Association of absolute amount of pattern 4 disease on prostate biopsy with oncologic outcomes in intermediate-risk prostate cancer: A systematic review

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ABSTRACT

Introduction: Managing intermediate-risk prostate cancer (IRPC) is challenging due to the heterogeneity in patient outcomes within this risk category. Evaluating the absolute amount of Gleason pattern 4 disease (GP4) at biopsy using the total linear length of pattern 4 (GP4-TL) or absolute percentage of pattern 4 (APP4) may enhance risk stratification. This review aimed to determine if these absolute measures predict oncologic outcomes in IRPC and to identify optimal prognostic thresholds.
Methods: A systematic review was conducted following PRISMA guidelines. Studies

KEY MESSAGES

- Absolute amount of Gleason pattern 4 disease offers an accessible and established method to enhance risk stratification.
- Total linear length of pattern 4 (GP4-TL) and absolute percentage of pattern 4 (APP4) are two methods for quantifying the absolute amount of Gleason pattern 4 disease in biopsy samples.
- GP4-TL and APP4 are strong predictors of biochemical recurrence, androgen deprivation therapy-free survival, distant metastasis, prostate cancer-specific mortality, all-cause mortality, and adverse pathology
- Further investigation is warranted to establish thresholds that can guide clinical decisions.

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included were those reporting the absolute amount of GP4 on biopsy and related outcomes in IRPC patients undergoing surgery or radiotherapy. Outcomes included biochemical recurrence, androgen deprivation therapy (ADT)-free survival, distant metastasis, prostate cancer-specific mortality, all-cause mortality, and adverse pathology.
Results: Seven studies with a total of 2523 patients were included. Analysis revealed that APP4 thresholds were highly predictive of biochemical recurrence, ADT-free survival, and distant metastasis. Both APP4 and GP4-TL were superior to relative %GP4 and Gleason grading (4+3 vs. 3+4) in predicting disease progression and mortality.
Conclusions: The absolute amount of GP4 shows consistent associations with important clinical outcomes and offers an accessible and established method to enhance risk stratification. Further research is needed to define optimal thresholds to guide treatment decisions.

INTRODUCTION

Risk stratification is a core concept in the diagnosis and management of men with prostate cancer. Along with PSA and clinical T-stage, the Gleason score obtained from prostate biopsies is integrated into the original D'Amico staging system of low-, intermediate- and high-risk localized prostate cancer.[1,2] NCCN guidelines have since further split these categories into more distinctive subgroups, using biopsy information such as the proportion of positive prostate biopsy cores.[2] Despite these efforts, clinical outcomes remain heterogeneous for men with intermediate-risk prostate cancer, reflecting different risk profiles within the same risk category. For example, current NCCN guidelines consider a patient with a PSA of 18 and 12/12 biopsy cores of Gleason 4+3 prostate cancer in the same unfavourable intermediate-risk category as a patient with a PSA of 11 and a single core of Gleason 3+4 prostate cancer.

The Gleason score has evolved substantially since its initial inception, with recommendations from the 2014 international consensus in Chicago recommending the relative percentage of Gleason pattern 4 reported on prostate biopsy reports.[3] This may have a major impact on treatment decisions;[4] for example, men with 5% or less of Gleason pattern 4 prostate cancer may now be considered reasonable candidates for active surveillance despite having intermediate risk-disease.[5]

To enhance prognostication for men with intermediate-risk prostate cancer, it may be beneficial to use measures that quantify the absolute amount of Gleason pattern 4. In this review, we identified two methods for accomplishing this: 1) by measuring the linear length of Gleason pattern 4 in prostate biopsies (GP4-TL) or 2) by calculating the Absolute Percentage of Pattern 4 (APP4). GP4-TL is obtained with the following equation: GP4-TL (mm) = sum of (cancer length × percentage of GP4 in each cancer-positive core).[6–10] APP4 (%) is calculated as (% of biopsy tissue positive for disease) x (percentage of disease that is pattern 4)/100%.[10–12] See Figure 1 for an example of these calculations.

