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Prostate Cancer

Active Surveillance—Is It Feasible for Intermediate-risk Localised Prostate Cancer?

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Abstract

Background: Although active surveillance (AS) is a well-recognised treatment option for localised low-risk prostate cancer (LRPC), its role in the management of localised intermediate-risk prostate cancer (IRPC) is not clear yet and the available literature is slightly contradictory.
Objective: To compare the outcome of AS between LRPC and IRPC patients.
Design, setting, and participants: Between November 2002 and August 2019, 372 men with localised prostate cancer (PC) underwent AS in our hospital based on local departmental protocol.
Outcome measurements and statistical analysis: The primary outcome measures were overall survival, disease progression–free survival, treatment-free survival, and biochemical recurrence–free survival. Survival times in the low- and intermediate-risk groups were compared using Cox regression analysis.
Results and limitations: Out of 372 localised PC patients, 276 (74%) had LRPC and 96 (26%) IRPC. Overall, 86 (31.2%) low-risk and 25 (26%) intermediate-risk patients developed disease progression, and 86 (31.2%) low-risk and 22 (23%) intermediate-risk patients underwent active treatment. Among the treated patients, eight (2.9%) LRPC patients and one (1%) IRPC patient developed biochemical recurrence. In total, only one patient (from the low-risk group) had metastasis and 25 patients passed away (18 from the low-risk and seven from the intermediate-risk group). No death was recorded due to PC in the cohort. There was no difference in any of the survival outcomes between LRPC and IRPC patients in unadjusted analysis as well as when analysis was performed after adjusting the potentially confounding factors. Limitations include relatively short median follow-up time and failure to objectively define the criteria for the selection of IRPC patients suitable for AS.
Conclusions: The option of AS could be considered for carefully selected and well-informed patients with IRPC provided close structured monitoring is maintained.

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Patient summary: In this report, we looked at various survival outcomes of active surveillance between low- and intermediate-risk prostate cancer patients in a large British population. There was no difference in any of the survival outcomes between the two groups. We concluded that carefully selected intermediate-risk prostate cancer patients could be offed the option of active surveillance.
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1. Introduction

Active surveillance (AS) or deferred treatment is a well-recognised treatment option for localised low-risk prostate cancer (LRPC) [1–5]. In the PRIAS study, Bokhorst et al. [5] presented prospective follow-up data of 5302 LRPC patients who were managed with AS across 18 countries. Patients with histological progression (Gleason score [GS] >6 or >2 positive biopsy cores), clinical stage progression (>cT2), or prostate-specific antigen (PSA) doubling time >3 yr (until 2014) were offered active treatment. It was observed that 52% of patients at 5 yr and 73% of patients at 10 yr discontinued expectant treatment after following the protocol. Surprisingly, it was noted that around one-third of men did not necessarily need active treatment as their tumour histology on radical prostatectomy specimen lacked unfavourable features. In this study, AS was considered to be a safe treatment option for LRPC men, and upgrading of GS as well as cT3 was proposed to be the only indicators for offering active intervention to LRPC men on AS.

Interestingly, the indication of AS has gradually expanded from the LRPC to the intermediate-risk prostate cancer (IRPC) group, and there is an increasing trend to manage IRPC patients expectantly. Here, we compared the outcome of AS between these two groups with an intention to assess the feasibility and safety of AS for the treatment of IRPC patients.

2. Patients and methods

2.1. Study population

Between November 2002 and August 2019, a prospective database was maintained for patients with localised prostate cancer (PC) who underwent initial expectant management in our hospital based on local departmental protocol.

