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Updates in bladder and prostate pathology: Diagnostic consensus and clinical relevance

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ABSTRACT

Accurate grading, staging, and classification are essential components of bladder and prostate cancer pathology, directly influencing clinical management and patient outcomes. Recent initiatives by the International Society of Urological Pathology (ISUP) and the Genitourinary Pathology Society (GUPS) have produced key consensus updates aimed at refining diagnostic criteria and resolving long-standing controversies. This review highlights high-impact developments in bladder and prostate pathology, including updated grading systems and T1 substaging in bladder tumors, the proposed hybrid grading approach, and the classification of urachal carcinoma. Evolving perspectives in prostate pathology are also discussed, encompassing intraductal carcinoma of the prostate (IDC-P), neuroendocrine and aggressive variant tumors, and the clinical relevance of Grade Group 1 (GG1) disease in the context of active surveillance. Recent literature and consensus statements are summarized with attention to diagnostic challenges and practical implementation. These focused updates highlight the dynamic nature of urologic pathology and reflect a broader movement toward greater diagnostic precision, reproducibility, and clinical relevance, with adoption of ISUP and GUPS frameworks essential for improving patient outcomes.

1. Introduction

Accurate histopathologic grading and classification are essential to the management of both bladder and prostate tumors. As our understanding of tumor biology evolves, so too must the frameworks we use to evaluate and report these malignancies. Recent years have seen significant advancements in refining diagnostic criteria and grading systems for urologic malignancies, particularly in bladder tumor grading and stratification of T1 substaging, along with the reappraisal of rare entities such as urachal carcinoma. In prostate pathology, debates persist regarding the grading of intraductal carcinoma of the prostate (IDC-P), neuroendocrine variants, and the classification surrounding Grade Group 1 (GG1) tumors, and pose a challenge in routine diagnostic practices. This paper aims to present a focused overview of these critical and evolving areas, synthesizing recent consensus statements by International Society of Urological Pathology (ISUP) and Genitourinary Pathology Society (GUPS), while addressing relevant controversies and practical implications for pathologists and clinical management.

2. Background and Rationale

2.1. Bladder Tumors

Historically, bladder tumor grading systems have transitioned from the WHO 1973 classification to the more recent WHO 2004/2016/2022 system, with an increased focus on clinical relevance and reproducibility [1]. Persistent interobserver variability, particularly for non-muscle-invasive bladder cancer (NMIBC), and inconsistent T1 substaging have prompted calls for harmonized criteria and prognostically meaningful categorization [1–12]. Urachal adenocarcinoma, though rare, presents unique diagnostic challenges and requires standardized criteria to differentiate urachal origin from other adenocarcinomas [13–15].

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Abbreviations:

Androgen deprivation therapy (ADT)
Androgen receptor (AR)
Artificial intelligence (AI)
Atypical intraductal proliferation (AIP)
Castration-resistant prostate cancer (CRPC)
Genitourinary Pathology Society (GUPS)
Grade Group (GG)
High-grade prostatic intraepithelial neoplasia (HGPIN)
International Society of Urological Pathology (ISUP)
Intraductal carcinoma of the prostate (IDC-P)
Large cell neuroendocrine carcinoma (LCNEC)
Microsatellite instability (MSI)
Neuroendocrine (NE)
Neuroendocrine prostate cancer (NEPC)
Non-muscle invasive bladder cancer (NMIBC)
Prostate-specific antigen (PSA)
Small cell neuroendocrine carcinoma (SCNEC)
World Health Organization (WHO)

2.2. Prostate Tumors

Similarly, prostate cancer grading has evolved from the Gleason system to contemporary Grade Groups to enhance diagnostic precision and prognostic accuracy [16]. Nevertheless, the overlapping features of intraductal carcinoma of the prostate (IDC-P) and atypical intraductal proliferation (AIP) contribute to diagnostic ambiguity. The classification of neuroendocrine tumors and aggressive variants of prostate cancers are particularly intricate, with significant therapeutic implications [17]. The debate surrounding Grade Group 1 (GG1), regarding its classification as a malignant entity or as a low malignant potential lesion, presents further complexity given its indolent behavior [18]. The ISUP and GUPS have been pivotal in addressing these evolving challenges through structured consensus conferences and evidence-based recommendations aimed at standardization and enhancement of diagnostic precision, ultimately improving patient outcomes.

