

Low-risk prostate cancer in India: Is active surveillance a valid treatment option?

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ABSTRACT

Introduction and Objective: Carcinoma prostate is considered highly aggressive in Asian countries such as India. This raises an argument whether active surveillance (AS) gives a false sense of security as opposed to upfront radical prostatectomy (RP) in Indian males with low-risk prostate cancer (PCa). We analyzed our prospectively maintained robot-assisted RP (RARP) database to address this question.

Materials and Methods: Five hundred and sixty-seven men underwent RARP by a single surgical team from September 2013 to September 2019. Of these, 46 (8.1%) were low risk considering the National Comprehensive Cancer Network criteria. Gleason grade group and stage were compared before and after surgery to ascertain the incidence of upgrading and upstaging. Preoperative clinical and pathological characteristics were analyzed for association with the probability of upstaging and upgrading.

Results: The mean age was 60.8 ± 6.8 years. Average prostate-specific antigen level was 6.7 ± 2.0 ng/mL. 40 (86.9%) patients had a T1 stage disease and 6 (13%) patients were clinically in T2a stage. A total of 25 (54.3%) cases were either upstaged or upgraded, 19 (41.3%) showed no change, and the remaining 2 (4.3%) had no malignancy on the final RP specimen. Upstaging occurred in 8 (17.4%) cases: 5 (10.9%) to pT3a and 3 (6.5%) to pT3b. Upgrading occurred in 23 (50%) cases: 19 (41.3%) to Grade 2; 3 (6.5%) to Grade 3; and 1 (2.2%) to Grade 4.

Conclusions: There is a 50% likelihood of upstaging or upgrading in Indian males with low-risk PCa eligible for AS. Decision to proceed with AS should be taken carefully.

INTRODUCTION

With the second highest incidence, prostate cancer (PCa) presents a huge public health concern, faring among the top five causes of cancer mortality amongst males.^[1] Active surveillance (AS) is the recommended modality of management in low-risk PCa.^[2] Recent large prospective randomized trials suggest the indolent nature of most of the PCAs, making it plausible to selectively consider AS as a viable option.^[3,4] However, most observational studies with prospective cohorts that turned treatment guidelines in favor of AS over active intervention barely included men of Indian descent.

Many recent studies suggest aggressive clinical features and higher chances of upstaging and upgrading in low risk Pca, who met criteria for AS, among Asians over their Western counterparts.^[5-10] A study assessing a large robot-assisted radical prostatectomy (RARP) cohort found a significantly higher percentage of extraprostatic extension among Asian Indians as opposed to the men of Caucasian descent (32.3 and 16.5, $P = 0.01$).^[5] Another study reported a higher postoperative rate of positive nodes and surgical margins among men of South Asian descent.^[6] Pathological upgrading or upstaging rates among men who underwent

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RP despite satisfying AS criteria were higher among Korean (44%–54%)^[7] and Japanese (27%–51%)^[8] studies, as compared to the Western men (21%–34%).^[9,10] A study that compared outcomes for low-risk PCa in Korean men to the Caucasians reported a higher rate of upstaging (16.2%) and upgrading (15.7%) in Koreans as compared to the later (4.9% and 4.4%).^[11] Such findings make it important to evaluate the risk of AS protocols in Indian men.

Age-standardized incidence rates of PCa in India has roughly increased by a third from 1990 to 2016.^[12] Evidence shows a global shift towards adoption of AS for low-risk PCa; most studies however, do not detail its adoption in the Indian cohort. When opting for AS, low-risk PCa Indian patients should therefore be informed regarding the expected outcomes. To our knowledge, there is a lack of data regarding pathological upgrading or upstaging among Indian men who satisfy the AS criteria. Given the data on aggressive PCa among Indian patients, it is important to ascertain whether AS is a safe strategy for them. We evaluated our data to address this concern.

MATERIALS AND METHODS

Patient selection

From our prospectively maintained database, we reviewed 567 records of consecutive patients who underwent RARP by a single surgical team from September 2013 to September 2019. All RP specimens were processed and analyzed using the standard guidelines.^[13] Prostate biopsies were either performed at our center or reviewed later by the pathologists at our tertiary care center. The same pathologists conducted in-house evaluation of the biopsy and the surgical specimens. TNM staging system (8th edition) of the American Joint Committee on Cancer was referred for staging.^[14]

We enlisted men fulfilling the criteria of low-risk Pca which included prostate-specific antigen (PSA) level at diagnosis <10 ng/mL, clinical T stage of T1 or T2a and Gleason grade Group 1, as per National Comprehensive Cancer Network 2019.^[2] We included low-risk patients, who though eligible for AS, underwent RP within 3 months of diagnosis. The prospectively collected data from these patients were analyzed retrospectively. Exclusion criteria included ongoing neoadjuvant androgen deprivation therapy.