2.2. Inclusion and exclusion criteria

This is a real-life experience of the management of PC by AS in a district general hospital in the UK. In the beginning, the inclusion and exclusion criteria were not very strict, and were partly influenced by the physicians and the patients. Initially, only low-risk patients were offered the option of expectant management; however, after development of confidence, selected intermediate-risk patients were also managed with AS. Most of the men with localised LRPC (PSA <10 ng/ml, GS 6, digital rectal examination [DRE] assessed clinical stage ≤cT2a) were offered the option of initial expectant management. In addition, some carefully selected patients with localised IRPC (PSA 10–20 ng/ml or GS 7 or clinical stage cT2b) were also given the same choice after discussion in the urology cancer multidisciplinary meeting (MDM). A magnetic resonance imaging (MRI) scan, when available, showed organ-confined disease in all cases. All patients underwent a detailed discussion in the clinic regarding the alternative options such as radical prostatectomy or radiotherapy, and thereafter, those who agreed for AS were included in this study. On the contrary, patients who denied the option of AS or wanted few months to make up their minds regarding the treatment and then finally decided to go for some active intervention were excluded.

2.3. Follow-up protocol

Our follow-up protocol was adapted mainly from the National Institute for Health and Care Excellence (NICE) guideline and was modified over a period of time. Our current follow-up policy since 2014 includes the following: (1) PSA testing every 3 mo for the 1st year, followed by every 6 mo for rest of the follow-up period; (2) DRE every 6 mo for the 1st year, followed by every 12 mo for rest of the follow-up period; (3) MRI scan at enrolment and subsequently every 2 yr; and (4) transperineal template biopsy at 1 yr unless already performed prior to that. MRI at enrolment was not performed routinely during the initial years, and transperineal biopsy was started in our hospital in 2011.

2.4. Evaluation

During the period of AS, if any patient had two consecutive rises in the PSA or change in the DRE finding (development of any new suspicious nodule), the case was discussed in urology cancer MDM and generally either repeat biopsy or active intervention was offered depending upon the merit of the case. Our latest protocol from 2014 suggests MRI scan in such patients before MDM discussion to help in decision-making. Patients who had worsening MRI findings or histological progressions (either higher GS or increased tumour volume in repeat biopsy compared with previous biopsy) were also offered active intervention after MDM discussion. In addition, patients who wanted to stop AS by themselves were treated actively. The primary outcome measures were overall survival, disease progression–free survival, treatment-free survival, and biochemical recurrence–free survival.

2.5. Statistical analysis

Statistical analysis was performed by an independent statistician. The first set of analyses compared the baseline characteristics of the low- and intermediate-risk groups. Continuous variables are summarised by the mean and standard deviation if normally distributed, and the median and interquartile range otherwise. Categorical variables are summarised by the number and percentage of patients in each category. Continuous variables found to follow a normal distribution were compared using the unpaired *t* test. The Mann-Whitney *U* test was preferred for continuous variables not found to be normally distributed. Categorical variables were compared between groups using the chi-square test.

Second, patient outcomes were compared between the two risk groups. The outcomes were all “survival” in nature and were thus analysed using survival analysis methods. The time to the event was

measured for those undergoing an event. Patients not undergoing an event were censored at the time of last known follow-up. Survival times in the low- and intermediate-risk groups were compared using Cox regression. All patients were included in the analyses for overall survival time, time to progression, and time to intervention. However, only patients undergoing an intervention were included in the time to relapse analysis. For this last analysis, the time to relapse was measured from the time of the intervention. Biochemical relapse was defined as PSA >0.2 ng/ml after radical prostatectomy and PSA >2 ng/ml above nadir value after radiotherapy.

Two sets of analyses were performed. The first "unadjusted" analysis compared the survival times of the two groups without considering any further factors. A second "adjusted" analysis adjusted the group differences for baseline factors found to significantly vary between the two groups from the first set of analyses. Adjustments were made only for factors that were not part of the risk group definitions. Serum PSA, GS, and clinical T stage were all part of the risk group definition and therefore not adjusted for. Additionally, as PSA density was based on the PSA values, which was part of the group definition, this was also not adjusted for.

Patients deemed to be of high risk were omitted from all analyses. Analysis has been two tailed, and $p < 0.05$ was considered statistically significant. Stata (version 15.1; Stata Corp., College Station, TX, USA) was used for statistical analysis.

