12)	12 (12–12)	12 (12–12)	12 (12–14)	12 (12–12)
Max % of cores positive	10 (5–20)	15 (10–30)	25 (12–40)	40 (25–80)	20 (10–35)
Confirmatory biopsy performed	112 (88.19)	181 (87.44)	147 (79.03)	28 (68.29)	468 (83.42)
Time to confirmatory biopsy, months	13 (11–17)	14 (11–22)	12 (11–18)	11.5 (10–14)	13 (11–19)
Surveillance biopsy performed	70 (55.12)	83 (40.10)	51 (27.42)	4 (9.76)	208 (37.08)
Number of surveillance biopsies performed	1 (0–2)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–1)
Follow-up duration, years	9.67 (3.17–12.83)	5.25 (2.50–9.75)	3.71 (2.42–6.04)	2.83 (1.92–6.13)	4.42 (2.50–9.58)
Grade progression	57 (44.88)	107 (51.69)	53 (28.49)	10 (24.39)	227 (40.46)
Time to grade progression, years	3.67 (1.13–8.29)	2.00 (1.17–5.42)	2.42 (1.00–4.54)	1.00 (0.79–4.15)	2.33 (1.08–5.83)
Volume progression	64 (50.39)	113 (54.59)	103 (55.38)	17 (41.46)	297 (52.94)
Time to volume progression, years	1.25 (1.00–5.04)	1.75 (1.08–3.38)	1.08 (0.92–2.75)	1.08 (0.96–2.71)	1.42 (1.00–3.29)
Active treatment	43 (33.86)	95 (45.89)	90 (48.39)	28 (68.29)	256 (45.63)
Time to active treatment, years	7.11 (1.76–11.49)	3.73 (1.88–7.72)	2.25 (1.35–3.98)	1.69 (1.26–3.26)	2.89 (1.64–6.54)
Metastasis	3 (2.36)	2 (0.97)	7 (3.76)	3 (7.32)	15 (2.67)
Prostate cancer deaths	1 (0.79)	1 (0.48)	3 (1.61)	2 (4.88)	7 (1.25)
Overall deaths	19 (2.36)	35 (16.91)	19 (10.22)	6 (14.63)	79 (14.08)

Data are presented as n (%) or median (interquartile range) unless otherwise indicated.

median age of 80 years (IQR 71–84), including seven deaths (1.2%) attributable to PCa (one VLR, one LR, three FIR, and two UIR). Both patients with VLR and those with LR disease who died of PCa received definitive external beam radiation therapy with androgen-deprivation therapy and died 11.5 and 12.7 years after initiating AS, respectively. The patient with VLR disease was diagnosed at age 69 years, demonstrated grade progression on biopsy after 6 years of surveillance, and died of metastatic castration-resistant PCa at age 81 years, 6 years after definitive treatment. The patient with LR disease was upgraded to high-volume GG 4 disease on repeat biopsy 2 years after diagnosis following a stable confirmatory biopsy. Among patients with IR disease, three with FIR disease experienced late grade progression, with two developing metastatic disease more than 10 years after diagnosis. Both patients with UIR disease were upgraded to high-risk disease on confirmatory biopsy at 12 months and nodal involvement at prostatectomy. Five-year OS remained high across all risk groups, ranging from 98.1% in patients with VLR disease to 91.8% in those with UIR disease (Table 2).

Metastatic progression occurred in 15 patients (2.7%) managed with AS, including 5/334 (1.5%) men with VLR/LR disease and 10/227 (4.4%) men with IR disease. The five with VLR/LR disease were all diagnosed before 2008 and had their grade reclassified to GG ≥2 within 2 years before receiving definitive treatment. Five-year MFS was 100% in patients with VLR and LR disease, 97.3% in those with FIR disease, and 96.7% in those with UIR disease (Table 2). UIR disease was associated with a significantly higher risk of metastasis than

Fig. 1 Treatment-free survival during active surveillance by National Comprehensive Cancer Network (NCCN) risk group. Kaplan–Meier estimates of time to initiation of definitive prostate cancer treatment, stratified by baseline NCCN risk group. Groups were compared using the log-rank test ($P < 0.001$). Numbers at risk are shown. FIR, favourable-intermediate risk; LR, low risk; UIR, unfavourable-intermediate risk; VLR, very low risk.



was VLR disease (HR 8.52; 95% CI 1.70–42.6; $P = 0.009$). MFS differed significantly by risk group, driven by higher event rates among patients with IR disease (Table S3).