Data collection

Data on age, body mass index (BMI), preoperative serum PSA level, prostate volume, PSA density (PSAD), number of positive cores, percentage positive cores on biopsy (ratio of positive cores to total cores), clinical stage, and Gleason grade group were collected. Clinical stage was ascertained using multiparametric magnetic resonance imaging (mpMRI) or digital rectal examination. In-house radiologists assessed the mpMRI of the study cohort. Radiographic variables such as tumor stage, extracapsular extension (ECE), presence

of enlarged lymph nodes (>1 cm diameter in short axis), and seminal vesicle (SV) invasion were considered for analysis. Pathologic factors of RP specimen included were pathological stage, Gleason grade group, positive surgical margins, SV invasion, ECE, and positive lymph nodes. T stage and Gleason grade groups were reported before and after RP.

Definition of upgrading and upstaging

Patients were evaluated by comparing the pathological features of post-RP specimens with preoperative biopsies. Primary outcomes were upgrading or upstaging. Upgrading was defined as any increase in pathologic Gleason grade group >1 in the RP specimen. Increase in pathological stage to \geq pT3 or lymph node positivity was defined as upstaging.^[15]

Postoperative data collection

Follow-up protocol included physical examination and catheter removal 8–10 days post-RP; serum PSA level assessment at 1 month after surgery and every 3 months thereafter in the 1st year, half-yearly in 2nd year, and annually from 3rd year onward. Biochemical recurrence (BCR) was defined as persistence or an increase in the post-RP total serum PSA \geq 0.2 ng/mL, which was confirmed on repeat analysis or any patient that required adjuvant therapy despite lower PSA levels. Urinary continence was defined as using 0 or 1 safety pad every 24 h. Erectile function was defined as the ability to achieve erection sufficient for penetrative intercourse after surgery. Normal pre-operative sexual function was defined as Sexual Health Inventory for Men score >21 without phosphodiesterase type 5 inhibitors use.

As our study was retrospective, an informed consent for inclusion in the study from participants was not taken. However, all the participants provided a written informed consent for undergoing RARP and we adhered to the principles of Helsinki Declaration, 1964 (amended in 2013). Furthermore, we confirm the availability of, and access to, all original data reported in this study.

Statistical analysis

We conducted a descriptive analysis of preoperative and pathologic factors. Several variables were tested for association with upstaging and upgrading. Categorical variables were presented as frequency and percentages and were assessed using Pearson's Chi-square test and Fisher's exact test (where applicable). The mean and standard deviation were reported for normally distributed continuous variables (Kolmogorov–Smirnov test) and Independent Samples *t*-test was applied; if not, median and interquartile range were reported and nonparametric (Mann–Whitney U) test was performed. Logistic regression models (univariate and multivariate) were applied to assess the effect of clinical and pathological parameters on the risk of upstaging and upgrading. To find out independent predictors for upstaging

and upgrading, univariate analysis was performed. Significant variables in the univariate analysis were later subjected to multivariate logistic regression model. Odds ratios (ORs) were reported with a 95% confidence interval, considering two-tailed $P < 0.05$ for statistical significance. Kaplan–Meier curves were generated to assess the differences in BCR-free survival between the different groups and were compared using the log-rank test; cases without recurrence were censored at the date of last PSA. Statistical Product and Service Solutions version (SPSS) v 22.0 (Armonk, NY: IBM Corp) was used for statistical analysis.

RESULTS

Of the 567 RARP patients, 46 low-risk disease patients were eligible for AS. The average duration between the transrectal biopsy and RP was 9 weeks (6–12 weeks).