3. Results

3.1. Baseline characteristics of the study population

During the study period of nearly 17 yr, 372 men with localised PC underwent AS in our hospital; out of them, 276 (74%) patients were at low risk and 96 (26%) were at intermediate risk. Four patients with IRPC had both PSA ≥10 and GS 3 + 4. No patients had primary Gleason 4 disease. Fifteen patients (4%) either were lost to follow-up or continued their care in some other hospitals. In total, 204 (55%) men—141 (51%) from the low-risk and 63 (66%) from the intermediate-risk group—had an MRI scan before enrolment for AS, and all of them showed organ-confined disease. A summary of the baseline characteristics of the low- and intermediate-risk groups is given in Table 1.

The results suggested that the low- and intermediate-risk groups differed significantly in terms of PSA levels, age, GS, clinical T stage, the type of the first biopsy, the number of biopsies, and PSA density. However, there was no significant difference between the two groups for prostate volume or the number of positive cores.

Patients in the intermediate-risk group were on average 2 yr older (mean age 63.6 yr for IRPC vs 65.5 yr for LRPC, $p = 0.01$) than the patients in the-low risk group. In addition, a significantly higher proportion of IRPC patients underwent initial transperineal template biopsy (32%) compared with LRPC patients (18%), and the number of biopsies was significantly higher in the intermediate-risk group; however, there was relatively little difference in the median value, which was 13 in the intermediate-risk group and 12 in the low-risk group.

3.2. Follow-up period

Intermediate-risk patients had a significantly shorter median total follow-up period (49 mo for IRPC vs 58.5 mo for LRPC, $p = 0.009$) than low-risk men. However, there was no significant difference in the median duration of AS between these two groups (32.5 mo for IRPC vs 36 mo for LRPC, $p = 0.53$). In total, 135 (49%) LRPC and 38 (40%) IRPC patients were observed for >5 yr, and 27 (10%) LRPC and three (3%) IRPC patients were observed for >10 yr. The follow-up period and overall outcomes of AS are compared between LRPC and IRPC patients in Table 2.

3.3. Follow-up biopsy, disease progression, and intervention

Altogether, 199 patients underwent the first follow-up biopsy (LRPC 151 [54.7%] and IRPC 48 [50%], $p = 0.43$) and 32 patients (LRPC 26 [9.4%] and IRPC six [6.3%], $p = 0.35$)

Table 1 – Baseline characteristics of low- and intermediate-risk prostate cancer patients

Variable	Category	Low risk (n = 276)	Intermediate risk (n = 96)	p value
PSA (ng/ml)	–	5.7 (4.2–7.0)	7.3 (4.2–10.8)	<0.001
PSA (categorised; ng/ml)	<10	276 (100)	57 (59)	<0.001
	≥10	0 (0)	39 (41)	
Age	–	63.6 ± 6.6	65.5 ± 6.7	0.01
Gleason score	3 + 3	276 (100)	41 (43)	<0.001
	3 + 4	0 (0)	55 (57)	
Clinical T stage	T1a	24 (9)	13 (14)	0.006
	T1b	11 (4)	5 (5)	
	T1c	194 (70)	52 (54)	
	T2a	47 (17)	23 (24)	
	T2b	0 (0)	3 (3)	
Type of first biopsy	TRUS	189 (68)	47 (49)	0.002
	Template	51 (18)	31 (32)	
	TURP	36 (13)	18 (19)	
Prostate volume	–	50 (37–70)	48 (33–67)	0.36
No. of biopsies	–	12 (12–15)	13 (12–30)	<0.001
No. of positive cores	–	1 (1–2)	1 (1–2)	0.57
PSA density	–	0.11 (0.09, 0.14)	0.15 (0.10, 0.21)	<0.001

Summary statistics are as follows: mean ± standard deviation, median (interquartile range), or n (%).
PSA = prostate-specific antigen; TRUS = transrectal ultrasound; TURP = transurethral resection of the prostate.