3. Diagnostic Consensus and Clinical Relevance in GU Pathology

3.1. Bladder Pathology: Standardization and Risk Stratification

3.1.1. Grading Revisions: The ISUP Hybrid System Explained

The ISUP has proposed a three-tier hybrid grading system for non-muscle-invasive bladder cancer (NMIBC), combining elements from previous WHO classifications [1]. By retaining a single "low-grade" category while separating "high-grade" categories into two distinct subclasses, this hybrid model aims to improve prognostic stratification and interobserver reliability, which have been problematic in prior grading systems. Studies indicate that the hybrid system significantly outperforms existing models in predicting tumor progression, thereby enhancing clinical decision-making [7–9]. The primary difference between the hybrid system and the WHO 2004/2016/2022 classification is the treatment of high-grade tumors. The WHO 2004/2016/2022 system classifies most T1 urothelial carcinomas as a single high-grade entity, which can limit the ability to distinguish between different clinical outcomes within this group. In contrast, the hybrid system reintroduces a sub-classification within this high-grade category. This is in response to the observation that a single low-grade category is more reproducible, while the single high-grade category can be further stratified for prognostic purposes [1,7,8].

For context, the WHO 1973 classification also used a three-tier system defining Grades 1–3 (G1–G3) for NMIBC. G1 tumors show minimal architectural atypia with few mitotic figures, while G3 tumors show marked nuclear pleomorphism, disordered architecture, loss of polarity, and frequent mitotic mitoses [19,20]. The intermediate G2 category, largely a diagnosis of exclusion, became a default classification for many NMIBCs [21,22]. Attempts to refine G2 by subdividing it into “a/b” categories (modified Bergkvist criteria) [23], increased interobserver variability, limiting clinical applicability. Unlike these earlier classifications, the hybrid system retains a reproducible single low-grade category while providing clinically meaningful stratification within the high-grade group.

The rationale for the hybrid grading system stems from the need for a more prognostically informative and reproducible framework. Comparative analyses show that both WHO 1973 and WHO 2004/2016/2022 systems have limitations in predicting NMIBC progression, whereas the hybrid three-tier system achieves superior prognostic performance. In multivariable analysis of progression-free survival, the hybrid three-tier system demonstrated a higher Harrell's concordance index (0.851) compared with the WHO 1973 (0.844) and WHO 2004 (0.846) systems [7,11].

Clinically, adoption of the hybrid grading system provides a more robust and reproducible approach for pathologists and clinicians. It improves risk stratification, identifying patients at a higher risk for progression who may benefit from more aggressive treatment or intensive surveillance, while promoting consistency in diagnostic reporting across institutions [7,12].

Recent consensus reviews further highlighted that traditional WHO 1973 and 2004 bladder cancer grading schemes, though foundational, remain limited by subjectivity and prognostic variability. Downes et al. consolidated evidence supporting a hybrid three-tier approach, which preserves the simplicity of the WHO 2004 low-grade category while subdividing high-grade tumors into G2 and G3 tiers (Fig. 1), thereby improving risk stratification and aligning with emerging molecular data. Collectively, the hybrid grading system represents a balanced evolution that harmonizes historical frameworks with contemporary diagnostic, molecular, and consensus-based practice [24].

3.1.2. T1 Substaging: Addressing Prognostic Ambiguity

T1 substaging provides clinically meaningful prognostic granularity beyond the binary T1 designation in NMIBC. Deeper lamina propria invasion (T1b), as opposed to superficial invasion (T1a) (Fig. 2), correlates with higher progression risk and worse outcomes, refining risk stratification that informs management decisions such as intravesical therapy intensity and early cystectomy consideration for select high-risk patients [2,3,6,10]. The dominant contemporary approach employs a three-tier framework situating invasion depth relative to the muscularis mucosae (MM) and subepithelial connective tissue. Endorsed and refined through the ISUP consensus, this system links invasion into or beyond the MM with adverse prognosis and practical applicability. A key refinement is the use of micrometric or semiquantitative depth criteria to define the transition between T1a and T1b disease. Early proposals measured subepithelial invasion depth as a continuous parameter to derive prognostically meaningful subcategories. The ISUP consensus discussions acknowledge the value of semiquantitative methods while recognizing variability in adoption and the need for standardized definitions [6,10].

The literature and the ISUP further underscore the importance of standardized reporting templates and reference standards to enhance interobserver concordance and cross-institutional prognostication. Structured criteria are critical for improving consistency in T1 substaging and enabling reliable multicenter comparisons [3]. The overarching goal is to promote uniform therapeutic escalation or intensified surveillance when deeper invasion is identified, consistent with contemporary NMIBC risk stratification paradigms [3]. Foundational discussions on diagnostic criteria and pitfalls highlight the importance of identifying true invasion versus artifacts or misinterpretation (e.g., micropapillary patterns, reactive changes), providing an empirical basis

