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Review

SIU-ICUD: Localized Prostate Cancer: Pathological Factors That Influence Outcomes and Management

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Abstract: Background/Objectives: Pathological factors are integral in the risk stratification and management of localized prostate cancer. In recent years, there has been an upsurge of studies that uncovered novel approaches and have refined prognostic factors for prostate cancer in needle biopsy and radical prostatectomy (RP) specimens. **Methods:** We conducted a review of literature and summarized the significant recent updates on pathological factors for localized prostate cancer. **Results:** Innovative factors derived from the traditional Gleason grading, such as the extent of Gleason pattern 4 and presence of cribriform pattern are now recognized to significantly improve discrimination of outcome. The components and rules of Gleason grading themselves underwent modifications, and the subsequent prognostic grouping of the different grades (Grade group) have resulted in enhanced stratification of behavior more meaningful in management decision. The approaches for grade reporting in systematic or targeted needle biopsies and in RP with multifocal cancers are also being optimized. Newer tumor growth pattern-based factors such as intraductal carcinoma and atypical intraductal proliferation can have ramifications in management, especially in the background of low to intermediate risk prostate cancers. Gleason grade considerations in the different post-treatment settings and for de novo and residual prostate cancers with varying treatment effects have also been explicated. Likewise, the application of more traditional factors in tumor extent and perineural invasion in biopsy, or positive surgical margin in RP, have also evolved. **Conclusions:** Some of these newer pathological factors are now officially recommended in standardized pathology reporting protocols and are applied in the management decision for localized prostate cancer.

Keywords: prostate; cancer; pathological; prognostic; factors; elements; reporting; biopsy; prostatectomy

1. Introduction

Pathological factors are among the major determinants that guide clinical decisions for localized prostate cancer [1–3]. Traditional factors in needle biopsy have long been used for risk stratification and preoperative prognostic tools or nomograms [4,5], and are also monitored in patients during active surveillance (AS) for potential reclassification [1,6,7]. After radical prostatectomy (RP), adverse factors are used in postoperative prognostic tools for further management decisions [5,8–10]. In recent years, there has been an upsurge in studies looking at the usefulness of nuanced histological factors in prostate cancer to enhance prognostication. New recommendations were made on prostate cancer grading and its derivatives in the 2014 and 2019 International Society of Urological Pathology (ISUP) consensus conferences and the 2019 Genitourinary Pathology Society (GUPS) white paper [11–14]. Many of these recommendations were codified in the 2022 World Health Organization (WHO) classification [15]. Because of the importance of pathological factors, standardized cancer reporting checklists such as the International Collaboration on Cancer Reporting (ICCR) datasets (http://www.iccr-cancer.org (accessed on 31 January 2025)) and the College of American Pathologists (CAP) cancer protocols (http://www.cap.org (accessed on 31 January 2025)) are being recommended or required for use by pathologists for consistency in reporting. Herein, we summarize the recent significant updates on pathological factors for localized prostate cancer, defined as up to clinical stage T3 (by digital rectal examination [DRE] prostate cancer without nodal or distant metastasis, in needle biopsy and RP.

2. Acinar Adenocarcinoma and Subtypes

The vast majority (>95%) of prostate cancers are acinar adenocarcinoma, which exhibits a range of histological patterns that correlate with its degree of differentiation [15,16]. This unique spectrum of histological patterns forms the basis for the Gleason grading system [17]. Tumors that are purely Gleason pattern (GP) 3 are overwhelmingly organ-confined with limited capacity for extraprostatic extension (EPE), and if resected, have virtually no risk for metastasis [18–21]. The presence and increasing proportion of higher-grade patterns in GP 4 and GP 5 increase the risk for local aggressiveness and metastasis. A minority of acinar adenocarcinomas also have unusual histological features [15]. The unusual adenocarcinoma patterns are diagnosed mostly as low-grade localized tumors, whereas adenocarcinoma subtypes such as signet-ring cell-like, sarcomatoid, and pleomorphic giant cell are aggressive and often present as locally advanced or metastatic tumors (Table 1). EPE has been reported in 46.1% of prostatic intraepithelial neoplasia (PIN)-like carcinoma and 46% of foamy gland carcinoma [22,23]. Cancer registries in the United States recorded 0.38% to 3.3% of prostate cancers as unusual histologies or subtypes of acinar adenocarcinoma [24,25].

Table 1. 2022 World Health Organization classification of carcinomas of the prostate gland.

	Carcinoma Types	Increases Risk *	Likelihood of Extent at Diagnosis
I.	*Adenocarcinoma of the prostate*		
1.	Acinar (usual) adenocarcinoma	No	Localized > non-localized
A.	*Acinar adenocarcinoma subtypes*		

Table 1. *Cont.*

	Carcinoma Types	Increases Risk *	Likelihood of Extent at Diagnosis
a.	Signet-ring cell-like acinar adenocarcinoma	Yes	Non-localized > localized
b.	Pleomorphic giant cell acinar adenocarcinoma	Yes	Non-localized > localized
c.	Sarcomatoid acinar adenocarcinoma	Yes	Non-localized > localized
d.	Prostatic intraepithelial neoplasia-like carcinoma	No	Localized > non-localized (EPE in 46.1%)
B.	*Unusual histological patterns of acinar adenocarcinoma*		
a.	Atrophic pattern adenocarcinoma	No	Localized > non-localized
b.	Adenocarcinoma with aberrant p63 positivity	No	Localized > non-localized
c.	Pseudohyperplastic adenocarcinoma	No	Localized > non-localized
d.	Microcystic adenocarcinoma	No	Localized > non-localized
e.	Foamy gland adenocarcinoma	No	Localized > non-localized (≥pT3 in 46%)
f.	Mucinous adenocarcinoma	No	Localized > non-localized
2.	Intraductal carcinoma **	Yes	Non-localized > localized
3.	Ductal adenocarcinoma	Yes	Non-localized > localized
4.	Adenocarcinoma with neuroendocrine differentiation	Yes	Non-localized > localized
II.	*Squamous carcinoma of the prostate*		
1.	Adenosquamous carcinoma	Yes	Non-localized > localized
2.	Squamous cell carcinoma	Yes	Non-localized > localized
3.	Adenoid cystic (basal cell) carcinoma	Yes	Non-localized > localized

* Risk for adverse pathology at RP, metastasis, and poorer outcome. ** Includes the vast majority of intraductal carcinoma with concomitant invasive adenocarcinoma. EPE, extraprostatic extension.

3. Modified Gleason Grading

3.1. Grade Group

The Gleason grading system has been applied for prostate cancer prognostication for more than half a century [17,26,27]. While the original Gleason grading approach of combining two grades or GPs to derive a Gleason score (GS) has remained, the current application of Gleason grading has evolved. The differences are in grading rules, pattern compositions, and, most importantly, their prognostic associations. Changes made over time were codified at the 2004, 2014, and 2019 ISUP consensus conferences and in the 2019 GUPS white paper [11–14,28]. Although there are a few discrepancies, the 2019 ISUP and 2019 GUPS recommendations on grading of prostate cancer are largely in agreement [29,30].