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While no major risk stratification system incorporates absolute measures of Gleason pattern 4, they can be a practical clinical tool to subdivide patients with intermediate-risk prostate cancer beyond NCCN classification. In this systematic review, we sought to appraise and assess studies which calculated APP4 or GP4-TL on prostate biopsies to determine if clinical outcomes (i.e. biochemical recurrence, ADT-free survival, distant metastasis, prostate cancer-specific mortality, all-cause mortality, and adverse pathology) can be predicted beyond standard risk classification systems, and if so, what the optimal cut points are.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature search

A systematic search was conducted in Embase, MEDLINE, and CENTRAL from inception to May 2023. Our search strategy was developed with the assistance of a reference librarian and included keywords such as prostate cancer, prostatectomy, Gleason grade 4 and pattern 4. The search strategy can be viewed in Appendix A. The reference lists of the identified studies were also checked to find additional articles relevant to our research question. Studies were screened in duplicate by two independent reviewers (M.S.S. and M.C.).

Study selection

The inclusion criteria were as follows: studies that evaluated amount of Gleason pattern 4 on prostate biopsy and reported clinical outcomes; original research published in English; studies involving patients with intermediate-risk localized prostate cancer who underwent surgery or radiotherapy, with or without hormone therapy. We included studies with mixed cohorts of low and intermediate-risk prostate cancer patients provided that data for each risk group was reported and analyzed separately. Studies screened at the title and abstract stage were excluded if they did not meet one or more of these inclusion criteria.

Exclusion criteria were studies that were published in abstract format only; not in English; and not an original article. Studies that measured volume of pattern 4 only in radical prostatectomy specimens (but not prostate biopsy samples) were excluded as they represent a different clinical scenario, and the aim of this review was to evaluate absolute amount of Gleason pattern 4 as a pre-treatment predictor of outcomes. Reasons for exclusions were recorded at the full-text screening stage.

Data extraction and analysis

Data was extracted by two authors independently (M.S.S. and M.C.) into a standardized collection form. Data abstracted from studies included primary author, year of article publication, study design, country, inclusion and exclusion criteria for study sample, number of patients analyzed, type of biopsy performed, and outcome measures. Patient characteristics included age, follow-up duration, treatment type and characteristics if specified (i.e. radiation

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dose and duration of androgen deprivation treatment). Outcomes of interest included biochemical recurrence, ADT-free survival, distant metastasis, prostate cancer-specific mortality, all-cause mortality, and adverse pathology. Measures of effect sizes of APP4 or GP4-TL and associated clinical outcomes were also collected from included studies. Due to the significant heterogeneity among studies, including variability in patient populations, treatment modalities, primary endpoints, and study design, it was not feasible to conduct a meta-analysis. A descriptive summary of the results is provided.

RESULTS

Literature search and study characteristics

The literature search resulted in 2038 articles. Our broad search strategy caught many studies that reported clinical outcomes of radiation and prostatectomy; however, many of these did not report outcomes based on absolute measures of GP4. At the title and abstract stage, 1091 articles were excluded for failing to meet one or more of our inclusion criteria. 53 articles underwent full review. 46 studies were excluded for the following reasons: does not report absolute amount of GP4 (n=36), full text not in English (n=3), review article (n=1), amount GP4 only reported in RP specimen (n=4), and not a full text (n=2). In total, 7 studies were included in the final analysis. Figure 2 details the study selection process.

Study and patient demographics are provided in Table 1. All studies were retrospective and conducted in the USA (3 studies), Canada (2 studies), Japan (2 studies), and Australia/New Zealand (1 study). A total of 2,523 patients with intermediate-risk prostate cancer were included in this review, of which 1297 (51%) underwent radical prostatectomy and 1226 (49%) underwent radiotherapy. Of those receiving radiotherapy, 227 (19%) received prostate stereotactic body radiotherapy (SBRT) +/- androgen deprivation therapy (ADT), and 999 (81%) had external beam radiotherapy (EBRT) with high-dose rate (HDR) brachy boost +/- ADT. Two articles evaluated APP4, four studies evaluated GP4-TL, and one study evaluated both. Biopsy strategy was reported in 1708 patients (5 studies), of which 1240 (73%) were systematic, 431 (25%) were targeted, and 37 (2%) were systematic plus targeted.