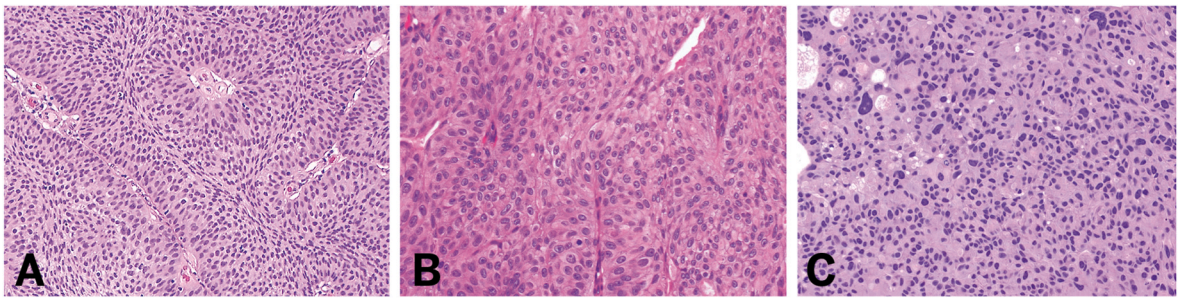

Fig. 1. Proposed hybrid grading system for urothelial carcinoma.
(A) Low-grade (G1), orderly architecture with mild nuclear atypia, minimal mitotic activity, and preservation of polarity.
(B) High-grade 1 (G2), increased architectural disorder and moderate nuclear pleomorphism, but less severe than G3; occasional mitoses.
(C) High-grade 2 (G3), marked nuclear pleomorphism, loss of polarity, disorganized architecture, and frequent mitotic figures.

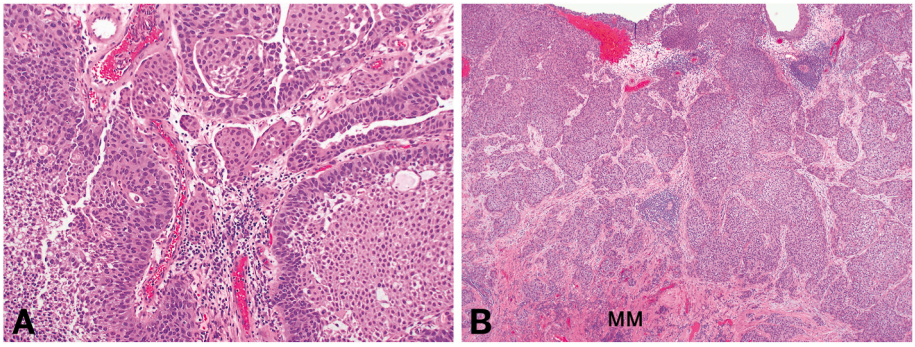

Fig. 2. Proposed T1 substaging (pT1a vs pT1b) in non–muscle-invasive bladder cancer.
(A) pT1a, Superficial lamina propria invasion confined above or adjacent to the muscularis mucosae (MM), with limited depth and extent. Tumor nests are separated from the MM by intervening connective tissue; absence of deep stromal infiltration.
(B) pT1b, Deeper lamina propria invasion extending into MM (bottom left).

for refining substaging thresholds and guiding pathologists in appropriate application of depth-based criteria in routine practice [6].

3.1.3. Classifying Urachal Tumors: Toward Diagnostic Clarity

Urachal tumors encompass a broad histologic spectrum that includes both nonglandular (urothelial, squamous, neuroendocrine) and glandular (mucinous, enteric, and signet-ring) components, often presenting in mixed patterns (Fig. 3). Signet-ring differentiation should be recognized only when predominant within a mucinous matrix [13]. Accurate distinction of urachal carcinoma from primary bladder adenocarcinoma or metastases requires a careful assessment of anatomical anchoring (urachal remnant, pre-vesical location) and embryologic origin, as most tumors arise from urachal remnant epithelium rather than adjacent bladder mucosa [13]. The WHO/ISUP consensus guidance emphasizes the importance of confirming urachal origin through identification of remnants and site-specific criteria, noting that findings such as cystitis cystica may complicate interpretation [15]. Immunophenotypic overlap with bladder and colorectal-type adenocarcinomas is common, with markers such as CDX2, CK7, CK20, and CEA lacking universal specificity; this reinforces the necessity for a panel-based approach, rather than reliance on a single marker, and interpretation considered within the appropriate anatomic and clinical context [15]. Urothelial lineage markers (GATA3, p63, S100P) may support urothelial differentiation but show variable expression, while Cadherin-17 may aid in some differential considerations in select cases [13].