A major departure from the traditional Gleason grading is the introduction of the Grade group (GG), also referred to as the WHO/ISUP grade, ISUP grade, or ISUP GG. Moreover, 13 GG is a compression of GSs into five clinically meaningful prognostic groups, namely GG 1 to GG 5. The GG is a culmination of a series of events that led to continued grading refinements and evolving clinical practices, especially with the rapid expansion of the AS program for lower-risk prostate cancer patients. First, there is a gradual disappearance of GP 1 and GP 2 in routine pathology practice. Most experts now recognize that the originally described GP 1 and GP 2 in the pre-immunohistochemistry era were benign adenosis (atypical adenomatous hyperplasia) [31]. Second, over the years there has

been a gradual narrowing of GP 3 with a shift of adverse architectural patterns toward GP 4 (Figure 1). The grade migration resulted in the contemporary GS 6 cancers being vastly localized tumors, and if resected, they have minimal to no incidence of metastasis or death [18–21,32]. Third, contemporary GS 7 cancers are much more heterogeneous, with a differing behavior between GS 3 + 4 and GS 4 + 3 cancers [33]. There also has been an inflation of GS 7 because of grade migration, additionally enhanced in RP as many GS 6 patients stayed on AS, further supporting the division of the large GS 7 group into two prognostic categories [34]. Fourth, studies identified the optimal groupings of the different GSs to include splitting of GS 7 and lumping of GS 9 and 10. Pierorazio et al. [35] showed biochemical recurrence (BCR)-free survival (BCRFS) rates in GS 6, GS 3 + 4, GS 4 + 3, GS 8, and GS 9–10 cancers of 94.6%, 82.7%, 65.1%, 63.1%, and 34.5%, respectively, and this study became the basis for the GGs.

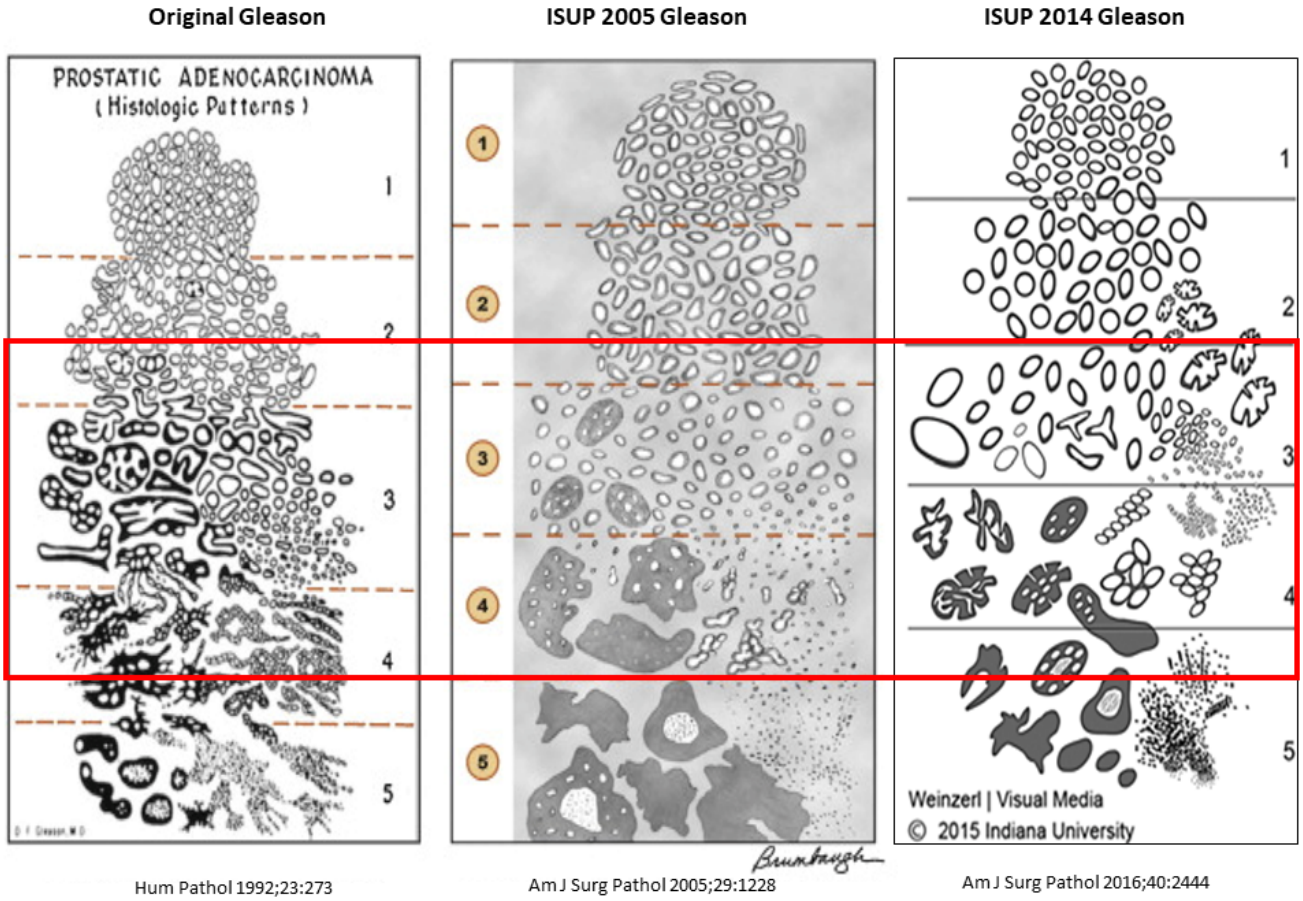


Figure 1. Evolution of Gleason patterns. One major change is the upgrading of adverse patterns from Gleason pattern 3 to Gleason pattern 4 (red box). Original Gleason image [17] published with permission from Elsevier. ISUP 2005 Gleason image [26] and ISUP 2014 Gleason image [13] published with permission from Wolters Kluwer Health, Inc. ISUP represents International Society of Urological Pathology.

The 5-tiered prognostic group consists of GGs 1 (GS 6), 2 (GS 3 + 4), 3 (GS 4 + 3), 4 (GS 8), and 5 (GS 9–10) (Table 2) [13]. The advantage of GG reclassification is that GG 1 is now the baseline lowest grade in the spectrum instead of GS 6, which may facilitate AS counseling of patients who may falsely perceive their low-risk tumor as an intermediate risk because it is in the middle of a GS 2 to 10 scale. Several studies have validated the use of GG, including in patients treated with surgery and radiotherapy [36–41]. The current recommended practice is to routinely report GG alongside GS. Although GG 4 appears

to be heterogeneous with GSs 4 + 4, 3 + 5, and 5 + 3, data so far show no difference in prognosis in these GSs, supporting their grouping into a single prognostic group [42].

Table 2. Histological definition of Grade group [13].

Grade Group	Gleason Score	Definition
1	6	Only individual, discrete, well-formed glands
2	3 + 4 = 7	Predominantly well-formed glands with a lesser component of poorly formed/fused/cribriform/glomeruloid glands
3	4 + 3 = 7	Predominantly poorly formed/fused/cribriform/glomeruloid glands with a lesser component of well-formed glands [1]
4	4 + 4 = 8, 3 + 5 = 8, 5 + 3 = 8	Only poorly formed/fused cribriform/glomeruloid glands *or* Predominantly well-formed glands and a lesser component lacking glands [2] *or* Predominantly lacking glands with a lesser component of well-formed glands [2]
5	4 + 5 = 9, 5 + 4 = 9, 5 + 5 = 10	Lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands [1]

[1] For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of <5% well-formed glands is not factored. [2] Poorly formed/fused/cribriform glands can be more of a minor component.