Discussion

The role of AS in IR PCa remains uncertain and continues to evolve [1,5]. Existing randomized trials comparing radical treatment and AS have largely focused on LR disease or employed watchful waiting, limiting their applicability to men with IR PCa. This study reports an 18-year real-world experience of AS that included a substantial proportion of patients with IR disease who would not have been eligible for many protocol-driven programmes.

IR PCa encompasses a clinically heterogeneous population defined by a combination of adverse yet variably weighted features [9]. Although these parameters are often grouped under a single risk category, their prognostic implications differ significantly depending on the presence, severity, and interplay of individual features. For example, a patient with GG 2 disease, PSA <10 ng/mL, and limited biopsy involvement may have a prognosis more akin to that of LR disease, whereas another with high-volume pattern 4, elevated PSA density, and cribriform architecture may approach the biology of high-risk cancer.

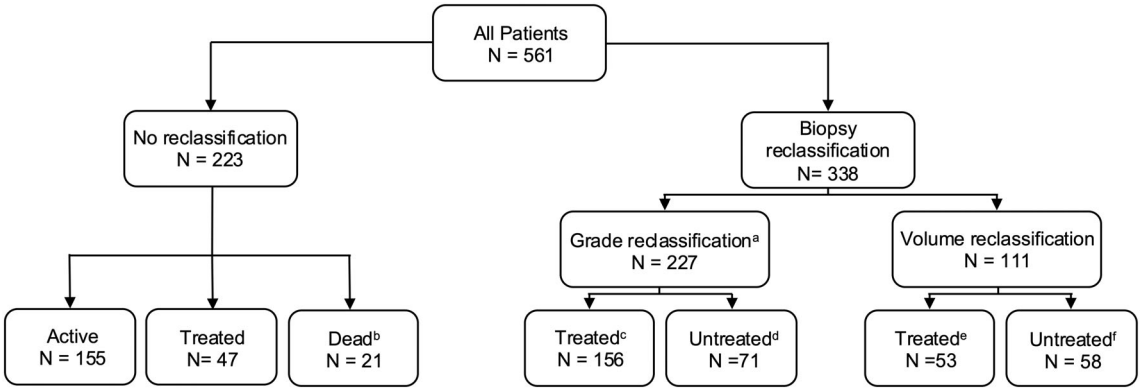
This heterogeneity is reflected in the composition of published IR AS cohorts. In the University of British

Table 2 Kaplan–Meier estimates and adjusted hazard ratios by National Comprehensive Cancer Network (NCCN) risk group across endpoints.

Endpoint	Risk group	Median (years, 95% CI)	5-year % (95% CI)	Adj HR vs VLR (95% CI); *P*-value
Treatment-free survival	VLR (ref.)	12.8 (11.3–14.4)	84.8 (76.5–90.3)	–
	LR	7.3 (6.3–8.6)	61.4 (53.0–68.7)	1.93 (1.35–2.78); <0.001*
	FIR	4.9 (3.9–6.2)	50.0 (41.0–58.3)	2.90 (2.00–4.21); <0.001*
	UIR	2.3 (1.6–4.3)	21.4 (7.6–39.7)	5.75 (3.53–9.36); <0.001*
	Global log-rank *P*: <0.001*; Wald (risk group) *P*: <0.001*			
Overall survival	VLR (ref.)	16.8 (16.8–NA)	98.1 (92.5–99.5)	–
	LR	17.0 (13.0–NA)	93.2 (87.6–96.3)	1.69 (0.96–2.95); 0.068
	FIR	NA (12.3–NA)	89.9 (81.8–94.6)	1.57 (0.83–2.99); 0.168
	UIR	14.4 (7.2–NA)	91.8 (71.1–97.9)	2.61 (1.04–6.56); 0.041*
	Global log-rank *P*: 0.132; Wald (risk group) *P*: 0.144			
Cumulative incidence of prostate cancer-specific death	VLR (ref.)	NA (NA–NA)	0.0 (0.0–0.0)	–
	LR	NA (NA–NA)	0.0 (0.0–0.0)	–
	FIR	NA (NA–NA)	0.0 (0.0–0.0)	–
	UIR	NA (11.8–NA)	0.0 (0.0–0.0)	–
	Grey's test *P*: 0.001*			
Metastasis-free survival	VLR (ref.)	NA (NA–NA)	100.0 (NA–NA)	–
	LR	NA (NA–NA)	100.0 (NA–NA)	0.60 (0.01–3.59); 0.574
	FIR	NA (NA–NA)	97.3 (91.9–99.1)	3.69 (0.94–14.48); 0.061
	UIR	NA (7.1–NA)	96.7 (78.6–99.5)	8.52 (1.70–42.57); 0.009*
	Global log-rank *P*: <0.001*; Wald (risk group) *P*: 0.008*			