Baseline patient characteristics

The mean age was 60.8 ± 6.8 years. Average PSA was 6.7 ± 2.0 ng/mL. Forty (86.9%) patients had clinical stage T1 (T1b + T1c) disease and 6 (13%) patients had T2a disease. The mean number of positive core was 3.2 (range, 1–8). For 42 patients, complete biopsy core data was available: 21 (50%) had <3 and the remaining had ≥ 3 positive cores [Table 1]. Sixteen (34%) patients underwent lymph node dissection, of which 7 (43%) underwent extended and 9 (57%) underwent standard lymph node dissection. The average number of lymph nodes retrieved was 12.56 (range, 1–26). No case had pathological positive lymph nodes; 1 (2.2%) had a positive margin (multifocal, posterior) whose final pathological T stage was pT2 and thus had neither upgraded nor upstaged.

Table 1: Clinicopathological characteristics of patients with low-risk prostate cancer managed with radical prostatectomy

| Clinical characteristics | Distribution |
|-----------------------------------------|--------------|
| <i>N</i> | 46 |
| Age (years), mean±SD | 60.8±6.8 |
| PSA (ng/mL), mean±SD | 6.7±2.0 |
| Clinical T stage, <i>n</i> (%) | |
| T1 (T1b + T1c) | 40 (86.9) |
| T2a | 6 (13.0) |
| Total biopsy cores, mean (range) | 11.40 (5-16) |
| Positive cores, mean (range) | 3.2 (1-8) |
| Percentage positive cores, <i>n</i> (%) | |
| <15% | 11 (26.2) |
| 15-30% | 14 (33.3) |
| >30% | 17 (40.5) |
| Pathological characteristics | |
| Upgrading, <i>n</i> (%) | 23 (50) |
| Gleason grade Group 2 | 19 (41.3) |
| Gleason grade Group 3 | 3 (6.5) |
| Gleason grade Group 4 | 1 (2.2) |
| Upstaging, <i>n</i> (%) | 8 (17.4) |
| pT3aN0 | 5 (10.9) |
| pT3bN0 | 3 (6.5) |
| Positive margins, <i>n</i> (%) | 1 (2.2) |

SD=Standard deviation, PSA=Prostate-specific antigen

Prevalence of upgrading and upstaging

Of the 46 cases, 17 (36.9%) showed upgrading only, 2 (4.3%) showed upstaging only, 6 (13%) showed both. In total, 25 (54.3%) cases were either upstaged or upgraded. Two (4.3%) cases showed no malignancy, and 19 (41.3%) had organ-confined grade Group 1 disease on the final histopathology after RP [Figure 1]. Upgrading occurred in 23 (50%) cases: 19 (41.3%) cases were upgraded to grade Group 2, 3 (6.5%) to grade Group 3 and 1 (2.2%) to grade Group 4 [Table 1 and Figure 2]. Of the patients that were upgraded, Gleason grade Group 2, 3, and 4 disease was found in the postoperative RP specimens of 19 (82.7%), 3 (13%), and 1 (4.3%) cases, respectively. In addition, 17.4% (8 of 46) patients were upstaged: 5 (10.9%) to pT3a and 3 (6.5%) to pT3b [Table 1 and Figure 2]. Of those upstaged, 5 (62.5%) had T3aN0 and 3 (37.5%) had T3bN0 disease.

Predictors of upgrading and upstaging

Independent samples *t*-test of association indicated that PSAD was significantly higher in patients who were upgraded over those who were not (0.22 ± 0.09 versus 0.15 ± 0.06 ng/ml/g, $P = 0.045$). Although not statistically significant, there was a trend toward an association between the incidence of upgrading and the percentage of positive cores (PPC) on the preoperative biopsy ($35.7 \pm 17.8\%$ versus $24.5 \pm 20.0\%$, $P = 0.065$). In upgraded patients, final tumor pathological volume was $13.4 \pm 9.7\%$ of the total prostate volume, but this factor was not significantly related to it. Upgrading was not associated with age, BMI, PSA, and clinical stage [Table 2].

PSAD and PPCs were significantly associated with the incidence of upstaging (0.26 ± 0.08 versus 0.16 ± 0.07 ng/ml/g, $P = 0.015$ and 43.2 ± 16.9 versus $26.7 \pm 19.1\%$, $P = 0.031$, respectively) [Table 3]. Although not statistically significant, an inclination towards an association between upstaging and preoperative PSA ($P = 0.051$) and the highest percentage of involvement of any core on the preoperative biopsy