3.2. Contemporary Gleason Patterns

The Gleason grading is based almost purely on histological architectures with the additional element of tumor necrosis for some of GP 5 architectures [11–13,15]. The pattern composition of the current GPs is different from the original GPs, with the most significant change being in GP 3 (Table 3).

Table 3. Contemporary architectures of Gleason patterns 3, 4, and 5.

Gleason Pattern (or Grade)	Gleason Architectural Patterns
3	Well-formed glands, branched well-formed glands
4	Cribriform, glomeruloid, fused, poorly formed glands Hypernephromatoid cancer no longer used
5	Single cells, cords, solid sheets, small solid cylinders, and solid medium-tolarge-sized nests with rosette-like spaces Unequivocal comedonecrosis, even if focal

GP 3 is now composed of individual discrete well-formed glands (Figure 2).

The basic architectures of contemporary GP 4 include cribriform, glomeruloid, fused, and poorly formed glands (Figure 3) [11–13,15].

A ductal pattern without necrosis is also considered GP 4. Among GP 4 architectures, the cribriform pattern is associated with worse outcomes, and its presence is now recommended to be reported in GS 7 and 8 prostate cancers [11,12,43–48]. Because of the importance of consistency in diagnosis, there have been recent attempts to formally define cribriform pattern (Table 4) [49,50].

Using the ISUP criteria, an interobserver study among nine prostate pathology experts showed 90% consensus (2/3 agreement) reached in diagnosing cribriform carcinoma [51]. Because of the association of cribriform to worse outcomes, some authors suggest designating cribriform as a separate prognostic group [48]. GP 5 is the least differentiated pattern, characterized by consolidation, dispersal, or necrosis of tumor cells (Figure 4) [11–13,15].

Outside of the architectural patterns (GPs), there are studies suggesting that grading can be further improved by the addition of other histological features such as reactive stroma (stromogenic cancer) and nuclear features [52–54].

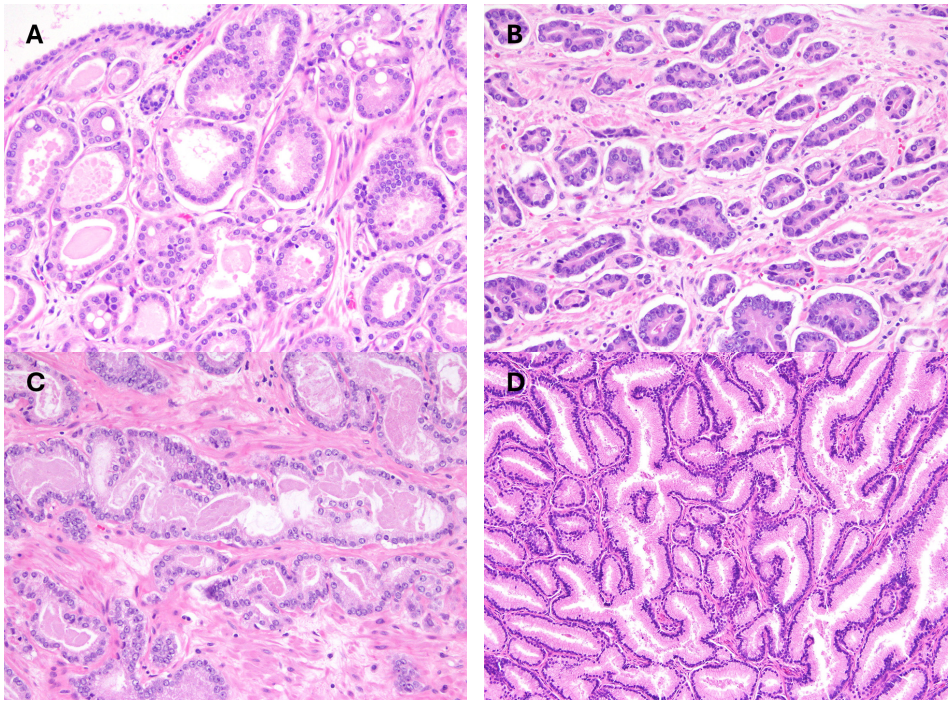


Figure 2. Gleason pattern 3 with (**A**) round, (**B**) small (microacinar), (**C**) elongated, and (**D**) large or branching glands.

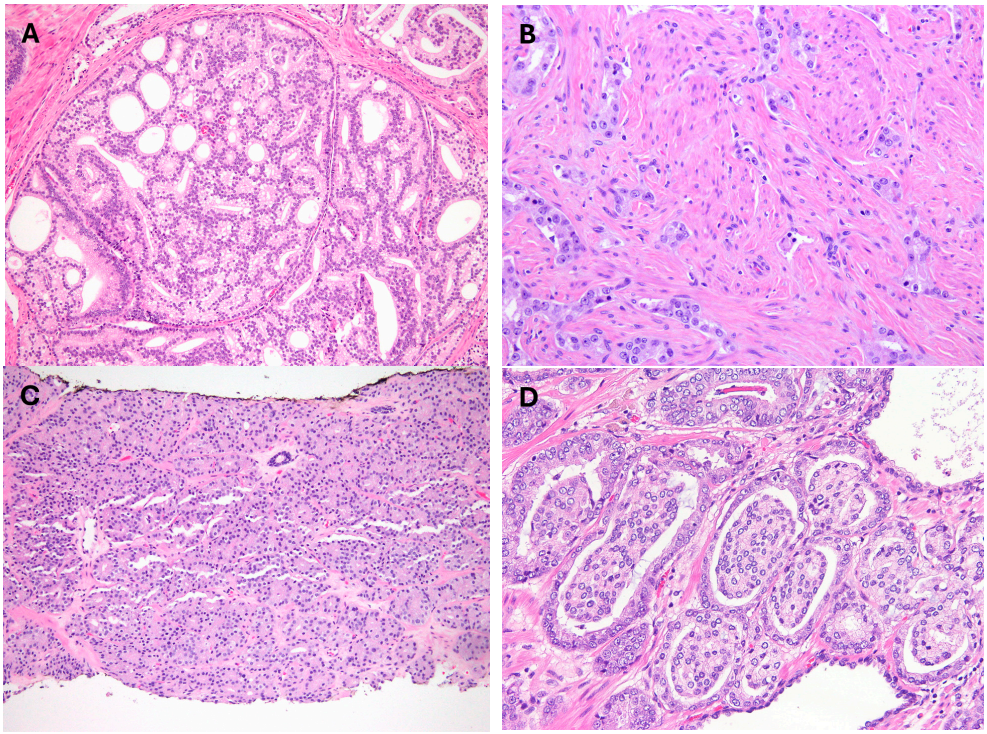


Figure 3. Gleason pattern 4 with (**A**) cribriform, (**B**) poorly formed, (**C**) fused, and (**D**) glomeruloid glands.

Table 4. Proposed definitions for cribriform glands. ISUP represents International Society of Urological Pathology.

Authors	Cribriform Definition
van der Kwast et al. (ISUP) [49]	A confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina easily visible at lower power (objective magnification 10×). There should be no intervening stroma or mucin separating individual or fused gland structures.
Shah et al. [50]	A dense sheet of tumor cells forming multiple lumens with transluminal bridging, imparting a "sieve-like" architecture, in which a majority of intraglandular cells are not in direct contact with stroma or mucin, and a clear luminal space along the periphery of the gland accounts for <50% of the glandular circumference.