*Kaplan–Meier analyses were performed for treatment-free, overall, and metastasis-free survival. Prostate cancer–specific death was summarized using cumulative incidence, with non–prostate cancer death treated as a competing event. Median time is reported in years with 95% CIs, and 5-year estimates are reported with 95% CIs. Cox proportional-hazards models were used for treatment-free, overall, metastasis-free, and progression-free survival to estimate adjusted HRs with 95% CIs, using VLR as the reference group. Global comparisons used the log-rank test (Kaplan–Meier endpoints) and Grey's test (competing risks). CI, confidence interval; FIR, favourable-intermediate risk; HR, hazard ratio; LR, low risk; NA, not applicable; UIR, unfavourable-intermediate risk; VLR, very-low risk. *P ≤ 0.05.*

Fig. 2 Flow diagram for the active surveillance cohort showing outcomes at the time of last follow-up. (a) Treatment is recommended in all cases of grade reclassification. (b) Includes no prostate cancer deaths among untreated patients. (c) Includes 21 deaths from non–prostate cancer causes and five from prostate cancer after treatment. (d) Includes 11 deaths from non–prostate cancer causes and no prostate cancer deaths. (e) Includes seven deaths from non–prostate cancer causes and one from prostate cancer after treatment. (f) Includes seven deaths from non–prostate cancer causes and none from prostate cancer. AS, active surveillance; PCa, prostate cancer.



Columbia, University of Toronto, and University of California, San Francisco, cohorts, 38.2%, 39.8%, and 68% of patients with IR disease, respectively, were classified based on a PSA of 10–20 ng/mL rather than biopsy GG ≥2 [12–14]. In contrast, 95% of patients with IR disease in our cohort were classified as IR based on diagnostic GG ≥2. Differences in tumour volume further underscore this point: the median percentage of positive biopsy cores was 17% in FIR disease and 50% in UIR disease in our series, compared with 12.5% and 13% reported for IR cohorts at the University of British Columbia and the University of California, San Francisco, respectively. These differences may reflect a higher burden of adverse pathology within our IR cohort that is not captured in the existing literature.

Our main finding was that the transition to definitive treatment differed significantly across all risk groups, with TFS declining stepwise from VLR to UIR disease. On multivariable analysis, older age, higher PSA density, and GP ≥2 disease were independent predictors of discontinuation of AS. These findings mirror the Canary Prostate Active Surveillance Study and Memorial Sloan Kettering Cancer Center experiences, both of which showed that patients with GG 2 disease underwent definitive treatment at higher rates despite similar frequencies of biopsy reclassification [15,16]. Likewise, in our cohort, the higher treatment rate was driven primarily by more frequent intervention among men with IR disease who were not reclassified than among men with LR disease who were not reclassified. This pattern likely reflects patient and provider risk tolerance, given ongoing uncertainty regarding AS for IR disease and counselling around the higher risk of progression and limited consensus supporting this practice.

Our cohort reflects real-world AS practice, with the use of surveillance biopsies guided by PSA kinetics and shared-decision making rather than strict adherence to a highly protocolized follow-up schedule. Prior data from the Prostate Cancer Research International Active Surveillance (PRIAS) study, which mandated repeat biopsies at 1, 4, 7, and 10 years after diagnosis, demonstrated that compliance with surveillance biopsies declined substantially over time, whereas adherence to PSA monitoring remained high [3,17]. Importantly, although reduced biopsy compliance was associated with higher rates of grade reclassification, most men continued to exhibit favourable disease characteristics. In this context, despite employing fewer surveillance biopsies than highly protocolized programmes – such as PRIAS or Johns Hopkins' annual biopsies – oncologic outcomes in our cohort remained excellent [3,18].