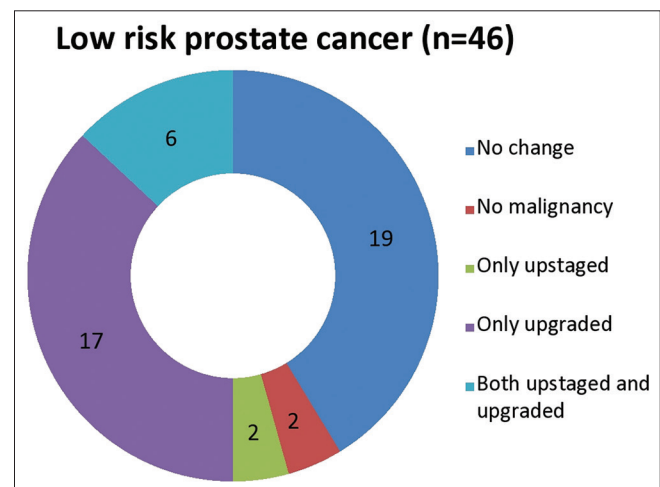


Figure 1: Distribution of stage and grade change in radical prostatectomy specimens of low-risk prostate patient

($P = 0.061$) was observed. Among the upstaged patients, final tumor pathological volume was $22.4 \pm 8.9\%$ of the total prostate volume, but was not significantly related to upstaging. Upstaging was not associated with age, BMI, clinical stage, and number of positive cores [Table 3]. Multivariable logistic regression analysis run for independent predictors of pathological upgrading and upstaging was not significant.

Postoperative outcomes

Follow-up data were available for 37 men, of which 2 (5.4%) who upgraded developed BCR. No upstaged patients had BCR. The average follow-up duration was 17 months (1–60 months). A case of BCR was reported at 18 months and another at 33 months. Overall, BCR-free survival rate was 94.6%.

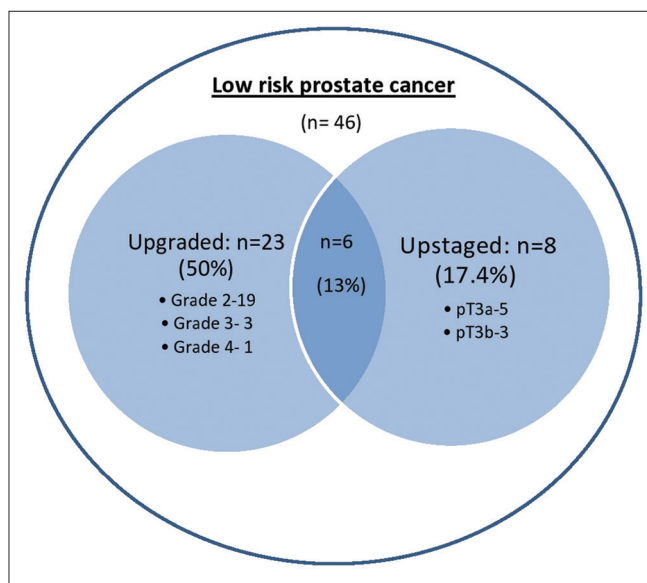


Figure 2: Distribution of upstaged and upgraded patients in radical prostatectomy specimens of low-risk prostate cancer

A Kaplan–Meier plot was generated for BCR-free survival for the upgraded and the nonupgraded patients [Figure 3], and the survival distribution was compared using the log-rank test. The upgraded and the nonupgraded group had an average follow-up duration of 17.3 months (1–60 months) and 16.6 months (1–54 months), respectively. Twenty one and 16 men were evaluable at 5 years for the upgraded and the nonupgraded group, respectively. Five-year BCR-free survival in the upgraded group did not differ significantly from the nonupgraded group (90.5% and 100%; $P = 0.215$, log-rank test). Our study observed no cancer-specific death.

After 1, 3, 6, and 12 months of RARP, 31.6%, 50%, 67.6%, and 87.5% patients achieved urinary continence, respectively. Out of the 2 patients who had normal pre-operative sexual

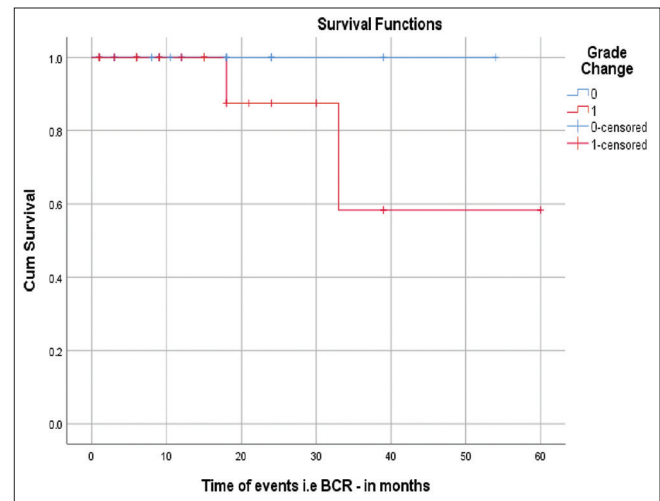


Figure 3: Kaplan–Meier curves of biochemical recurrence free survival in upgraded patients compared to nonupgraded patients. (0 – nonupgraded; 1 – upgraded)