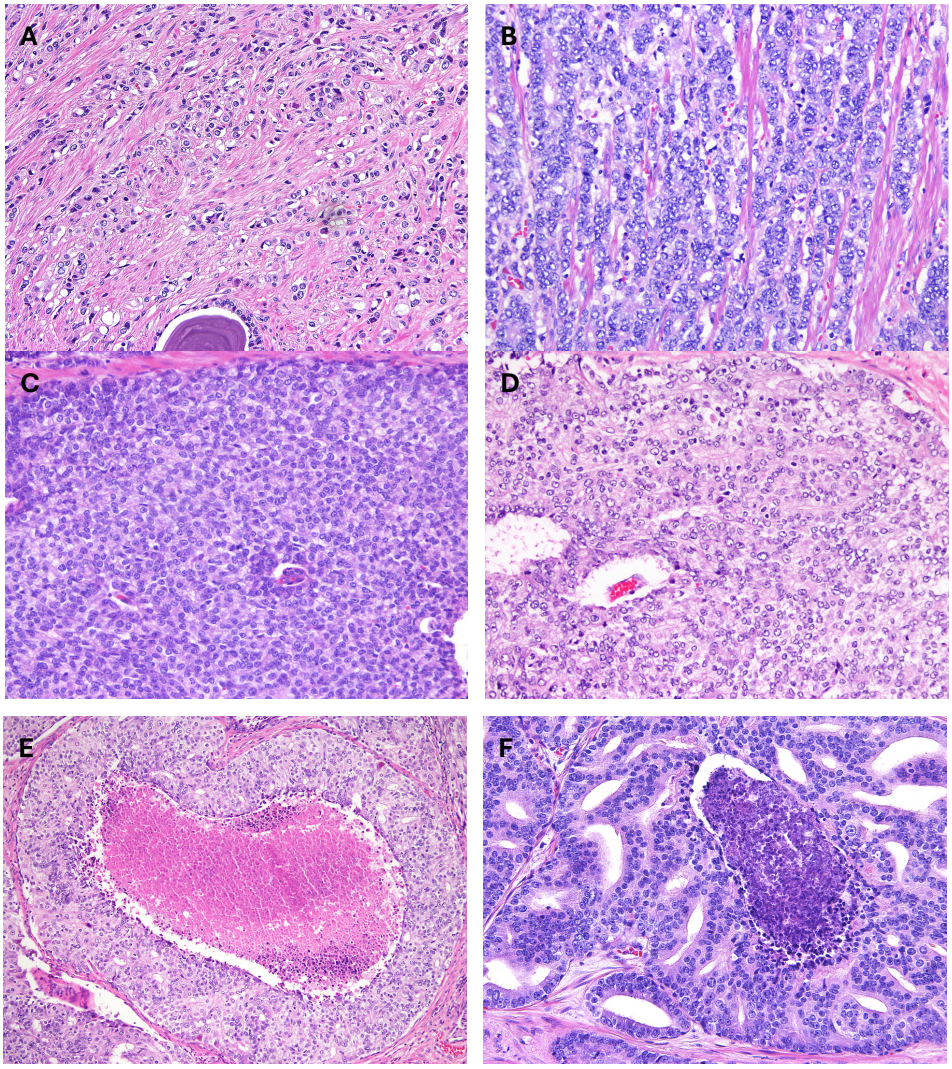


Figure 4. Gleason pattern 5 with (**A**) single infiltrative cells, (**B**) cylinders, (**C**) solid, (**D**) solid with pseudorosettes, (**E**) comedonecrosis, and (**F**) cribriform glands with necrosis patterns.

3.3. Modern Gleason Grading Rules

The original concept devised by Dr. Donald F. Gleason in the 1960s of grouping several architectures into GPs and then combining GPs for a GS (sum of two addends referred to as primary GP and secondary GP) has remained [17,26,27]. However, additional modifications or exceptions to these rules were made in the last two decades [11–13,28]. The series of

modifications in grading through the years had shifted and enhanced the prognostic ability of the contemporary GS. Grading rules between needle biopsy and RP have variations as well (Table 5). Van der Slot et al. [55] showed that interobserver agreement for GS is substantial (Krippendorff's α 0.626). Studies suggest that GS 7 with minimal (<5%) GP 4 in biopsy has similar pathologic parameters in RP and outcome compared to GS 6 tumors [56,57].

Table 5. Current Gleason score rules in biopsy and RP specimens. RP represents radical prostatectomy and ISUP represents International Society of Urological Pathology.

Number of GP Present	Biopsy	RP	Example Scenarios
One	Double the GP as *primary* (first addend) and *secondary* (second addend) GPs	Similar	100% GP 3 **GS 3 + 3 = 6**
Two	Primary GP is most prevalent Secondary GP is less prevalent	Similar	60% GP 3 40% GP 4 **GS 3 + 4 = 7**
	Exception: secondary GP not included in GS if of lower grade and minimal (≤5%)	Similar	95% GP 4 5% GP 3 **GS 4 + 4 = 8**
		Exception: secondary GP if of higher GP and minimal (≤5%) is not included in GS and is reported as *minor* GP (ISUP only)	95% GP 3 5% GP 4 Biopsy: **GS 3 + 4 = 7** RP: **GS 3 + 4 = 7 or GS 3 + 3 = 6, with minor GP 4** (ISUP only)
Three (GPs 3, 4 and 5)	Primary GP is most prevalent Secondary GP is the second most prevalent	Similar	65% GP 4 25% GP 5 10% GP 3 **GS 4 + 5 = 9**
	Exception: If *tertiary* GP (least prevalent) is higher than secondary GP, it is included in GS as secondary GP	Exception: If tertiary GP is higher than secondary GP and is >5%, it is included in GS as secondary GP	60% GP 4 30% GP 3 10% GP 5 Biopsy and RP: **GS 4 + 5 = 9**
		Exception: If tertiary GP is higher than secondary GP but is ≤5%, it is not included in GS and reported as *minor tertiary* GP	60% GP 4 37% GP 3 3% GP c5 Biopsy: **GS 4 + 5 = 9** RP: **GS 4 + 3 = 7, with minor tertiary GP 5**

GP, Gleason pattern; GS, Gleason score. Bolded, represent the scenarios and corresponding GS.

4. Reporting of Grades

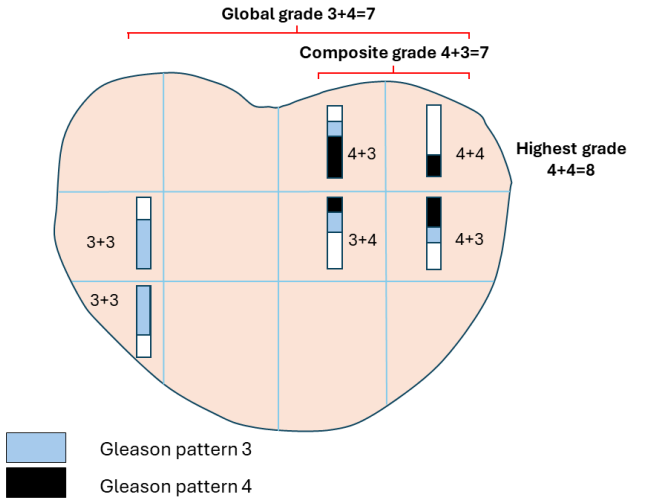
4.1. Reporting Grade in Biopsy

At the specimen level (or per site), systematic biopsy reporting and individual grades for every cancer-positive specimen should be rendered [58–61]. At the case level (or aggregate sites) of systematic biopsy reporting, there are different approaches for reporting the grade of a biopsy set with multiple positive specimens, including by highest grade and global grade, with the highest grade more commonly used by clinicians for decision-making (Table 6) [62–64].