Molecularly, *KRAS* mutations have been reported in approximately 39 % of mucinous urachal adenocarcinomas, while *BRAF* mutations have been typically absent. Microsatellite instability (MSI) occurs in a minority of instances and appears mutually exclusive with *KRAS* mutations, indicating distinct oncogenic pathways compared to colorectal cancers [13]. Nuclear β-catenin favoring colorectal lineage is noted, though it is not exclusive, as frequent cytoplasmic staining occurs across

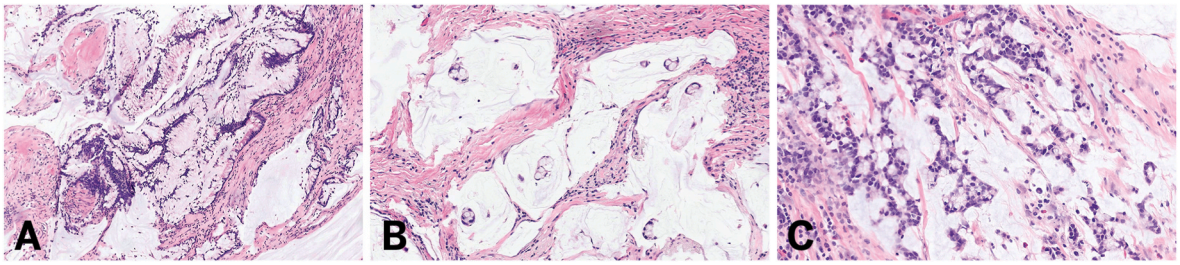

Fig. 3. Adenocarcinoma arising from urachus.
(A) Tumor displaying glandular architecture with enteric features, closely resembling colonic adenocarcinoma.
(B) Abundant extracellular mucin with clusters of free-floating tumor cells within mucin pools.
(C) Poorly differentiated malignant tumor showing anastomosing glandular and cribriform structures within mucin pools.

urachal, bladder, and colorectal adenocarcinomas. Markers like SATB2 and gynecologic markers (PAX8/ER) have limited standalone discriminatory value but can assist in context, especially when gynecologic primaries are considered. Overall, the classification of urachal tumors relies on integrated morphology, confirmation of site-specific urachal origin criteria, a targeted immunohistochemical panel, and selective molecular testing (*KRAS, BRAF*, MSI) to inform prognosis and potential therapy, aligning with the ISUP recommendations and emerging WHO criteria for urachal neoplasms [14,15].

Rare but recurrent *TERT* promoter mutations have been reported in urachal adenocarcinomas and may represent a more lineage-specific molecular signature than nuclear β-catenin localization, which can occur across mucinous adenocarcinomas of varied origin [25]. While infrequent, their presence can support urachal origin, particularly given that *TERT* promoter mutations are exceedingly uncommon in colorectal adenocarcinoma [26]. Incorporation of *TERT* promoter mutation testing, when available, may therefore assist in challenging differential diagnoses where anatomic or immunophenotypic findings are equivocal.

3.2. Prostate Pathology: Emerging Insights and Controversies

3.2.1. Grading the IDC-P–AIP Continuum: Where Do We Draw the Line?

Intraductal carcinoma of the prostate (IDC-P) and atypical intraductal proliferation (AIP) exist on a morphologic continuum that has prompted extensive discussion regarding diagnostic criteria, grading, and clinical implications. IDC-P is a distinct entity characterized by intraductal growth patterns commonly associated with high-grade invasive carcinoma, adverse prognosis, and molecular alterations typical of aggressive disease [27,28]. AIP resembles IDC-P histologically but lacks all defining criteria, and its biological significance remains debated [18].

Recent consensus highlights that high-grade prostatic intraepithelial neoplasia (HGPIN) may coexist with IDC-P but is not equivalent to it, emphasizing careful morphologic distinction between AIP, IDC-P, and HGPIN [18,27]. Luminal cribriform architecture, basal cell marker alterations, and nuclear atypia support differentiation among these entities [18]. IDC-P frequently exhibits PTEN loss, often cytoplasmic and uniform, and *ERG* alterations, distinguishing it molecularly from HGPIN and reinforcing its association with high-risk disease [18,29]. These molecular findings align IDC-P with aggressive carcinoma and poor prognosis [29].

Incorporation of IDC-P into grading systems can alter prognostic assessment and influence treatment planning [30]. Although grading systems vary in approach, consensus supports recognizing IDC-P as a prognostic modifier rather than grading it identically to invasive carcinoma [27,30]. Reviews advocate for documentation of IDC-P whenever present, given its frequent coexistence with high-grade invasive cancer and impact on risk stratification [27,29,30]. Given its prognostic weight, IDC-P should be clearly reported and differentiated from AIP and HGPIN, with attention to its relationship to adjacent invasive carcinoma [27,30]. Morphologic recognition can reduce dependence on extensive basal cell immunohistochemistry while maintaining diagnostic precision [30]. Integration of morphologic and molecular data, particularly PTEN and ERG status, has been recommended to enhance grading consistency and prognostication [18,28,29].