Metastatic progression remained very low overall (2.67%) but was significantly more frequent in patients with UIR disease (7.32%). All metastatic events in the VLR and LR groups occurred early in the study period when diagnostic sampling and risk stratification were less refined than in contemporary practice. PCa-specific mortality was low, at 1.25%, but again highest in patients with UIR disease. Our results are consistent with those from the University of Toronto AS cohort, which demonstrated significantly worse MFS and PCSS in the IR cohort than in the LR cohort [13]. These results reaffirm the oncologic safety of AS in patients with LR and FIR disease, while highlighting elevated risks among men with UIR disease.

Our results align closely with recent guideline updates and expert consensus. The 2024 European Association of Urology guidelines endorse AS as a viable option for select patients with FIR disease, and the DETECTIVE systematic review and consensus study published in 2022 provides a structured framework for inclusion [5,19]. The DETECTIVE group

Table 3 Treatment-free survival (TFS) by baseline predictors in men on active surveillance.

a

	Univariate		Multivariate	
	Adjusted HR (95% CI)	***P*-value**	**Adjusted HR (95% CI)**	***P*-value**
Age	1.03 (1.01–1.05)	0.001*	1.02 (1.00–1.04)	0.026*
Log2PSA density	1.90 (1.62–2.22)	<0.001*	1.78 (1.48–2.14)	<0.001*
Grade group (1 vs ≥2)	2.04 (1.58–2.63)	<0.001*	1.52 (1.13–2.06)	0.006*
% Positive cores	1.02 (1.01–1.03)	<0.001*	–	–
Max % cancer/core	1.01 (1.01–1.02)	<0.001*	–	–

b

Predictor	**Median TFS, years (95% CI)**	**Log-rank *P*-value**	**HR (95% CI)**	**Cox *P*-value**
Age <65 (ref.)	10.08 (7.75–11.42)			
Age ≥65	5.92 (4.50–7.83)	0.002*	1.47 (1.15–1.89)	0.002*
PSA density <0.15 (ref.)	12.50 (11.00–14.42)			
PSA density ≥0.15	4.42 (3.75–5.25)	<0.001*	2.79 (2.06–3.80)	<0.001*
Grade group 1 (ref.)	10.08 (8.17–11.50)			
Grade group ≥2	4.33 (3.50–5.33)	<0.001*	2.04 (1.58–2.63)	<0.001*

*(a) Multivariable Cox regression showing associations between baseline predictors and time to treatment. (b) Kaplan–Meier analysis of TFS by age, PSA density, and grade group. CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen. *P ≤ 0.05.*

recommended AS in patients with low-volume GG 2 (up to three positive cores, ≤50% core involvement), PSA density <0.15 ng/mL/cm^3, and absence of cribriform or intraductal histology. Most patients with FIR disease in our cohort met these criteria, and their outcomes were similar to those of patients with LR disease. The consensus group also recommends confirmatory biopsy within 2 years and continued surveillance biopsies at least every 3 years in protocols not incorporating routine mpMRI, mirroring our institutional practice. Conversely, outcomes for patients with UIR disease suggest that AS should be offered with caution, if at all.

Future Directions

The growing use of mpMRI has improved risk stratification and lesion localization in PCa, including among men on AS [20,21]. An upfront MRI and an MRI-guided biopsy led to a reduction in AS cessation rate from 59% to 20% in a 4-year follow-up period [22]. MRI-targeted biopsy enhances detection of clinically significant disease, but its implications for patients with IR disease continue to evolve. Recent large cohorts provided important insights. In a University of California, Los Angeles, study of nearly 900 men, MRI reliably identified stable cancers and predicted non-progression in 70% of patients with IR disease [23]. Similarly, a UK cohort of 1150 patients in an MRI-led, risk-adapted AS programme found that MRI visibility and secondary GP4 were strongly associated with treatment and progression, with 5-year event-free survival ranging from 91% in MRI-invisible GG 1 to 44% in MRI-visible GG 2 disease [24]. Notably, metastatic progression occurred only in men who did not comply with MRI or biopsy recommendations, underscoring the safety of MRI-driven protocols when adhered to. Collectively, these findings suggest that MRI may reduce reliance on scheduled biopsies, but further studies are needed to determine how MRI findings should best guide eligibility, intensity of follow-up, and intervention triggers in IR populations.

Beyond GG progression, other markers of disease burden such as percent GP4 or GP4 length may be used as a predictor of adverse outcomes in patients with IR disease. One study showed that ≥2 mm of GP4 on biopsy significantly increased the risk of adverse pathology and biochemical recurrence [25]. Similarly, another study found that patients with GG 2 and <20% GP4 had a relatively low risk of adverse pathology and were more suitable for AS [26]. Notably, some patients with rising GP4 length would not be flagged by traditional criteria for GG 3, underscoring the limitations of categorical upgrading alone. Incorporating GP4 quantification, tissue-based genomic classifiers, and blood-based markers such as circulating tumour cells/DNA into surveillance protocols could refine treatment thresholds and improve individualized decision-making for patients with IR disease.