Table 2: Predictors of pathological upgrading

| Variable | Upgraded | Not upgraded | P |
|--------------------------------------------|------------|--------------|-------|
| Age (years) | 62.3±7.6 | 59.3±5.6 | 0.14 |
| BMI (kg/m ²) | 25.89±3.99 | 26.70±3.42 | 0.485 |
| PSA (ng/ml) | 6.8±2.0 | 6.6±2.0 | 0.74 |
| PSAD (ng/ml/g) | 0.22±0.09 | 0.15±0.06 | 0.045 |
| Number of cores positive | 3.8±2.2 | 2.7±1.9 | 0.081 |
| Percentage of positive cores (%) | 35.7±17.8 | 24.5±20.0 | 0.065 |
| Max percentage involvement of any core (%) | 42.7±30.8 | 31.2±21.2 | 0.21 |

BMI=Body mass index, PSA=Prostate-specific antigen, PSAD=PSA density

Table 3: Predictors of pathological upstaging

| Variable | Upstaged | Not upstaged | P |
|--------------------------------------------|-------------|--------------|-------|
| Age (years) | 63.5±7.27 | 60.21±6.60 | 0.21 |
| BMI (kg/m ²) | 26.96±4.99 | 26.16±3.46 | 0.608 |
| PSA (ng/ml) | 7.93±1.51 | 6.45±1.95 | 0.051 |
| PSAD (ng/ml/g) | 0.26±0.08 | 0.16±0.07 | 0.015 |
| Number of cores positive | 4.5±2.07 | 2.91±1.99 | 0.051 |
| Percentage of positive cores (%) | 43.18±16.89 | 26.70±19.06 | 0.031 |
| Max percentage involvement of any core (%) | 52.86±33.02 | 32±22.78 | 0.061 |

BMI=Body mass index, PSA=Prostate-specific antigen, PSAD=PSA density

function, one patient (50%) regained sexual function after 5.5 months of RP.

DISCUSSION

Only 46 men with low-risk PCa could be identified among 567 consecutive men who underwent RARP at our care. This presents the clinical profile of patients seeking care for PCa in India, suggesting a significantly higher proportion of intermediate and high-risk disease in our population as compared to the West. Delayed diagnosis of the disease in our part of the world, attributable to the absence of a routine screening practice, or a more aggressive disease profile could be the possible reason. This emphasizes the need to practice caution while adopting Western standards for AS in Indian men.

In our study cohort, 54.3% of the men had either pathological upgrading or upstaging. Of these, 50% were upgraded to Gleason grade Group >1 and 17.4% were upstaged to T3 disease. Our high upgrading and upstaging rates among low-risk PCa bear contrast to the Western data^[9,10] while being congruent with studies on Asian men.^[7,8] Our study adds to the limited evidence on the Indian AS cohort.

We found that PSAD was significantly associated with both upstaging and upgrading, while PPCs was significantly associated with upstaging only. These results are similar to other studies.^[16-19] Dinh *et al.*^[16] reported that positive cores >25% were significantly associated with upgrading and upstaging. PSAD is a significant factor for upgradation of low-risk PCa. Many AS guidelines such as the Prostate Cancer Research International AS protocol therefore use PSAD in AS selection criteria (PSAD cutoff of 0.20).^[20] PSAD was also found to strongly affect adverse reclassification in men on AS.^[21] Results from the current study suggest PSAD as one of the critical factor while selecting Indian low-risk PCa men for AS

There is discordant evidence regarding the association of preoperative PSA with the probability of upgrading and upstaging in low-risk PCa.^[22] Our study did not find a significant association between PSA levels and upgrading, although there was a trend towards association with upstaging ($P = 0.051$). This calls for further research.