While not recommended for routine application, PTEN and ERG immunohistochemistry are valuable ancillary tools for distinguishing IDC-P from AIP and HPGIN when morphology alone is equivocal [31]. Cytoplasmic PTEN loss is a strong marker for IDC-P and is rarely observed in HGPIN, whereas ERG expression, driven by *TMPRSS2:ERG* fusion, occurs in a subset of IDC-P and AIP cases [18,32]. In needle biopsies, PTEN loss is seen in approximately 60–75 % of IDC-P lesions and 50 % of borderline intraductal proliferations, while it is absent in HGPIN. Cases of AIP with PTEN loss have shown higher rates of subsequent carcinoma detection compared with PTEN-intact lesions, supporting its role as a marker of unsampled high-grade disease [31,33,34]. Therefore, PTEN and ERG IHC should be considered in diagnostically challenging or "borderline" intraductal lesions rather than used uniformly [34]. When applied judiciously, these markers can refine morphologic assessment, confirm IDC-P in ambiguous settings, and assist in risk stratification without necessitating routine testing in all cases (Table 1).

The 2025 GUPS-ISUP consensus efforts resolved prior discrepancies regarding IDC-P classification and grading. The expert panel reaffirmed that IDC-P typically reflects intraductal spread of high-grade invasive carcinoma and should generally be incorporated into Gleason grading when present, except when spatially distinct or associated solely with Gleason pattern 3 carcinoma. Pure IDC-P and "AIP, suspicious for IDC-P" should not be graded but clearly documented, given their association with adverse pathology. Diagnostic confirmation should adhere to strict criteria with basal cell immunohistochemistry, while PTEN loss and ERG expression are supportive but not definitive. The consensus excludes IDC-P–positive Grade Group 1 (GG1) tumors from active surveillance, integrating morphologic and molecular data for risk stratification, and considering germline or somatic testing for DNA-repair defects. These unified guidelines standardize IDC-P reporting and reduce interobserver variability, aligning grading practices across institutions [35].

Recent proposals have explored whether IDC-P and related cribriform morphologies could anchor alternate, simplified risk-stratification systems. Nguyen et al. [36] introduced a dichotomous "unfavorable histology" model defined by the presence of large cribriform or intraductal carcinoma and other adverse architectures (e.g., complex anastomosing cords, intraluminal papillary growth). This system demonstrated superior sensitivity and specificity for predicting metastasis compared with conventional Grade Group or pathologic stage, particularly by subdividing Grade Group 2 (GG2) cancers into

Table 1
Diagnostic criteria and immunohistochemical guidance for atypical intraductal proliferation (AIP) and intraductal carcinoma of the prostate (IDC-P)

Histologic Features	
Architectural Pattern	Solid or dense cribriform pattern with expanded ducts/acini retaining basal cells
Cytologic Atypia	Marked nuclear enlargement (>6x normal), prominent nucleoli, or bizarre/pleomorphic atypia may alone be diagnostic in rare cases
Necrosis	Comedonecrosis frequent but not required
Basal Cell Layer	Present but often attenuated; confirm with p63, 34βE12, CK903 when uncertain
Association with Invasive Carcinoma	Often co-exists with high-grade invasive carcinoma; interpret with caution in GG1 cases

Immunoprofile

Marker	Role in Prostate Pathology	Recommendation for Use	Typical Staining Pattern
PTEN	Prognostic marker of tumor aggressiveness; loss indicates higher-grade disease and poorer outcomes	Use in diagnostic dilemmas to distinguish IDC-P from HGPIN or borderline intraductal lesions Assess in HGPIN/IDC-P to identify patients at higher risk of unsampled aggressive disease	Cytoplasmic PTEN loss frequent in IDC-P; more common when invasive carcinoma is present
ERG	Marker confirming prostatic adenocarcinoma (*TMPRSS2::ERG* fusion); correlates with advanced tumor stage	Use as ancillary marker with PTEN to classify difficult intraductal proliferations Not prognostic alone, interpret in combination with PTEN status	ERG expression common in IDC-P, often with PTEN loss; ERG negativity may indicate high-grade invasive disease

Abbreviations: AIP, atypical intraductal proliferation; GG1, Grade Group; HGPIN, high-grade prostatic intraepithelial neoplasia; IDC-P, intraductal carcinoma of prostate

Table 2
Immunohistochemical panel for characterization of high-grade neuroendocrine prostate cancer