Table 2 – Follow-up period and overall outcomes of active surveillance of low- and intermediate-risk prostate cancer patients

Variable	Category	Low risk (*n* = 276)	Intermediate risk (*n* = 96)
Total follow-up period (yr)	–	4.9 (2.6–7.8)	4.1 (2.2, 6.1)
Period of active surveillance (yr)	–	3.0 (1.5–5.6)	2.7 (1.7, 4.9)
Follow-up after treatment (yr)	–	4.0 (2.2–6.0)	3.7 (1.5, 5.8)
Disease progression	–	86 (31.2)	25 (26)
Disease progression (categorised)	Histological	55 (20)	11 (11.5)
	Radiological	17 (6.2)	3 (3.1)
	Biochemical	14 (5.1)	11 (11.5)
Definitive treatment	–	86 (31.2)	22 (23)
Definitive treatment (categorised)	RP	62 (22.5)	10 (10.4)
	EBRT	21 (7.6)	10 (10.4)
	Brachytherapy	3 (1.1)	2 (2.1)
Overall survival probability	5 yr	93 (88, 96)	93 (81, 97)
	10 yr	90 (83, 94)	80 (50, 93)
Disease progression–free survival probability	5 yr	62 (55, 69)	64 (51, 75)
	10 yr	54 (44, 62)	64 (51, 75)
Treatment-free survival probability	5 yr	63 (55, 69)	69 (56, 79)
	10 yr	54 (44, 62)	69 (56, 79)
Biochemical recurrence–free survival probability [a]	5 yr	90 (79, 95)	100 (–)

Summary statistics are as follows: *n* (%), median (interquartile range), or % (95% confidence interval).
EBRT = External beam radiotherapy; RP = Radical prostatectomy.
[a] Analysis for patients undergoing active treatment only.

had the second follow-up biopsy. An upgrade in GS was observed in 57 patients (LRPC 48 out of 151 [31.8%] and IRPC nine out of 48 [18.8%], $p = 0.084$) after the first follow-up biopsy and six patients (LRPC six out of 26 [23%] and IRPC zero out of six [0%], $p = 0.2$) after the second follow-up biopsy.

Overall, 111 (29.8%) patients had disease progression—86 (31.2%) from the low-risk group and 25 (26%) from the intermediate-risk group, with no significant difference between them ($p = 0.35$). Noticeably, no disease progressed beyond the scope of active treatment.

Seven (2.5%) patients from the low-risk group and three (3%) patients from the intermediate-risk group denied active treatment despite the evidence of disease progression. Another patient from the low-risk group who had histological progression on repeat biopsy passed away from lymphoma before active intervention. On the contrary, eight patients, all from the low-risk group, chose active treatment without having any features of disease progression because of anxiety associated with AS. Therefore, active treatment was ultimately offered to 108/372 (29%) patients. This comprised 86 (31.2%) LRPC patients and 22 (22.9%) ILPC patients, again without any difference between these two groups ($p = 0.12$).

Histology result was available for 71/72 patients who underwent radical prostatectomy—61 from the LRPC group and 10 from the IRPC group. It was observed that 53/61 LRPC patients (87%) and four out of 10 IRPC patients (40%) had progression in GS in final histology compared with initial biopsy ($p = 0.006$).

3.4. Biochemical recurrence and metastasis

Of the 108 men treated, nine (8.3%) experienced biochemical recurrence, representing 2.4% of the overall cohort (nine/372 patients). Among the nine patients with PSA relapse, eight (2.9%) belonged to the LRPC group (mean time for PSA recurrence from diagnosis was 5.3 yr and that from curative treatment was 2.7 yr) and one (1%) to the IRPC group (time for PSA recurrence from diagnosis was 7 yr and that from curative treatment was 5.8 yr) without any significant difference between them ($p = 0.310$).