Outcomes

Biochemical recurrence

Four studies reported outcomes related to biochemical recurrence (BCR) defined as nadir + 2.0 ng/ml[11,12] or as 2 non-consecutive rises in PSA of ≥0.1 ng/ml starting 6 weeks post-radical prostatectomy.[7,8] Two studies used multivariable competing risk models to generate optimized APP4 cut-points that were significantly predictive of BCR (Table 2). Glicksman et al. found that a 5% cut-point was significantly associated with BCR four years after SBRT.[12] Of note, eleven (4.9%) patients had ADT use with radiation. Martell et al. reported an optimal APP4 threshold of 3.3% for BCR four years after EBRT with HDR brachy boost.[11] Perera et al. calculated the risk

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of BCR after radical prostatectomy alone in mm of GP4-TL; patients with 2 mm of pattern 4 disease had a risk of 13% of BCR at 3 years, with 1-2% additional risk per mm increase.[8]

ADT-free survival
One study evaluated ADT-free survival, which consisted of the time from the date of EBRT with HDR brachytherapy boost to the date of any last follow-up or to the date of ADT initiation for BCR.[11] This study found an APP4 threshold of 6.6% to be highly predictive of ADT-free survival at 4 years following EBRT with HDR brachy boost.

Distant metastasis and mortality
Three studies investigated outcomes related to metastasis, prostate cancer-specific mortality and all-cause mortality. Glicksman et al. found that APP4 > 20% was significantly associated with distant metastasis four years after SBRT.[12] Martell et al. yielded a similar threshold of APP4 > 17.5% for distant metastasis at four years after EBRT with HDR brachy boost.[11] In the analysis of Delahunt et al., APP4 was identified as the best prognostic factor for distant progression using the Akaike Information Criteria (AIC) and Harrell's C-index. Their data demonstrated that APP4 had the lowest AIC and highest C-index for distant metastasis, prostate cancer-specific mortality and all-cause mortality, outperforming Gleason grading (4+3 vs. 3+4), % GP4 (total length GP4/total length malignant tissue), and GP4-TL (see Supplementary Table 1).[10]

Adverse pathology
Three studies evaluated GP4-TL and subsequent frequency of adverse pathology at radical prostatectomy, defined either as Gleason score 4+3 = 7 or higher, pT3a/b disease or lymph node metastasis.[7–9] Perera et al. estimated a 45% risk of adverse pathology for patients with 2 mm of GP4-TL, with the risk increasing by 5-8% for each additional mm of GP4.[8] Dean et al. demonstrated that GP4-TL had the largest increase in the area under the curve on multivariable modeling, improving the model's predictive performance more than other variable tested including overall % GP4 (GP4 tissue in all cores/total mm of cancer in all cores) and max % Gleason pattern 4 (the single core with the greatest involvement by pattern 4).[9] They also demonstrated that GP4-TL was the most effective measure in predicting adverse pathology on decision curve analysis.

DISCUSSION
This systematic review studied two methods of quantifying the absolute amount of Gleason Pattern 4 on biopsy in intermediate risk prostate cancer patients and found consistent associations between the absolute amount of Gleason Pattern 4 and clinically important outcomes. Additionally, there is evidence to suggest that absolute Gleason Pattern 4 may serve as a better prognostic factor for survival outcomes compared to relative %GP4 and Gleason 3+4 vs 4+3. No definitive thresholds for treatment decisions can be recommended based on the current evidence due to the small number of studies evaluating this tool.

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The %GP4 represents the proportion of Gleason pattern 4 within the tumor, which is influenced by the amount of Gleason pattern 3. In contrast, absolute measures reflect the percentage or length of pattern 4 relative to the total biopsied tissue, encompassing both benign and malignant areas. This helps to provide a more comprehensive assessment of the potentially aggressive tumor burden within the sampled tissue; for instance, it reduces the risk of underestimating aggressiveness when Gleason pattern 3 predominates in the biopsy but an overall significant amount of pattern 4 is present across all biopsy cores. Conversely, it reduces the risk of overestimating aggressiveness when pattern 4 constitutes a large proportion of the tumour within the biopsy core, when in fact, the overall tumor size is small.