Neuroendocrine markers	Synaptophysin	Positive	Supports neuroendocrine differentiation
	Chromogranin A		
	INSM1		
	CD56		
Prostatic lineage markers	PSA	Negative or weak	Supports prostatic origin; assess androgen signaling status; high-grade NEPC is typically PSA/AR negative with strong neuroendocrine marker expression; mixed tumors may retain partial PSA or AR positivity
	PSAP		
	NKX3.1		
	AR	Negative	
Proliferation/aggressive behavior	Ki-67	High (>50–90 %)	Estimate tumor proliferation index
Differential diagnosis/ exclusion markers	TTF-1	Variable	Helps excludes metastatic small cell lung carcinoma, urothelial carcinoma, or squamous differentiation
	p63, CK5/6	Negative	
	GATA3	Negative	
Optional markers for research/prognosis	EZH2, AURKA, MYCN	Positive	Assess aggressive molecular features associated with NEPC
	DLL3	Positive	Potential therapeutic target for ADC
	P53, RB	Loss	Frequent inactivation in high-grade NEPC

Abbreviations: ADC: antibody–drug conjugates; NEPC: Neuroendocrine prostate cancer

biologically indolent versus high-risk subsets. Incorporation of IDC-P into such models supports its role as a biologically adverse morphology that may refine existing nomograms and provide a pragmatic framework for clinical reporting. However, widespread adoption will require prospective validation and consensus regarding implementation within contemporary grading and management guidelines. The frequent association of IDC-P with high-grade, high-stage disease typically warrants aggressive management, often prompting radical or combination therapies rather than active surveillance [28,30]. Nonetheless, isolated IDC-P or IDC-P accompanying low-risk carcinoma may warrant individualized management, as prognostic effects vary by context [30]. Persistent or molecularly aggressive IDC-P after treatment may guide intensified follow-up strategies [29].

3.2.2. Neuroendocrine and Variant Prostate Cancer: Consensus and Complexity

Prostatic neuroendocrine (NE) differentiation spans a morphologic and biological continuum, from conventional acinar adenocarcinoma with focal NE features to overt neuroendocrine prostate cancer (NEPC), including small cell neuroendocrine carcinoma (SCNEC), large cell neuroendocrine carcinoma (LCNEC), and mixed adenocarcinoma–NEPC phenotypes. This spectrum is increasingly recognized in modern classification systems, particularly in metastatic castration-resistant prostate cancer (CRPC), where NE differentiation often emerges under therapeutic pressure [37–39]. Immunohistochemical profiling supports NE differentiation through markers such as synaptophysin and chromogranin A, though marker expression can be focal or variable and may be observed alongside residual androgen receptor (AR) signaling, reflecting the biological diversity of NEPC and related variants [37,39]. In addition, *ERG* rearrangements, while a hallmark of many prostatic carcinomas, have been detected in a subset of prostatic SCNEC, contributing to the molecular overlap with conventional adenocarcinoma and informing differential diagnosis in high-grade NE contexts [38,39].

The pathobiology of NE differentiation involves lineage plasticity driven by treatment pressure (e.g., AR pathway inhibition) and basal progenitor-like cell contribution, supporting a model in which NE tumors arise de novo or evolve from preexisting adenocarcinoma [38,39]. Clinically, NEPC and related variants tend to present aggressively with rapid progression, high tumor burden, and discordant serum prostate-specific antigen (PSA) levels relative to disease extent. Radiologic and pathologic patterns often show bulky, high-grade tumors, SCNEC/LCNEC subtypes may develop osteolytic bone metastases and resistance to androgen deprivation therapy (ADT) [38,39].

Diagnosis in the CRPC era emphasizes an integrated, multimodal approach combining morphologic assessment, immunohistochemical panels, and selective molecular profiling to capture AR pathway alterations, *ETS* fusions, and genomic events linked to lineage plasticity. The evolving framework also considers digital pathology, spatial profiling, transcriptomic signatures, and epigenetic profiling as refinements to subclassify CRPC and standardize interpretation in NE-rich settings [38]. Recognition that NE markers can be variably expressed, within high-grade neoplasms, necessitates correlating immunohistochemistry results with histomorphology and clinical history to avoid misclassification, especially when NE markers demonstrate focal reactivity in otherwise conventional acinar carcinoma [39]. In de novo and therapy-induced NEPC, AR signaling or *ERG* rearrangements may coexist with NE phenotypes, further emphasizing the need for a comprehensive diagnostic approach [38,39].

A standardized immunohistochemical panel including neuroendocrine markers (synaptophysin, chromogranin A, INSM1, CD56), prostatic lineage markers (PSA, PSAP, NKX3.1, AR), proliferation (Ki-67), and differential/exclusion markers (TTF-1, p63, CK5/6, GATA3) is recommended for accurate classification, differentiation of mixed phenotypes, and molecular triage. Optional markers (EZH2, AURKA, MYCN, DLL3, P53, RB) may provide prognostic insight (Table 2).