During the period of our study, only one patient from the low-risk group with a presenting PSA level of 5.2 ng/ml and GS of 3 + 3 = 6 on transrectal ultrasound biopsy developed metastasis 7.5 yr after diagnosis. He did not have a prebiopsy MRI scan. There was histological progression (GS 4 + 4) on repeat biopsy, and he received neoadjuvant hormone treatment with external-beam radiotherapy. He subsequently developed biochemical recurrence after 1.5 yr and bony metastasis after 5.5 yr. He was still alive at the time of final data collection.

3.5. Mortality

Among 378 patients, 25 (6.6%) died (18 from the low-risk group and seven from the intermediate-risk group, $p = 0.8$) and the remaining 353 are alive (censored rate, 93.4%). All deaths were from confirmed other medical reasons; no death was recorded due to PC in the cohort.

3.6. Survival analysis

Graphical illustrations of the survival outcomes are shown in Figures 1–4, and a summary of the results is given in Table 3. First shown are the hazard ratios (HRs) from the survival analyses, which are presented with corresponding confidence intervals (CIs). These give the hazard (or risk) of each outcome occurring at any stage in the follow-up in the intermediate-risk group relative to the hazard in the low-risk group. The *p* values indicating the significance of the group differences are also presented. The results suggested that there was no significant difference in any of the survival outcomes between groups in the unadjusted analyses,

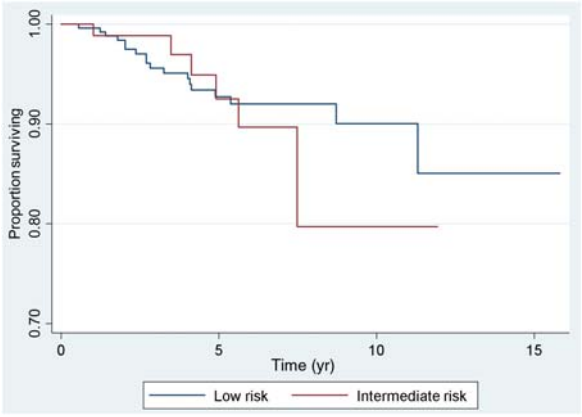

Fig. 1 – Kaplan-Meier plot of overall survival.

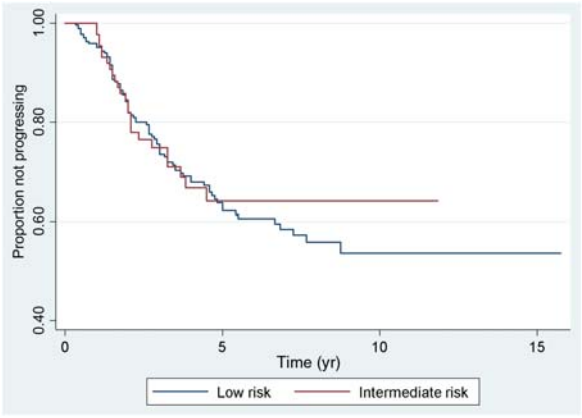

Fig. 2 – Kaplan-Meier plot of time to progression.

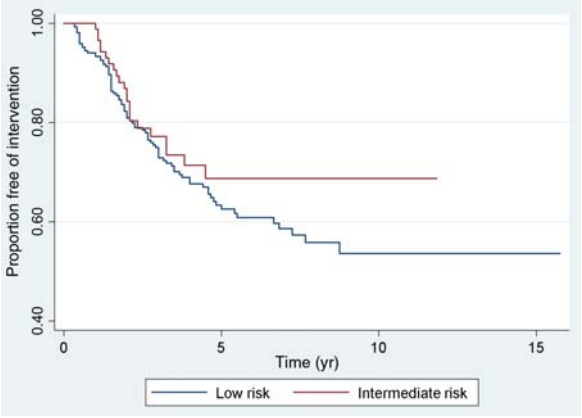

Fig. 3 – Kaplan-Meier plot of time to intervention.

when the baseline factors were not taken into consideration. After adjusting for potentially confounding variables, there was also no significant difference in any of the survival times between the two risk groups.