Accurate characterization of the Gleason pattern components on biopsy is important because Gleason pattern 3 alone does not appear to be associated with metastasis.[13] A recent editorial by Vickers et al. reanalyzed data from two studies included in this review to evaluate whether Gleason pattern 3 is predictive of risk in men with grade groups 2-4.[14] Their multivariable model found that neither the length of pattern 3 nor the relative proportion of pattern 4 was predictive of adverse pathology. Additionally, their analysis on the predictive value of PSA showed that while adding the volume of Gleason pattern 3 was statistically significant, it did not substantially improve the R^2 value. This suggests that pattern 3's predictive value is limited when compared to pattern 4. Another recent study demonstrated that a multivariable model incorporating the volume of pattern 4 or 5 was a more robust predictor of metastasis after radical prostatectomy (c-index 0.86) than a model incorporating grade groups (c-index 0.74).[15] These results reinforce the findings of this systematic review that suggests that the absolute of pattern 4 may be a better predictor of outcomes in localized cancer.

Incorporating absolute amount of GP4 in practice and management guidelines is feasible and relatively inexpensive. Unlike novel stratification tools such as genomic risk stratifiers and artificial intelligence biomarkers, which are hindered by high costs and concerns over generalizability,[16,17] absolute amount of GP4 offers an accessible and established method. In various institutions, parameters needed to calculate absolute amount of GP4 are routinely included in biopsy reports. This can be calculated in clinic and used to inform decisions on active surveillance, addition of androgen deprivation therapy to radiation, dose escalation with brachytherapy boost, or integration of boost in external beam radiation therapy.[11]

MRI-fusion targeted biopsies are known to increase the detection of clinically significant tumors.[18] Consequently, it raises the question of whether targeted biopsies might oversample pattern 4 when compared to the traditional systematic biopsy. In the study by Perera et al., involving 208 MRI-targeted and 249 systematic biopsies, the biopsy method did not significantly affect GP4 quantification (all p-values >0.063).[8] Notably, no other studies performed separate analyses by biopsy type and two studies in this review did not report biopsy strategy. Future research should ensure standardized reporting of biopsy methods and consider separate analyses to assess how biopsy technique may impact amount of pattern 4 detected at biopsy.

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This study is the first to synthesize the available data on absolute amount of Gleason pattern 4, underscoring a promising area for further research; however, our study has some important limitations. The included studies are heterogeneous in terms of study populations, interventions, outcomes, and methodologies. This variability precluded the possibility of conducting a meta-analysis, thereby limiting the extent of our conclusions. Two of the included studies were conducted by the same author group, resulting in overlapping patient cohorts. While cohorts can skew the perceived amount of evidence supporting the conclusion, we decided to include both studies as they performed distinct data analyses.[8,9] Another limitation of our systematic review is the absence of a formal risk of bias analysis. Future studies should incorporate risk of bias assessments to evaluate the presence of bias which may affect the overall validity and generalizability of results.

CONCLUSIONS

The absolute amount of Gleason pattern 4 at biopsy is a practical tool with consistent associations to clinically important outcomes and has the potential to improve risk stratification models for intermediate-risk patients. Further investigation is needed to establish thresholds that may help guide treatment recommendations. Future studies would benefit from consistently reporting biopsy strategies used in their study sample.

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FIGURES AND TABLES

Figure 1. Example case for GP4-TL and APP4 calculations. Core lengths are standardized to 10 mm.