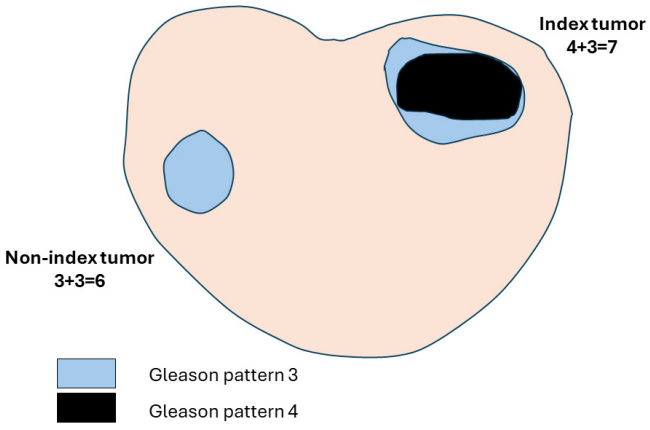
Tolonen et al. [65] compared the worst GS and overall GS and showed that both are strong predictors of BCR, and no significant prognostic difference was shown between these two grades. Arias-Stella et al. [66] introduced the composite grade to correlate the grade in biopsies to the presumed dominant nodule and showed a better overall correlation with RP GS (Figure 5).

Table 6. Approaches in reporting grades at the case level for biopsies with prostate cancer.

Grade	Definition
Highest or worst grade	Highest grade in any positive specimen in a biopsy set.
Global or overall grade	Grade derived by considering all positive specimens in a biopsy set.
Grade in the largest-volume cancer	Grade of the specimen with the largest tumor volume in a biopsy set.
Composite grade	Assign a grade to the entire biopsy set on the basis of positive cores from contiguous anatomic locations of the presumed dominant nodule. Tumor morphology in these separate cores is required to be similar to be included.



(**A**)



(**B**)

Figure 5. (**A**) Example of a biopsy set with different highest (Gleason Score (GS) 4), global (GS 3 + 4), and composite (GS 4 + 3) grades. (**B**) Corresponding radical prostatectomy shows index (GS 4 + 3) and non-index (GS 3 + 3) tumors.

A global grade should be reported for every magnetic resonance imaging (MRI)-targeted lesion [11,12]. Deng et al. [67] compared global grade, highest grade, and largest volume grade in MRI-targeted biopsies and showed that global, highest, and largest volume grades had substantial agreement with RP-targeted lesion grade. However, targeted lesion global grade yields slightly better agreement than either targeted highest or largest volume grade. The risk of undergrading when using only MRI-targeted biopsy without systematic

biopsy should also be underscored [68]. The volume of biopsy with tumor area has also been shown to influence correlation with RP grade, including with variant histologies [69,70].

4.2. Reporting Grade in Radical Prostatectomy

Prostate cancer is commonly multifocal, and in this situation, grade can be derived based on the largest tumor, highest stage tumor, highest grade tumor, and global (overall) grade (Table 7). If GSs of the largest, highest-stage, and highest-grade lesions are not identical, it is recommended that the different grades should be reported separately (Figure 6) [11]. Studies showed that in RP with multifocal tumors and grade heterogeneity, grade is best determined by the highest grade instead of the grade of the largest lesion or by global grade [71,72]. The problem of using global grade is it introduces spurious lowering of the grade by non-index tumors with GP 3 in the prostate; many of these secondary lesions are clinically insignificant.

Table 7. Approaches in reporting grades in radical prostatectomy with multifocal tumors.

Grade	Definition
Highest grade	Highest grade among the multiple tumor nodules.
Grade of the largest tumor	Grade of the largest among the multiple tumor nodules.
Grade of the highest-stage (pT) tumor	Grade of tumor nodule with extraprostatic extension or seminal vesicle extension.
Global grade	Aggregate grade of all the tumor nodules.

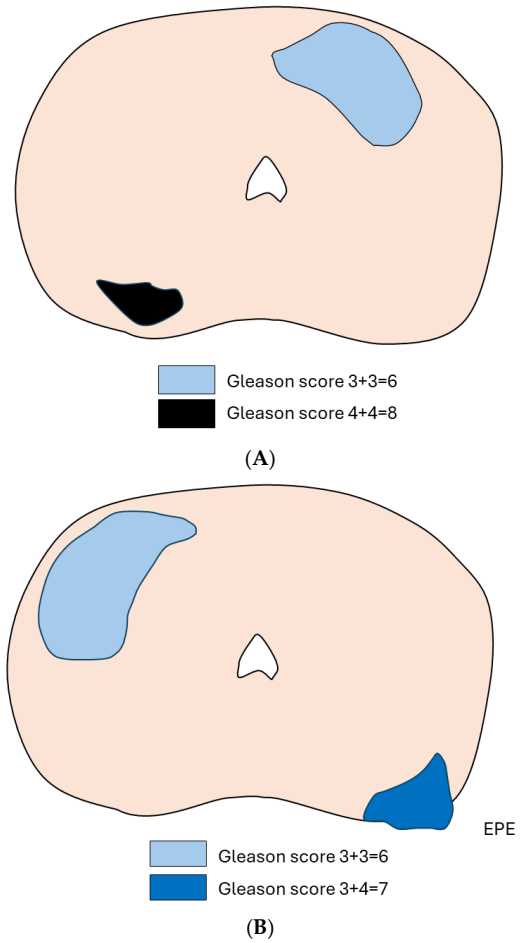


Figure 6. Examples of multifocal radical prostatectomy with grades are different between the (**A**) larger and smaller higher-grade tumors and (**B**) larger and smaller higher-stage tumors. In these examples, the smaller tumors are considered the index tumor. EPE represents extraprostatic extension.

5. Prognostic Impact of Gleason Patterns

5.1. Cribriform Pattern

Cribriform gland is associated with a greater risk for adverse pathology at RP, worse BCR, metastasis, and prostate cancer-specific mortality (CSM) [43–46,48]. In biopsy, cribriform architecture is independently associated with worse disease-specific survival (DSS) [19]. Studies by Kweldam et al. [73–75] in prostate biopsies showed that cribriform architecture (invasive cribriform and/or intraductal carcinoma [IDC]) in GS 3 + 4 tumors was an independent predictor of BCR [73], and that GS 3 + 4 without cribriform glands did not have a statistically different DSS than GS 6 cancers [74], and similarly that GS 7 cancers without cribriform glands did not have a statistically different BCRFS after RP compared to GS 6 tumors [75]. Thus, patients with prostate cancer showing cribriform glands in needle biopsy should be considered suboptimal for AS. The presence of cribriform glands in GS 7 and GS 8 prostate cancers should be reported in biopsy and RP [11,12]. Several studies have explored the effect of the size of cribriform glands in stratifying outcome [76–78]. Chan et al. [76] identified 0.25 mm as the optimal cut-off to identify aggressive disease. Using a simpler definition for large cribriform, i.e., at least twice the size of adjacent benign glands for large cribriform gland, Hollemans et al. [78] showed that large cribriform glands in GS 3 + 4 cancer in RP were an independent predictor of BCRFS.