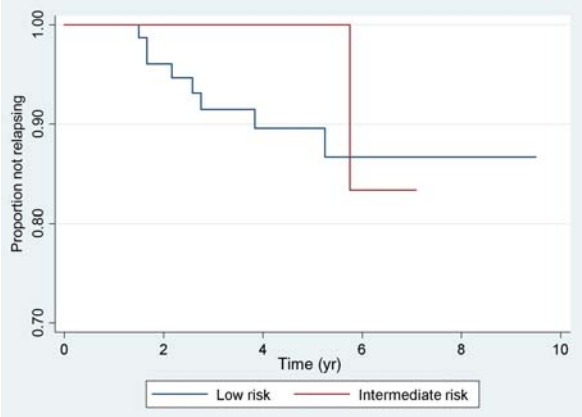

Fig. 4 – Kaplan-Meier plot of time to relapse (for patients undergoing intervention).

4. Discussion

AS essentially delays or preferably avoids active intervention and associated complications for men with localised PC, whilst retaining the option of definitive treatment for those patients who manifest evidence of disease progression without losing the window of curability [6,7]. It thus minimises the risk of overtreatment for men with clinically insignificant PC [8]. This strategy is widely accepted as one of the treatment options for LRPC patients along with radical prostatectomy and radical radiotherapy [1–5]. However, there is a general hesitation to suggest AS for men with IRPC, and evidence available in the literature is slightly contradictory.

On the one hand, some studies suggest that AS has increased risks when used for IRPC. For example, Godtman et al [9], who managed 474 patients with AS including 104 (22%) IRPC patients for a median period of 8.0 yr, found that both LRPC and IRPC patients were more likely to have active intervention and AS failure compared with very-low-risk patients.

Likewise, Musunuru et al. [10] compared the survival outcomes of 732 LRPC and 213 IRPC patients from their AS database, with a median follow-up of around 6.6 yr. About 60% of the IRPC patients had GS 7 at presentation. IRPC patients had inferior 15-yr overall survival, cause-specific survival, and active treatment–free survival compared with the LRPC group. In addition, the reported 15-yr metastasis-free survival for IRPC men was 82%, which was 95% for LRPC patients (HR 3.14, 95% CI 1.51–6.53, $p = 0.001$).

Additionally, Park et al. [11] analysed the outcome of 534 LRPC and 81 IRPC (due to GS 3 + 4 only) patients who underwent radical prostatectomy, and noted that IRPC men had significantly higher adverse pathological features (16.7% vs 49.4%, $p < 0.001$) and significantly lower biochemical recurrence–free survival ($p < 0.001$) in comparison with LRPC patients. GS 3 + 4 was found to be the only variable to predict PSA recurrence (HR 3.567, $p < 0.001$).

On the other hand, some studies suggest that AS is a reasonable management option for IRPC patients. Cooper-

Table 3 – Unadjusted and adjusted survival outcomes of low- and intermediate-risk prostate cancer patients

Outcome	Risk group	Unadjusted		Adjusted [a]	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Overall survival	Low	1	0.68	1	0.69
	Intermediate	1.21 (0.48, 3.09)		0.79 (0.25, 2.47)	
Disease progression	Low	1	0.80	1	0.34
	Intermediate	0.94 (0.60, 1.47)		1.26 (0.78, 2.03)	
Active treatment	Low	1	0.30	1	0.89
	Intermediate	0.78 (0.49, 1.25)		0.96 (0.58, 1.59)	
Recurrence [b]	Low	1	0.58	1	0.25
	Intermediate	0.56 (0.07, 4.48)		0.24 (0.02, 2.82)	

CI = confidence interval; HR = hazard ratio.
[a] Adjusted for age, type of first biopsy, and number of biopsies.
[b] Analysis for patients undergoing active treatment only.

berg et al. [12] compared the outcome of 376 LRPC patients (GS 2–6 and Cancer of the Prostate Risk Assessment [CAPRA] score 0–2) with 90 IRPC men (GS 7 and/or CAPRA score 3–5) who were managed with initial deferred treatment. Twenty-seven patients had GS 3 + 4 (International Society of Urological Pathology [ISUP] grade 2) and two patients had GS 4 + 3 (ISUP grade 3) diseases at diagnosis. There was no significant difference in progression-free survival (54% for LRPC vs 61% for IRPC, $p = 0.22$) and the proportion of patients requiring active treatment (30% for LRPC vs 35% for IRPC, $p = 0.88$) between the two groups within the first 4 yr of diagnosis. None of the patients undergoing surgery had node-positive disease or PSA recurrence within 3 yr.