This study has several limitations. First, its retrospective design is subject to inherent biases, including selection and information bias. Although patients were prospectively enrolled in an AS registry, management decisions were made through shared decision-making, and surveillance protocols were not strictly standardized across the study

period. Relatedly, not all patients had subsequent surveillance biopsies if their PSA remained stable (Table S1), which may have influenced the detection of upgrading. Surveillance biopsy intensity in this cohort was relatively low, with many patients undergoing only one or no surveillance biopsies during follow-up. As a result, the true rate of grade reclassification may be underestimated compared with highly protocolized AS programmes that mandate more frequent repeat biopsies. Additionally, some patients were lost to follow-up, which may have resulted in under-ascertainment of adverse oncologic outcomes such as adverse pathology at surgery, biochemical recurrence after treatment, or metastatic progression. Second, mpMRI is underutilized at our institution and was not uniformly applied, particularly in the earlier years of the cohort, potentially introducing variability in diagnostic accuracy and progression detection. MRI data were therefore incomplete and not systematic across the cohort, limiting our ability to present and evaluate MRI findings as standardized predictors. Third, although we excluded men ultimately managed with watchful waiting, misclassification may still have occurred in some borderline cases. Fourth, reporting of GP4 burden (volume or percent) was inconsistent across pathology reports. Fifth, race and/or ethnicity were not captured in the database and could not be evaluated. Lastly, although our median follow-up of 4.5 years is adequate for assessing treatment patterns and early progression, longer follow-up is necessary to fully evaluate metastatic and cancer-specific outcomes in patients with IR disease.

Conclusion

In this real-world AS cohort, the likelihood of remaining on surveillance differed substantially by baseline risk, with UIR disease associated with earlier transition to treatment and higher risks of progression. Older age, higher PSA density, and GG ≥2 were independently associated with discontinuation of AS. Despite the less intensive surveillance protocols, the rates of metastatic progression and pCA-specific mortality remained low, particularly among patients with LR or FIR disease, supporting AS as a viable management strategy in carefully selected men beyond LR disease.

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Disclosure of Interests

None declared.

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References

1 **Eastham JA, Auffenberg GB, Barocas DA et al.** Clinically localized prostate cancer: AUA/ASTRO guideline, part I: Introduction, risk assessment, staging, and risk-based management. *J Urol* 2022; 208: 10–8
2 **Klotz L, Vesprini D, Sethukavalan P et al.** Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol* 2015; 33: 272–7
3 **Bokhorst LP, Valdagni R, Rannikko A et al.** A decade of active surveillance in the PRIAS study: an update and evaluation of the criteria used to recommend a switch to active treatment. *Eur Urol* 2016; 70: 954–60
4 **Carlsson S, Benfante N, Alvim R et al.** Long-term outcomes of active surveillance for prostate cancer: the memorial Sloan Kettering cancer center experience. *J Urol* 2020; 203: 1122–7
5 **Cornford P, Van Den Bergh RCN, Briers E et al.** EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer—2024 update. Part I: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2024; 86: 148–63
6 **Schaeffer EM, Srinivas S, Adra N et al.** Prostate cancer, version 3.2024: featured updates to the NCCN guidelines. *J Natl Compr Cancer Netw* 2024; 22: 140–50
7 **Zumsteg ZS, Spratt DE, Pei I et al.** A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol* 2013; 64: 895–902
8 **Masic S, Cowan JE, Washington SL et al.** Effects of initial Gleason grade on outcomes during active surveillance for prostate cancer. *Eur Urol Oncol* 2018; 1: 386–94
9 **Preisser F, Cooperberg MR, Crook J et al.** Intermediate-risk prostate cancer: stratification and management. *Eur Urol Oncol* 2020; 3: 270–80
10 **Hamdy FC, Donovan JL, Lane JA et al.** Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2023; 388: 1547–58
11 **Wilt TJ, Jones KM, Barry MJ et al.** Follow-up of prostatectomy versus observation for early prostate cancer. *N Engl J Med* 2017; 377: 132–42
12 **Savdie R, Aning J, So AI, Black PC, Gleave ME, Goldenberg SL.** Identifying intermediate-risk candidates for active surveillance of prostate cancer. *Urol Oncol Semin Orig Investig* 2017; 35: 605.e1–605.e8
13 **Musunuru HB, Yamamoto T, Klotz L et al.** Active surveillance for intermediate risk prostate cancer: survival outcomes in the Sunnybrook experience. *J Urol* 2016; 196: 1651–8
14 **Cooperberg MR, Cowan JE, Hilton JF et al.** Outcomes of active surveillance for men with intermediate-risk prostate cancer. *J Clin Oncol* 2011; 29: 228–34
15 **Waisman Malaret AJ, Chang P, Zhu K et al.** Evaluating the outcomes of active surveillance in grade group 2 prostate cancer: prospective results from the canary PASS cohort. *J Urol* 2022; 207: 805–13
16 **Carlsson S, Benfante N, Alvim R et al.** Risk of metastasis in men with grade group 2 prostate cancer managed with active surveillance at a tertiary cancer center. *J Urol* 2020; 203: 1117–21
17 **Bokhorst LP, Alberts AR, Rannikko A et al.** Compliance rates with the prostate cancer research international active surveillance (PRIAS) protocol and disease reclassification in noncompliers. *Eur Urol* 2015; 68: 814–21