Molecular diagnostics and targeted testing focus on identifying AR signaling alterations and *ETS* family fusions (e.g., *TMPRSS2::ERG*), alongside other chromosomal events that define NE lineage plasticity. Although *ERG* rearrangements serve as a useful discriminator for prostatic origin in certain high-grade NE tumors, their absence does not exclude NEPC, as the broader molecular landscape, including *AR* amplification and other AR axis alterations, exhibits variability across NE subtypes [38,39]. Notably, INSM1 has emerged as a NEPC-specific marker with high specificity, although expression can occur in non-NE entities; therefore, interpretation should integrate morphology and a broader panel of NE markers [38]. Increasing attention to the tumor microenvironment and immune landscape supports ongoing exploration of targeted and immunotherapeutic strategies [38].

The NEPC spectrum includes pure NE carcinomas, mixed or amphicrine phenotypes, and hybrid tumors co-expressing luminal and NE markers. Morphology remains the diagnostic anchor, supplemented by IHC and molecular data to avoid overreliance on single NE markers [38]. High-grade NE morphology may occur even without marker positivity, warranting ancillary molecular confirmation [38].

A key theme across contemporary analyses indicates that NE differentiation reflects both de novo emergence and therapy-driven lineage plasticity. Persistence of AR signaling in some NE tumors demonstrates that AR pathway dependence is not uniformly lost, influencing prognosis and potential sensitivity to targeted approaches [39]. Additional genomic events, including *ERG* rearrangements, *ASCL1, and REST* signaling changes, and *SRRM4*-mediated splicing, further define the molecular mechanisms driving NE transdifferentiation and offer potential therapeutic targets [37,39].

NE differentiation confers aggressive clinical behavior and resistance

to AR-targeted therapy, prompting investigation of alternative approaches, including DLL3-directed agents, radiopharmaceuticals, and epigenetic or immunotherapeutic treatments [40]. Comprehensive reporting should document histologic subtype (pure, mixed, or hybrid), NE marker profile, AR/ERG status, and relevant molecular alterations, integrating clinical context, such as prior AR-targeted therapy [38].

Overall, NEPC represents a morphologically and molecularly heterogeneous disease spectrum arising through lineage plasticity or de novo transformation. An integrated diagnostic approach, combining morphology, immunophenotype, and molecular data, best supports accurate classification, risk assessment, and individualized therapy [37–39].

3.2.3. Grade Group 1: Reconceptualizing Low-Risk Prostate Cancer

The GUPS-ISUP white paper proposes reconsidering the cancer label for ISUP Grade Group 1 (GG1) prostate cancer, reflecting ongoing debate about whether these generally indolent lesions warrant malignant designation [35]. Evidence from tumor biology, sampling limitations, and the high prevalence of clinically insignificant disease supports aligning nomenclature with biological and clinical risk [35]. Molecular and clonal data further reveal that GG3/4 lesions may share clonal origins with adjacent GG1 foci, supporting intraprostatic heterogeneity and the potential for undersampling to misrepresent "pure" GG1 biology [35].

Observational and registry-based studies show that most GG1 cases managed non-curatively (active surveillance or watchful waiting) remain stable without grade progression, consistent with low malignant potential [41]. Guideline updates emphasize MRI-targeted biopsy and serial imaging or biomarker surveillance to reduce reclassification risk, with MRI-confirmed low-risk findings and favorable PSA density correlating with indolent behavior and supporting surveillance-based management [16].

The GUPS-ISUP paper advocates diagnostic communication that reflects GG1 heterogeneity, suggesting tempered labeling to minimize overdiagnosis and overtreatment while maintaining vigilance for higher-grade disease [35]. Reclassification discussions should be accompanied by patient education and structured follow-up (PSA, DRE, MRI, repeat biopsy) within active surveillance protocols [16]. Integration of MRI-targeted with systematic biopsy enhances risk stratification, improves detection of clinically significant cancer [16]. Registry data further illustrate variable active surveillance uptake and outcomes across healthcare systems [41].

Current evidence supports viewing GG1 disease as biologically low-risk but not uniformly benign [16,35]. A cautious, risk-adapted framework, emphasizing MRI, PSA density, and repeat biopsy, balances the goal of reducing overtreatment against the need to detect progression promptly, aligning diagnostic terminology with true clinical behavior [16,35].

4. Clinical Integration, Limitations, and Future Perspectives

The refinements discussed reflect an overarching effort to align histopathologic evaluations with clinical outcomes, improving reproducibility and patient-centered decision-making across urologic pathology. While consensus efforts have significantly enhanced diagnostic precision, several unresolved challenges remain, particularly in T1 substaging reproducibility and the IDC-P–AIP diagnostic boundary [16]. Recent updates discussed in this review represent critical refinements in the grading, classification, and risk stratification of bladder and prostate tumors. Collectively, these changes reflect an ongoing effort to align histopathologic criteria with clinical outcomes, highlighting the ISUP and GUPS consensus role in advancing standardized, evidence-based practice though expert guidance.