Similarly, out of 451 patients who were followed up on AS by Thostrup et al. [13] for a median period of 5.1 yr, 111 (24.6%) had IRPC. There was no significant difference in the 5-yr treatment-free survival among men with very-low-risk PC, LRPC, and IRPC (62.1%, 54.0%, and 70.9%, respectively; $p = 0.18$). Likewise, the 5-yr biochemical recurrence–free survival rates were 95.5% for very-low-risk, 93.5% for low-risk, and 85.6% for intermediate-risk patients, without any difference ($p = 0.21$). Thus, IRPC patients had the similar risk of having active treatment to patients with LRPC in the short to intermediate time frame, without compromising PSA recurrence-free survival.

In addition, both Wong et al. [14] and Lee et al. [15] observed that AS may be suitable for favourable GS 3 + 4 IRPC patients. Wong et al. [14], who retrospectively analysed their 929 radical prostatectomy patients (399 men with GS 3 + 3 and 530 with GS 3 + 4 at initial biopsy), found that men with GS 3 + 4 at diagnosis had an increased risk of adverse pathology (upgrading to $\geq$GS 4 + 3 and/or upstaging to $\geq$pT3) after radical prostatectomy compared with men with GS 3 + 3 disease, but over a median follow-up of 26 mo, biochemical recurrence–free survival was similar in the two groups. Interestingly, favourable GS 3 + 4 patients with PSA density $\leq$0.2 ng/ml/cm^3 and two or fewer positive cores did not have any difference in adverse pathology in final histology compared with the GS 3 + 3 group. Likewise, in the study by Lee et al. [15], who evaluated the data of 1491 patients undergoing radical prostatectomy, the favourable GS 3 + 4 group (PSA density $\leq$0.2 ng/ml/cm^3, core involvement $\leq$50%, and two or fewer positive cores with a maximum one core of GS 3 + 4) exhibited similar clinicopathological outcomes to GS 3 + 3 patients, suggesting possible expansion of AS for men with favourable GS 3 + 4 at initial biopsy.

Recently, the European Association of Urology Prostate Cancer Guideline Panel has published some consensus statements for Deferred Treatment with Curative Intent for Localized Prostate Cancer from an International Collaborative Study (DETECTIVE Study) [16]. It has been mentioned that GS 3 + 4 = 7 (ISUP grade 2), PSA >10 ng/ml, or clinical stage cT2b by itself should not be an automatic exclusion criterion for AS for PC; rather, other associated factors should be taken into account before making a final decision. For example, men with GS 3 + 4 = 7 (ISUP grade 2) PC can be considered for AS if other characteristics are favourable, such as PSA <10, clinical stage $\leq$cT2a, and low core positivity on prostate biopsy. Similarly, men with PSA >10 but low PSA density and other favourable features could be offered the option of AS. However, GS 4 + 3 = 7 (ISUP grade 3) or clinical stage $\geq$T2c should not be considered for AS.

In our study, one quarter of the total cohort of 372 men had IRPC. No patients had primary GS 4 disease. Patients with both GS 3 + 4 and PSA >10 were four. There was no recorded death due to PC, and only one patient from the low-risk group developed metastasis. In a study by Klotz et al. [17], who managed 993 LRPC and IRPC patients with AS for a median period of 6.4 yr, 2.8% patients developed metastasis and only 1.5% patients died from PC. Our finding of zero mortality due to PC and only one metastasis may be because of the relatively short median follow-up period of 4.5 yr.