5.2. Other Gleason Patterns

Glomeruloid glands, including those with complex architecture, appear to be associated with better outcomes when compared to cribriform glands and other GP 4 architectures in GS 7 tumors. In the study by Choy et al. [46] of GS 7 cancers in RP, glomeruloid gland was associated with better survival when compared to GS 7 cancers without this architecture. Hollemans et al. [79] divided glomeruloid glands into simple and complex architectural growths and showed that, in contrast to cribriform, simple or complex glomeruloid glands were not independent predictors of BCRFS in GS 3 + 4 tumors [79]. Data suggest that among GP 4 architectures in GS 7 tumors, fused and poorly formed glands appear to be intermediate between cribriform glands associated with worse outcomes and glomeruloid glands associated with favorable outcomes [46,80]. Among GP 5 architectures, comedonecrosis pattern is suggested to be able to substratify the poor outcome of high-grade prostate cancer [81–83]. Data are limited on the prognostic effects of other GP 5 architectures individually in high-grade prostate cancer.

6. Quantitative Grading

Studies have shown a strong correlation between the increasing percentage of GP 4 (% GP 4) and prostate cancer aggressiveness. Incremental increase in % GP 4 in GS 7 cancers in biopsy independently predicts adverse pathology in RP and BCR [84]. Quantifying % GP 4 in biopsy can identify various intermediate risk groups with the corresponding RP grade [85]. Reporting % GP 4 is recommended in GS 7 cancers in biopsy [11,12]. An advantage of reporting % GP4 is that it further substratifies GS 3 + 4 tumors, as the prognosis of small % GP4 and high % GP 4 will be different. Information on % GP 4 is important in selecting patients for AS, especially in favorable intermediate-risk patients being considered for AS. Sadimin et al. [86] showed that reproducibility in assessing % GP 4 in biopsy had substantial agreement if there was a significant amount of cancer (>10%) in a biopsy core. If the tumor focus in a core was small (<10%), agreement in % GP 4 was only moderate. Several studies suggest that a minimal (<5%) amount of GP 4 has no prognostic impact on GS 3 + 4 tumors compared to GS 6 tumors [56,57,87,88]. If other factors are acceptable, patients with GS 3 + 4 cancers and a small % GP 4 in biopsy can be considered for AS.

There are other methods to report the absolute extent of GP 4 in biopsy (Table 8).

Table 8. Different approaches in recording the extent of Gleason pattern (GP) 4 in biopsy.

Measure	Definition
Individual % GP 4	mm of GP 4 tissue/total mm of cancer in a core or site
Overall % GP 4	mm of GP 4 tissue (all cores)/total mm of cancer (all cores)
Maximum % GP 4	Single core with the greatest involvement by GP 4
Total length (mm) GP 4	Sum of the total length in mm of GP 4 across all cores
Length (mm) of GP in greatest core	Length in mm of GP 4 in greatest core with highest GP 4

Length in millimeters (mm) of GP 4 in GS 3 + 4 tumors in biopsies may have better predictive ability for adverse pathology in RP and BCR than % GP 4 [89,90]. Dean et al. [89] applied 3 different quantitation methods for GP 4 in biopsies with GS 3 + 4 tumors and showed that maximum % GP 4 in any single core, overall % GP 4 (GP 4 mm/total cancer mm), and total length in mm of GP 4 across all cores were all significantly associated with increased risk of adverse pathology in RP.

The incremental increase in % GP4 in RP also corresponds to an increasing risk of BCR; however, its additive clinical value beyond common clinicopathologic factors needs to be confirmed [46,85,91]. Sauter et al. [85] demonstrated a continuous increase in risk for BCR with increasing % GP 4 fractions and with small differences in outcome at clinically important thresholds (0% vs. 5% or 40% vs. 60% GP 4). Choy et al. [46] divided % GP 4 into 1–20%, 21–50%, 51–70%, and >70% and showed a 5-year BCRFS of 84%, 74%, 66%, and 32%, respectively. Other studies used different metrics for the amount of GP 4 in RP [92–94]. Andolfi et al. [94] reported that for each 1 cm3 of GP 4 in RP, there was an associated 6- to 8-fold higher serum PSA level in comparison to GP 3.

The importance of % GP 4/5 to predict BCR and survival has long been recognized [95]; that led to acceptance of reporting tertiary GP 5 in GS 7 tumors. The study by Berney et al. [56] in needle biopsies of localized prostate cancer showed that the worst % GP 4/5 (% GP 4/5 in worst positive core) and overall % GP 4/5 (global % GP 4/5) were both significant predictors of prostate cancer death and suggested that either approach can be used.

7. Intraductal Carcinoma

IDC is significantly associated with adverse outcomes for prostate cancer in needle biopsy and RP (Figure 7) [44,96–101]. The meta-analysis by Miura et al. [96] showed that IDC in localized prostate cancer was associated with lower BCRFS and cancer-specific survival (CSS). In biopsy, the presence of IDC had been associated with high-grade and high-stage cancer in RP, distant metastasis at presentation, poorer CSS, and overall survival (OS) [98,100]. Thus, IDC in biopsy with GS 3 + 4 prostate cancer should be considered sub-optimal for AS. Several criteria have been proposed for the diagnosis of IDC [96,99,100,102], but the most applied definition is that by Guo and Epstein [100]. Using the different definitions, IDC is significantly associated with lower BCRFS, CSS, and OS by Guo and Epstein [100] (pooled HR 1.86 for BCRFS; pooled HR 2.6 for CSS; pooled HR 1.61 for OS), McNeal and Yemoto [102] (pooled HR 2.58 for OS), Cohen et al. [99] (pooled HR 1.86 for BCRFS), 2016 WHO [103] (pooled HR 5.78 for CSS), and a combination of these published criteria (pooled HR 2.5 for BCRFS) [96].

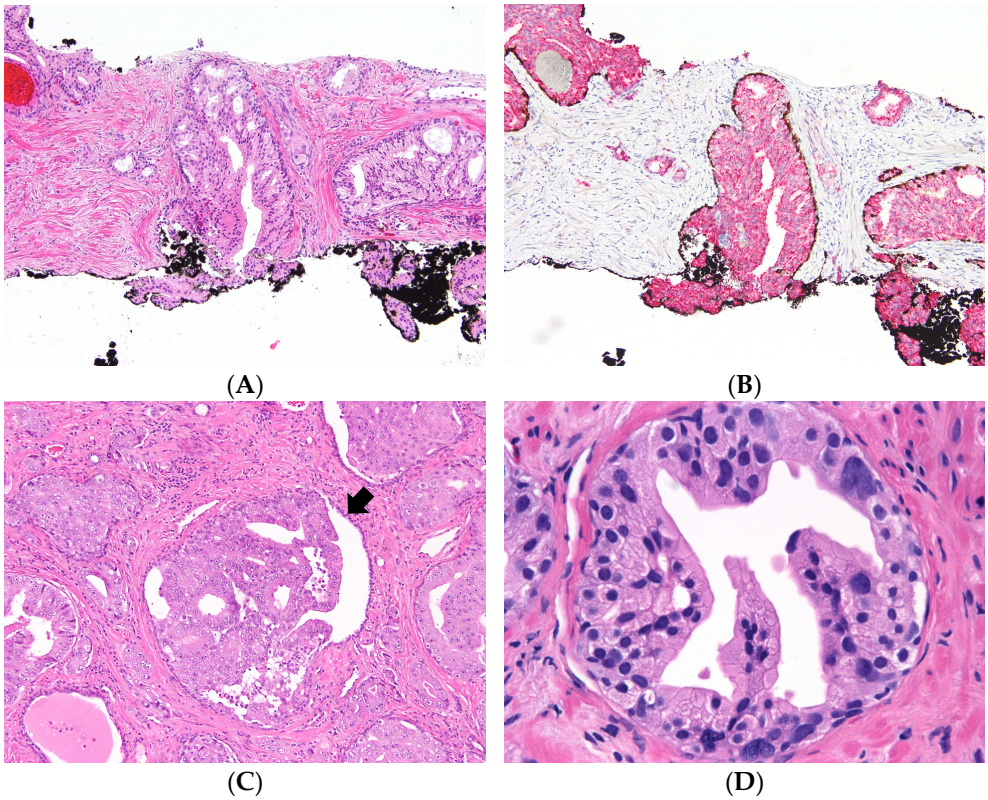


Figure 7. (**A**) Intraductal carcinoma in biopsy with (**B**) basal cell marker expression. (**C**) Intraductal carcinoma with basal cells discernible in H&E (arrow). (**D**) Non-cribriform Intraductal carcinoma with markedly pleomorphic nucleoli.