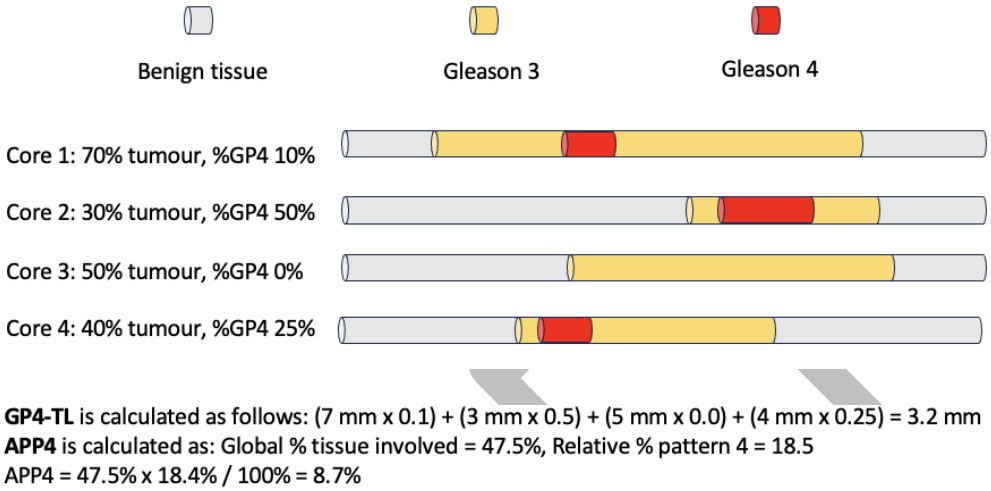

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Figure 2. PRISMA diagram.

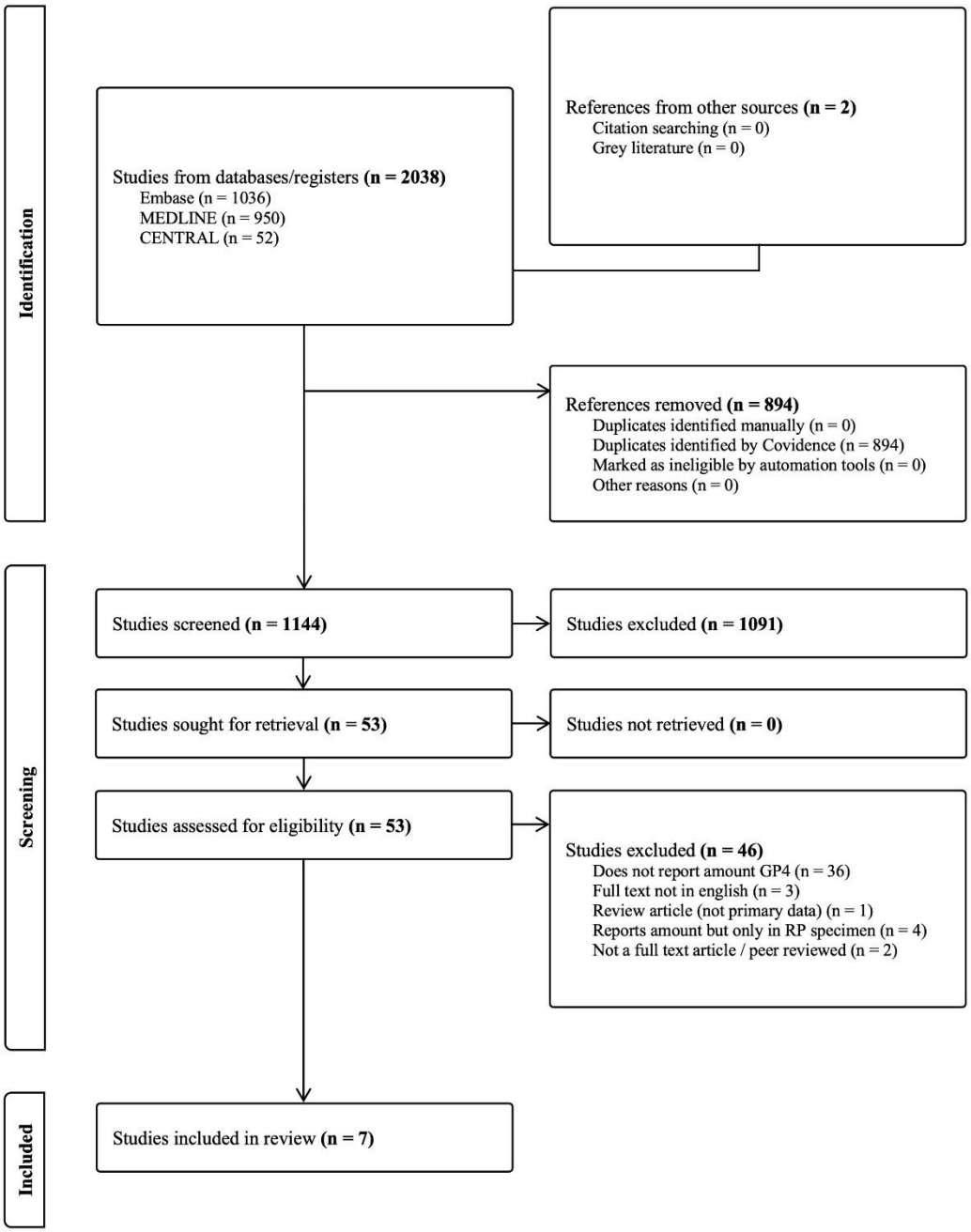

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Table 1. Study characteristics