4.1. Clinical Impact and Integration into Practice

The proposed hybrid grading system for bladder tumors and consensus-based T1 substaging holds promise for more accurate prognostication and tailored management of NMIBC. Similarly, clearer classification criteria for urachal carcinoma may aid in distinguishing it from mimickers and enable more consistent reporting. In prostate pathology, reaffirming IDC-P as a distinct, high-risk lesion, potentially exempt from grading, resolves prior ambiguity, while reclassification of neuroendocrine and aggressive variant prostate carcinomas based on molecular and morphologic features strengthens diagnostic precision and therapeutic guidance. Perhaps most paradigm-shifting is the reconsideration of Grade Group 1 (GG1), challenging its malignant designation and opening the door for more nuanced approaches to active surveillance.

4.2. Ongoing Controversies and Limitations

Despite consensus progress, several unresolved issues remain. Reproducibility of T1 substaging in bladder cancer varies across institutions, and distinguishing IDC-P from AIP remains difficult, particularly in limited biopsy samples. The biological behavior of Grade Group 1 (GG1) lesions, while often indolent, is not be uniformly benign, raising caution about a universal reclassification. Ongoing questions also concern effective communication these evolving concepts to clinicians and patients, especially where subspecialty pathology expertise is limited.

4.3. Unmet Needs and Areas for Further Research

Prospective validation studies are needed to assess the clinical utility of proposed grading and staging modifications. Molecular profiling may offer complementary tools to reinforce or challenge histologic impressions, particularly in borderline or ambiguous cases. In prostate pathology, greater clarity is needed on how to report and manage rare or emerging tumor variants, especially in the context of evolving treatment modalities.

4.4. Future Directions in GU pathology

Looking forward, the field of GU pathology is poised for continued transformation. The integration of artificial intelligence (AI) and digital pathology may aid in standardizing grading and enhancing diagnostic reproducibility through algorithm-assisted grading, molecular marker quantification, and pattern recognition in complex lesions. AI-driven models that integrate histologic, molecular, and clinical data may further refine prognostication and enable individualized treatment selection.

Molecular subclassification is likely to play an increasingly central role in guiding targeted therapy and stratifying patient outcomes. Continued collaboration among ISUP, GUPS, and other professional societies will be essential to harmonize diagnostic criteria globally, support training and education, and develop comprehensive reporting frameworks that reflect both histologic complexity and clinical relevance.

Looking forward, the field of genitourinary pathology is poised for further transformation. Integration of AI and digital pathology platforms will likely enhance the precision and reproducibility of diagnosis through algorithm-assisted grading, quantification of molecular markers, and pattern recognition in complex lesions. AI-driven models that combine histologic, molecular, and clinical data could also refine prognostication and enable individualized treatment selection.

Molecular subclassification is expected to play an increasingly central role in guiding targeted therapy and stratifying patient outcomes. Continued collaboration among ISUP, GUPS, and other professional societies will be critical to harmonize diagnostic criteria, support

training and education, and develop comprehensive reporting frameworks that reflect both histologic complexity and clinical relevance.

Finally, the modified IDC-P criteria (Table 1) outlines current consensus definitions intended to improve diagnostic consistency while recognizing areas that remain interpretive, but provides a practical reference for applying these evolving criteria within the broader framework of standardized grading and reporting.

5. Conclusion

Recent updates in bladder and prostate pathology reflect concerted efforts by the ISUP and GUPS to enhance diagnostic accuracy, reproducibility, and clinical relevance. Key developments include the proposed hybrid grading system and T1 substaging framework for bladder tumors, refined classification criteria for urachal carcinoma, and evolving approaches to complex entities in prostate pathology such as IDC-P, neuroendocrine carcinoma, and Grade Group 1 (GG1) disease. These initiatives represent a broader movement toward standardization, evidence-based pathology that integrates biological insight with patient-centered care. Their successful implementation will depend on continued collaboration among professional societies, harmonization of diagnostic terminology, and validation of proposed systems through research and education. Ongoing innovation in molecular and digital diagnostics will further strengthen translation of consensus recommendations into practice, supporting improved outcomes for patients with urologic malignancies.

CRediT authorship contribution statement

Katrina Collins: Conceptualization, Writing – original draft, Writing – review & editing. **Sounak Gupta:** Conceptualization, Writing – original draft, Writing – review & editing. **Liang Cheng:** Conceptualization, Writing – original draft, Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no conflicts of interest pertaining to the content of this manuscript.

Data availability

Not applicable.

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