The majority of IDC is considered an intraductal spread of cancer at the later phase of prostate carcinogenesis. Loss of PTEN expression, which is strongly associated with advanced prostate cancer, is present in 84% of IDC, further supporting its advanced state [104]. There is also a strong association of comedonecrosis (traditionally a GP 5 pattern) with IDC [105]. Some authors suggest that IDC can also be a "precursor-like" lesion, especially those that occur in isolation or are associated with adjoining microcarcinoma [106]. Rarely, IDC occurs without a concomitant invasive carcinoma in biopsy [107]. Even if IDC is identified in isolation in biopsy, it is suggested that therapy similar to that used in non-low-risk invasive carcinoma should be considered. A repeat biopsy, with MRI to detect a lesion, is a prudent approach since most cases of IDC are associated with high-grade cancers that likely will be sampled in the follow-up biopsy. There are extremely rare examples of IDC in a fully examined prostate purely confined within the ducts and without a concomitant invasive adenocarcinoma [108,109]. There are also uncommon cases of IDC with concomitant few GS 6 glands [110].

There is divergence in the recommendations for grading of IDC. Both ISUP and GUPS recommend that isolated IDC should not be graded, and its presence should be reported [11,12]. However, there is discordance when IDC occurs with concomitant invasive carcinoma. ISUP recommends that IDC should be incorporated into grades, whereas GUPS recommends that IDC should not be incorporated into grades [11,12]. However, Rijstenberg et al. [111] showed that disparity in grading approaches by ISUP and GUPS only had minimal impact, with grade change affecting only 1.6% of prostate biopsy and 0.6% of RP specimens. This issue will be addressed in a joint GUPS and ISUP expert consultation in March 2025. Because of the challenge in separating IDC and invasive cribriform gland and their shared clinical significance, several studies and reporting checklists have merged these two adverse tumor growths into "IDC and/or cribriform" or as high-grade cribriform

patterns [58,62,112,113]. This may be beneficial in parts of the world where the availability of immunohistochemical stains is limited.

8. Atypical Intraductal Proliferation

Atypical intraductal proliferation (AIP) shows architectural complexity and/or cytological atypia greater than that seen in high-grade prostatic intraepithelial neoplasia (HGPIN) but falling short of the morphologic criteria for IDC (Figure 8) [114]. Lesions that were formerly referred to as "cribriform HGPIN" are now classified as AIP [12,115,116]. AIP in biopsy is potentially a marker of undersampled cancer, including IDC, and of adverse pathological features in RP [114,117–119]. Several studies demonstrated overlap in ERG expression and loss of PTEN staining between AIP and IDC, showing that AIP and IDC can be part of a morphological spectrum and can be seen in transition [117,118,120]. Presence of AIP in biopsy, whether with low-risk prostate cancer or in isolation, should warrant repeat biopsy, including MRI targeting, to search for higher-grade cancer, including IDC.

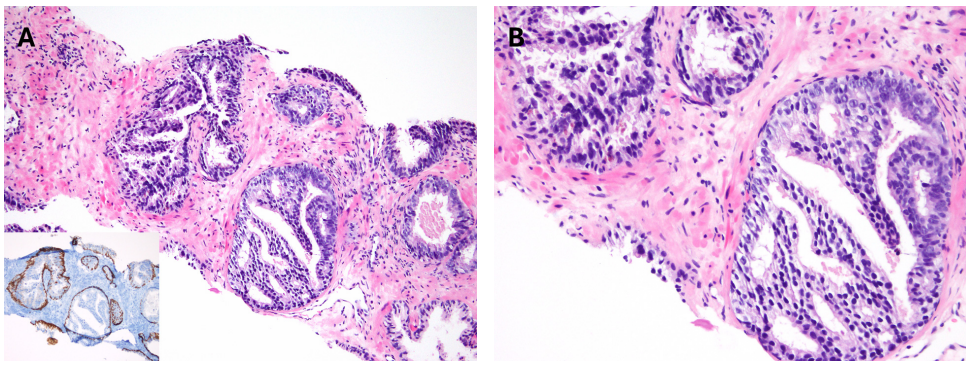


Figure 8. (**A**,**B**) Atypical intraductal proliferation in biopsy confirmed by presence of basal cell marker expression (inset).

9. Treatment-Related Effects

Radiation therapy (RT), such as external beam delivery or brachytherapy seed implant, is one of the management options for localized prostate cancer. RT can cause alterations in cancer morphology that vary from minimal to marked changes [121–123]. Carcinoma with RT effects should not be graded (Figure 9). Treatment effects may also be minimal or absent in cancer after RT. Especially in the setting of rising levels of PSA, this may represent a recurrence or new onset (de novo) cancer after RT. GS can be rendered to cancer with absent or minimal treatment effects in a post-RT biopsy setting. Ablative treatments such as high-intensity focused ultrasound (HIFU) and cryotherapy are increasingly used as focal therapies for localized prostate cancer [121–126]. In HIFU and cryotherapy, residual cancer will not show significant morphologic changes, and thus, a grade can be rendered. Androgen deprivation therapy (ADT) is usually given with RT in localized prostate cancer, and treatment effects overlap with the histological findings after RT [1,2,121–123]. Similar to RT, prostate cancer with profound hormonal treatment effects should not be graded.

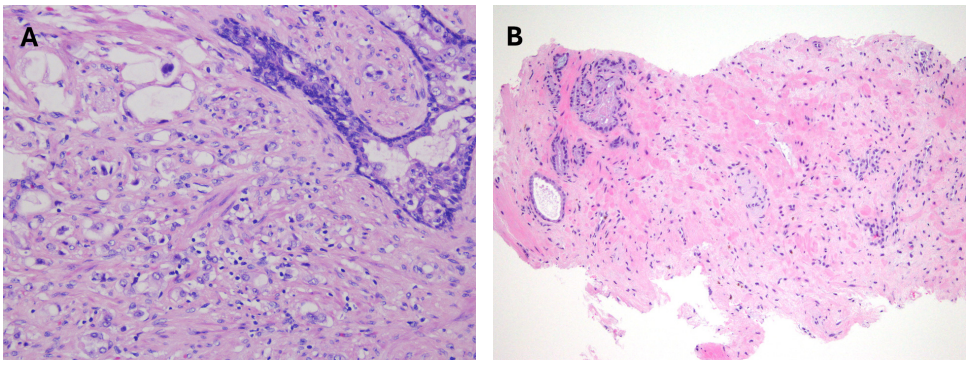


Figure 9. (**A**) Adenocarcinoma with radiation treatment effects. (**B**) Residual cancer adjacent to the high-intensity focused ultrasound-treated area.