Studies suggest an influence of age on the pathological upgrading and upstaging.^[16] Gershman *et al.* found that age >60 years was associated with an increase in the risk of upgrading in patients with Gleason 6 disease.^[23] Richstone *et al.* observed a higher incidence of Gleason score upgradation among patients >70 years of age.^[24] Age is therefore an important marker of disease aggressiveness, thus warranting an equally aggressive treatment plan. However, in our study, age and pathological upgrading and upstaging were not significantly associated. Furthermore, in

contrast to other studies,^[18,22] no significant association was established with BMI.

Factors such as inadequate biopsy samples, cancer at atypical site, or incongruence among the pathologists leads to upgrading and upstaging in post-RP specimens. Although the shift from sextant biopsies to at least 12 needle cores has somewhat reduced the undersampling,^[20] atypical sites still remain a concern. Systematic biopsy protocol often misses high-grade tumors located in the anterior prostate due to noninclusion in the protocol.^[25] Furthermore, low-risk PCa patients, though considered appropriate AS candidates, are susceptible to anterior dominant nodule.^[25] A study by Eminaga *et al.* reported that more foci of Gleason score 6 disease were in the posterior periphery of the prostate, whereas foci with Gleason score >6 were mostly housed in the anterior parts and the base. The study was however not restricted to the low-risk patients.^[26]

It is important to accurately identify men eligible for AS. Expertise of the pathologists is thus extremely crucial. A study by Majoros *et al.*^[27] found that pathologists working in the high-load centers (>100 specimens/year) were more accurate in the diagnosis as compared to those at the low-load nonacademic setups.

The American Urological Association guidelines for clinically localized PCa has recommend AS, irrespective of the racial differences.^[28] However, aggressive pathological features among Asian men who fulfill the AS criteria^[6] warrants adequate risk communication.

A report from SEER database^[29] found relatively more aggressive cancers among Indians and Pakistanis as compared to the Caucasians. Another study reported a greater risk of higher Gleason grade disease and metastasis among Asian Indians as opposed to the European Americans.^[30] Adverse outcomes among Asians are likely to translate into cancer specific mortality. A California Cancer Registry-based study observed that the 10-year risk of dying from PCa tipped 40% towards the South Asians as compared to the Caucasians.^[31] However, there is a lack of evidence regarding the cancer-specific survival in Indian versus the Caucasian AS cohorts. In our study, cancer-specific survival and BCR-free survival were not significantly different in the upgraded/upstaged cohorts as compared to the nonupgraded/nonupstaged cohorts.

Being retrospective and unicentric in conduct, our study has its limitations. First, our patient cohort is primarily based on the specific referrals for RARP and thus may not represent PCa prevalence at the population level. Second, we lacked the facility for a central pathological review of all the biopsy slides by a single uropathologist prior to RARP, thereby potentially introducing interobserver bias. In our study, not all the patients were biopsied at our

center and not all of them underwent a standard 12 core biopsy. Thus, biopsy characteristics such as tumor location, perineural invasion, and lymphovascular invasion could not be uniformly reported in all the patients. Moreover, this being a retrospective study, some data could not be completely assessed and there may be a selection bias. As data could be collected only for low-risk PCa cases treated with RP, the study does not report outcomes of low-risk PCa treated by other modalities. Short follow-up period also restricted the assessment of late oncological parameters such as the cancer-specific survival and the recurrence or metastasis.

Despite its limitations, our study enhances the limited AS evidence in India. Although popular as the ideal treatment for low-risk PCa, the evidence in its favor underrepresents the Indian population. We may not be doing justice to our patients by applying the in vogue AS protocols without careful consideration. Hopefully, evidence presented in our study will help in providing a greater insight into the applicability of AS in the Indian patients and provide a tool to the clinician to counsel these patients appropriately. While AS may still be the preferred modality for selected Indian males with low-risk disease, further research needs to be done to develop and implement better tools to classify them into more accurate prognostic groups. These may include improvement and standardization of biopsy templates, genomic testing, multiparametric magnetic resonance imaging, better selection criteria, and altered follow-up protocols.

CONCLUSIONS

One in two low-risk PCa patients eligible for AS are likely to upgrade on RP and one in six may harbor a nonorgan-confined disease. AS-based strategy should thus be vetted as it may not be ideal for a substantial fraction of Indian males with low-risk PCa. While PSAD and percentage positive cores on the preoperative specimen may facilitate decision making, further studies are required for more accurate prognostic classification in the Indian cohort.

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