18 **Tosoian JJ**, **Mamawala M**, **Epstein JI et al.** Active surveillance of grade group 1 prostate cancer: long-term outcomes from a large prospective cohort. *Eur Urol* 2020; 77: 675–82
19 **Willemse PPM**, **Davis NF**, **Grivas N et al.** Systematic review of active surveillance for clinically localised prostate cancer to develop recommendations regarding inclusion of intermediate-risk disease, biopsy characteristics at inclusion and monitoring, and surveillance repeat biopsy strategy. *Eur Urol* 2022; 81: 337–46
20 **Kasivisvanathan V**, **Rannikko AS**, **Borghi M et al.** MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018; 378: 1767–77
21 **Kim SP**, **Karnes RJ**, **Mwangi R et al.** Contemporary trends in magnetic resonance imaging at the time of prostate biopsy: results from a large private insurance database. *Eur Urol Focus* 2021; 7: 86–94
22 **Dieffenbacher S**, **Nyarangi-Dix J**, **Giganti F et al.** Standardized magnetic resonance imaging reporting using the prostate cancer radiological estimation of change in sequential evaluation criteria and magnetic resonance imaging/transrectal ultrasound fusion with transperineal saturation biopsy to select men on active surveillance. *Eur Urol Focus* 2021; 7: 102–10
23 **Martin SC**, **Gonzalez S**, **Kwan L et al.** Evolution of active surveillance of prostate cancer: impact of magnetic resonance imaging, magnetic resonance imaging–guided biopsy, and focal therapy. *J Urol* 2025; 214: 177–87
24 **Englman C**, **Adebusoye B**, **Maffei D et al.** Magnetic resonance imaging–led risk-adapted active surveillance for prostate cancer: updated results from a large cohort study. *Eur Urol* 2025; 88: 167–75
25 **Perera M**, **Assel MJ**, **Benfante NE et al.** Oncologic outcomes of total length Gleason pattern 4 on biopsy in men with grade group 2 prostate cancer. *J Urol* 2022; 208: 309–16
26 **Cole AI**, **Morgan TM**, **Spratt DE et al.** Prognostic value of percent Gleason grade 4 at prostate biopsy in predicting prostatectomy pathology and recurrence. *J Urol* 2016; 196: 405–11

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Abbreviations: AS, active surveillance; CI, confidence interval; FIR, favouravle intermediate risk; GG, grade group; GP4, Gleason pattern 4; HR, hazard ratio; IQR, interquartile range; IR, intermediate risk; LR, low risk; MFS, metastasis-free survival; mpMRI, multi parametric magnetic resonance imaging; OS, overall survival; PCa, prostate cancer; PCSS, prostate cancer-specific survival; PSA, prostate specific antigen; TFS, treatment-free survival; UIR, unfavourable intermediate risk; VLR, very low risk.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Cohort selection and NCCN risk-group stratification for the active surveillance study.

Table S1. Observed biopsy intensity during follow-up by risk group.

Table S2. Ten-year event estimates corresponding to endpoints in Table 2.

Table S3. Metastasis-free survival: pairwise log-rank *P* values between NCCN risk groups in men on active surveillance.