We did not find any difference in overall survival, disease progression–free survival, treatment-free survival, and biochemical recurrence–free survival between low- and intermediate-risk group patients in unadjusted analysis as well as when analysis was performed after adjusting the potentially confounding factors such as age, type of the first biopsy, and number of biopsies. We started recruiting IRPC patients relatively late in the study that can explain a shorter total follow-up period for IRPC patients than for LRPC men. Our IRPC group was relatively older than the

LRPC group, as we were more inclined to do active treatment for younger men with IRPC.

We would expect men with LRPC to have better overall outcomes than men with IRPC. This is a possible explanation of the findings of some of the studies mentioned above. However, prostate diagnostics have changed significantly over the past 10 yr, and we have moved from traditional 12-core transrectal prostate biopsy used in older studies to prebiopsy MRI scans, transperineal prostate biopsy, and targeted biopsies. The added accuracy of these approaches reduces the risk of underdiagnosis and gives greater confidence in risk stratification, which should translate into improved outcomes for men with IRPC managed with AS. In our cohort, men with IRPC were included later, and a much greater proportion of them had prebiopsy MRI scans and transperineal prostate biopsy at diagnosis, reflecting higher confidence in risk classification. Moreover, some LRPC patients were probably underclassified as 31.8% of low-risk men who underwent the first follow-up biopsy showed an upgrade in GS compared with 18.8% of intermediate-risk patients ($p = 0.084$), and a significantly higher number of LRPC patients who underwent radical prostatectomy had progression in GS in final histology in comparison with IRPC patients (LRPC 87% and IRPC 40%, $p = 0.006$). These are a few probable explanations for our finding of equivalent outcomes in both LRPC and IRPC men when managed with AS.

This study has some limitations. First, the median follow-up period of 4.5 yr is relatively short considering the slow growing nature of the disease. Second, we are unable to objectively define the criteria for the selection of IRPC patients as the process has been evolving gradually. However, we stayed away from GS 4 + 3 = 7 (ISUP grade 3), clinical stage $\geq$T2c, and presumed high-volume or aggressive disease after MDM discussion, while considering MRI finding (eg, Prostate Imaging Reporting and Data System 5) and prostate biopsy result (eg, number of involved cores $>$33% and maximum core length $>$6 mm). Finally, as our inclusion period (2002–2019) is very long, the inclusion criteria as well as the follow-up protocol changed during this period, which may result in heterogeneity. However, a large sample size and the prospective nature of the data collected were the strengths of this study. In addition, over half of the patients had multiparametric MRI at enrolment for AS and over one-fifth had initial transperineal prostate biopsy, which provided detailed information about the disease before subjecting the patients to deferred treatment.

5. Conclusions

In conclusion, our findings suggest that AS is an appropriate option for carefully selected patients with intermediate-risk localised PC, provided that the patient is well informed about the risks and benefits and a close structured monitoring is maintained. However, long-term data are limited, and randomised control trials directly comparing AS with active interventions will be helpful for establishing this with more certainty.

***Author contributions*:** Sanjeev Madaan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Madaan, Mukherjee, Promponas.
Acquisition of data: Promponas, Mukherjee, Abbaraju, Hossain, Petrides.
Analysis and interpretation of data: Mukherjee, Promponas, Madaan.
Drafting of the manuscript: Mukherjee.
Critical revision of the manuscript for important intellectual content: Madaan, Mukherjee, Petrides, Hossain, Abbaraju, Promponas.
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CRediT authorship contribution statement

Subhabrata Mukherjee: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Ioannis Promponas:** Conceptualization, Methodology, Investigation, Writing - review & editing, Visualization. **Neophytos Petrides:** Investigation, Writing - review & editing. **Dafader Hossain:** Investigation, Writing - review & editing. **Jayasimha Abbaraju:** Investigation, Writing - review & editing, Supervision. **Sanjeev Madaan:** Conceptualization, Methodology, Writing - review & editing, Resources, Visualization, Supervision, Project administration.

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