10. Tumor Volume or Extent

10.1. Tumor Volume in Biopsy

Tumor quantitation in biopsy has been traditionally performed by reporting the number of positive core(s) and percentage of core involvement by tumor. Inclusion of the number of positive cores enhances the predictive accuracy of preoperative nomograms. Further, the overall percentage or the greatest percentage in the most involved core are independent predictors of BCR and clinical outcomes regardless of treatment, with the percentage deemed superior to counting the number of positive cores [127]. There are several ways of measuring tumor extent in a biopsy set; however, the optimal method remains unclear [128–130]. Several studies assessed the significance of tumor volume in biopsy of the AS cohort [131–134]. Reporting of tumor volume or extent in biopsy should remain integral for monitoring of patients on AS.

Tumor involvement in a biopsy core can be continuous or discontinuous with intervening benign tissue segments. Discontinuous tumors can be measured either by collapsing the multiple tumor foci or by measuring the entire length of tumor foci together with the interfocal benign segments from one end to the other end (end-to-end) (Figure 10). Studies showed that measuring discontinuous tumor end to end is superior to aggregating the tumor segments and skipping the benign parts. End-to-end measurement correlates better with tumor extent in RP, organ-confined disease, predominant GS 7 in cores, and risk of margin positivity [135–137]. Discontinuous tumors in prostate biopsy corresponded to a single tumor nodule on the corresponding region in RP in 78% of cases [135].

10.2. Tumor Volume in Radical Prostatectomy

Data are conflicting on the significance of tumor volume in RP in predicting outcome [138–148]. Some studies, including more contemporary investigations, showed that tumor volume, including the size of the index tumor, is an independent predictor of BCR, metastasis, or CSM [138–143]. However, other studies failed to show the prognostic significance of tumor volume once other factors were considered [145–148]. Several methods have been described for measuring tumor volume in RP, which include non-practical and simple approaches [144]. It is recommended that at the minimum, some form of quantitative measurement for tumor volume in RP should be undertaken without prescribing a specific method [144].

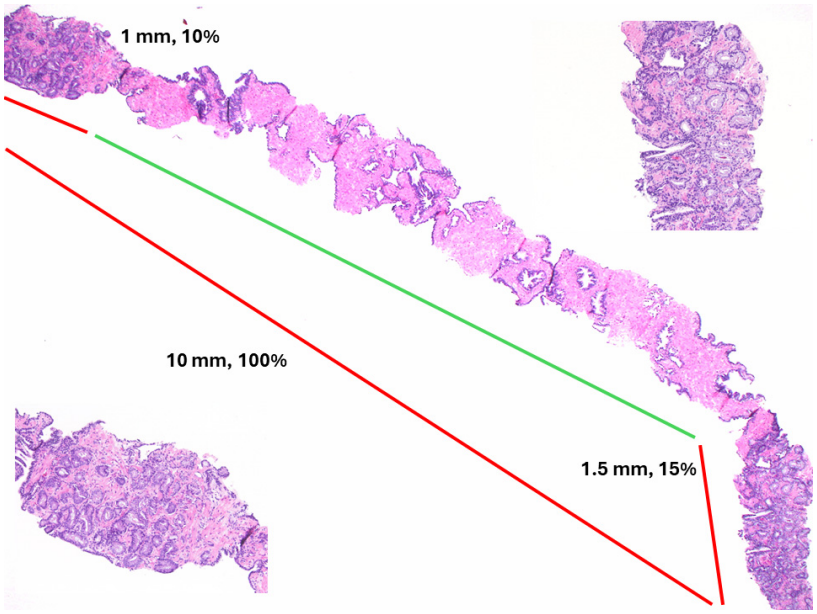


Figure 10. Biopsy with discontinuous foci of cancer. Discontinuous cancer can be measured as 100% involvement or as 25% (10 + 15%) involvement of the core.

11. Perineural Invasion

Perineural invasion (PNI) is reported in 10–34% of biopsies of clinically localized prostate cancer [149–151]. Data are conflicting on PNI in biopsies as an independent prognosticator, although more recent studies tend to support its importance [149–153]. A systematic review and meta-analysis by Wu et al. [154] concluded that biopsy PNI is correlated with adverse pathology in RP and worse BCR prognosis after RP. The incidence of PNI at baseline biopsy of patients undergoing AS is low at 2.2% to 7.4% [155–158]. Several studies have investigated the role of PNI in stratifying prostate cancer risk at initiation and during AS with promising results [156,157]. Moreira et al. [156] reviewed 302 men on AS for low-risk prostate cancer and showed that PNI in baseline biopsy was associated with increased risk of clinical progression. Interestingly, Baraban et al. [159] studied AS patients who were reclassified to GS 3 + 4 and underwent RP and found out that low PSA and absence of PNI had the lowest risk of adverse pathology in RP, comparable to GS 6 patients who were not reclassified to GS 3 + 4 preoperatively. Thus, there is a potential role in biopsy PNI in stratifying risk and monitoring patients under AS, including patients reclassified to intermediate risk (GS 3 + 4). In RP, studies on RP are conflicting, although more studies are against PNI as an independent predictor of BCR [160–162].

12. Lymphovascular Invasion

Lymphovascular invasion (LVI) is reported in 8% of RP regardless of stage [163]. Studies have shown LVI in RP to be an independent predictor of worse outcome [164]. In a systematic review and meta-analysis by Jiang et al. [165], LVI was associated with higher BCR in multivariate analysis and closely correlated with EPE, GS > 7, lymph node invasion (LNI), higher pathological stage (>T3), positive surgical margin (PSM), and seminal vesicle invasion (SVI). However, in localized prostate cancer (pT2), LVI in RP has been inconsistent as an independent predictor. When only pT2 tumors were assessed, some studies did not show LVI as an independent predictor of BCR or OS [163,166,167]. LVI is a rare finding in needle biopsies, with no data available on its significance.

13. Margin Status in Radical Prostatectomy

PSM at RP is associated with poorer BCRFS, CSS, OS, CSM, and overall mortality (OM) [168–170]. Zhang et al. [168] showed that whether patients had pT2 (organ-confined) or pT3 pathologic stage, PSM was associated with higher CSM, with CSM higher in pT3 than pT2 disease. The length of PSM is independently prognostic of prostate cancer outcome after RP [171–173]. PSM length of >3 mm was shown as an independent predictor of clinical failure in localized prostate cancer after RP [172,173]. Higher GS at PSM is also associated with increased risk for BCR, progression, or death from prostate cancer [174–176]. In a systematic review and meta-analysis by John et al. [175], GS > 6 at PSM was predictive of BCR compared to GS 6, with an increasing hazard ratio for GS 3 + 4 (HR 2.35), GS 4 + 3 (HR 3.95), GS 8 (HR 7.17), and GS 9–10 (HR 12.37). Thus, it is recommended that both the length and tumor GS at PSM are to be reported.

14. Conclusions

Traditional pathological factors remain essential in risk stratification of localized prostate cancer, and additional novel pathological elements and approaches offer promise in further enhancing the prognostication and management of these tumors. It is important for pathologists to be precise in deriving and in reporting these pathological factors in biopsy and RP specimens. While some new pathological factors remain in flux and subject to refinements, clinicians should be fully aware of those factors that are clinically impactful, and particularly those that have already made their way into management recommendations.

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