Author, year	Country	Study type	Absolute amount GP4	Inclusion criteria	N analyzed	Median age (y) (IQR)	Follow up (IQR)	Biopsy strategy	Treatment	Outcome measure
Dean, 2019	U.S.	R	GP4-TL	GG2 with 12 or more reviewed cores on biopsy	457	61.5 (56– 66)	–	Systematic n=249, targeted n=208	Radical prostatectomy	Adverse pathology (GG3/Gleason 4+3 or higher, extraprostatic extension, seminal vesicle involvement, lymph node metastases)
Martell, 2019	Canada	R	APP4	IRPC patients; sufficient information on biopsy to calculate APP4	411	66 (61–71)	5.2 y (2.9 –6.6)	Systematic n=411	HDR brachy boost + EBRT	Biochemical failure (nadir + 2.0 ng/ml) ADT use for biochemical failure Metastatic disease
Sato, 2020	Japan	R	GP4-TL	Gleason 6–7 on biopsy	155 (with GP4 >5% analyzed) (Gleason 6, reference group n=115)	65 (61–69)	5.0 y (3.2–7)	Systematic n=140, MRI targeted n=15	Radical prostatectomy	Adverse pathology (Gleason 4+3 or higher, pT3b, positive lymph nodes) Biochemical recurrence
Delahunt, 2022	Australia New Zealand	R	GP4-TL APP4	IRPC or high-risk prostate cancer; both pattern 3 and 4 on biopsy sample	588	68.5 (63.3–72.9)	10.8 y (9.0–11.9)	–	Radiotherapy (66/70/74 Gy EBRT; HDR brachy boost);	Distant progression Prostate cancer specific mortality All-cause mortality

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									6 or 18 months ADT	
Glicksman, 2022	Canada U.S.	R	APP4	IRPC	227	70 (64–75)	56.5 months (33.5–60.9)	Systematic plus targeted biopsy, number not reported	SBRT (40/5 or 26/2) ± ADT Median duration 4 months; 4.9% used ADT	Biochemical failure (nadir + 2.0 ng/ml) Distant metastasis-free survival
Perera, 2022	U.S.	R	GP4-TL	Gleason 7 prostate cancer, at least 12 cores	457	62 (57–66)	3.0 y (1.7–3.7)*	Systematic n=249, targeted n=208	Radical prostatectomy	Biochemical failure (2 non-consecutive rises in PSA of ≥0.1 ng/ml starting 6 weeks post-RP)
Sato, 2023	Japan	R	GP4-TL	IRPC	228	65 (60.75–69)	–	Systematic n=191 Systematic plus targeted biopsy n=37	Radical prostatectomy	Adverse pathology (Gleason 4+3 or higher, pT3b, positive lymph nodes)

*Followup period only among those who did not experience biochemical recurrence. ADT: androgen deprivation therapy; APP4: absolute percentage pattern 4GG: grade group; EBRT: external beam radiotherapy; GP4: Gleason pattern 4; GP4-TL: total linear length of Gleason pattern 4; HDR: high dose rate; IRPC: intermediate-risk prostate cancer; R: retrospective; SBRT: stereotactic body radiation therapy.

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Table 2. Outcomes stratified by absolute percentage pattern 4 (APP4) cut point			
Study, year **Outcome**	**Time point**	**Optimal cut point**	**Cumulative incidence below and above cut point**
Martell 2019 BCR ADT use for BCR Distant metastasis	At 4 years	 APP4 3.3% APP4 6.6% APP4 17.5%	 2% vs. 10% 2% vs. 10% 0.4% vs. 5.2%
Glicksman 2022 BCR Distant metastasis	At 4 years	 APP4 5% APP4 20%	 2.3% vs. 23.6% 1% vs. 12.5%

ADT: androgen deprivation therapy; BCR: biochemical recurrence.

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