

Genitourinary Pathology Society and International Society of Urological Pathology White Paper on Defining Indolent Prostate Cancer.

Title: Genitourinary Pathology Society and International Society of Urological Pathology White Paper on Defining Indolent Prostate Cancer.

Publication year: 2025

Journal: The American journal of surgical pathology

Authors: Division of Anatomic Pathology, University of Texas Southwestern Medical Center, Dallas.

Society: European Respiratory Society

Origin country: International (Europe)

Target countries: Europe

DOI: 10.1097/PAS.0000000000002425

PMID: 40444986

Source: <https://pubmed.ncbi.nlm.nih.gov/40444986/>

pmc Am J Surg Pathol Am J Surg Pathol 319 nihpa 7707904 The American journal of surgical pathology 0147-5185 1532-0979 pmc-is-collection-domain yes pmc-collection-title NIHPA Author Manuscripts PMC12509221 PMC12509221.1 12509221 12509221 NIHMS2112291 40444986 10.1097/PAS.0000000000002425 NIHMS2112291 NIHPA2112291 1 Article Genitourinary Pathology Society (GUPS) and International Society of Urological Pathology (ISUP) White Paper on Defining Indolent Prostate Cancer: Call for a Multidisciplinary Approach Shah Rajal B 1 * Paner Gladell P 2 Cheng Liang 3 De Marzo Angelo M 4 Magi-Galluzzi Cristina 5 Varma Murali 6 Zhou Ming 7 Amin Ali 8 Amin Mahul B 9 Aron Manju 10 Cunha Isabela W 11 Epstein Jonathan I 12 Fine Samson W 13 Haider Aiman 14 Iczkowski Kenneth A 15 Kench James G 16 Kunju Lakshmi Priya 17 Mohanty Sambit K 18 Montironi Rodolfo 19 Netto George J 20 Pan Chin-Chen 21 Rao Priya 22 Srigley John R 23 Sauter Guido 24 Tan Puay Hoon 25 Tsuzuki Toyonori 26 van der Kwast Theodorus H 27 van Leenders Geert J 28 Kristiansen Glen 29 * 1 Division of Anatomic Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA 2 Departments of Pathology and Surgery (Urology), University of Chicago, Chicago, IL, USA 3 Department of Pathology, Alpert Medical School of Brown University, Providence, Rhode Island, USA 4 Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA 5 Department of Pathology, The University of Alabama at Birmingham, Birmingham, AL USA 6 Department of Cellular Pathology, University Hospital of Wales, Cardiff, UK 7 Department of Pathology, Mount Sinai School of Medicine, New York, NY, USA 8 Department of Pathology, Alpert Medical School of Brown University, Providence, Rhode Island, USA 9 Department of Pathology and Laboratory Medicine, University of Tennessee Health Science System, Memphis, TN & Department of Urology, USC Keck School of Medicine, Los Angeles, CA, USA 10 Department of Pathology and Urology, USC Keck School of Medicine, Los Angeles, USA 11 D'Or Institute for Research and Education (IDOR) and Department of Pathology, Rede D'Or/Sao Luiz Hospital, Sao Paulo, Brazil, 12 Integrate Medical Professionals Pathology, Garden City, NY, USA 13 Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA 14 Department of Pathology, University College London Hospital, London, UK 15 Department of Pathology and Laboratory Medicine, University of California – Davis Health, Sacramento, CA, USA 16 Department of Tissue Pathology and Diagnostic Oncology, NSW Health Pathology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia 17 Department of Pathology, University of Michigan, Ann Arbor, MI, USA 18 Department of Pathology, CORE Diagnostics, Gurgaon, India 19 Department of Pathology, Molecular Medicine and Cell Therapy Foundation, c/o Polytechnic, University of the Marche Region, Ancona, Italy 20 Department of Pathology, University of Pennsylvania, Philadelphia, USA 21 Department of Pathology, Taipei Veterans General Hospital, Taipei, Taiwan 22 Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, USA 23 Department of Laboratory Medicine and Pathobiology, University of Toronto,

Toronto, Ontario, Canada 24 Department of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany 25 Department of Anatomical Pathology, Luma Medical Center, Singapore, Singapore 26 Department of Surgical Pathology, Aichi Medical University, Nagakute, Japan 27 Laboratory Medicine Program, University Health Network, University of Toronto, Toronto, ON, Canada 28 Department of Pathology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands 29 Institute of Pathology, University Hospital Bonn, Bonn, Germany *

Corresponding authors : Rajal B Shah, M.D, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas, USA, Rajal.shah@utsouthwestern.edu , Glen Kristiansen, M.D., Institute of Pathology, University Hospital Bonn, Bonn, Germany, glen.kristiansen@ukbonn.de 01 12 2025 30 5 2025 49 12 498591 e27 e32 01 10 2025 10 10 2025 10 10 2025 18 01 2026 This file is available for text mining. It may also be used consistent with the principles of fair use under the copyright law. Prostate cancer Indolent Grade group 1 Active surveillance pmc-status-qastatus 0 pmc-status-live yes pmc-status-embargo no pmc-status-released yes pmc-prop-open-access no pmc-prop-olf no pmc-prop-manuscript yes pmc-prop-open-manuscript yes pmc-prop-legally-suppressed no pmc-prop-has-pdf yes pmc-prop-has-supplement no pmc-prop-pdf-only no pmc-prop-suppress-copyright no pmc-prop-is-real-version no pmc-prop-is-scanned-article no pmc-prop-preprint no pmc-prop-in-epmc yes I. What is the definition of indolent PCa? The goal of this white paper is to help identify a path toward a meaningful multidisciplinary solution to address the pervasive problem of overdiagnosis of indolent prostate cancer (PCa) and its downstream negative effects. Our emphasis is not on the Grade Group (GG1) PCa renaming debate, but on reviewing the evidence base regarding the current state, limitations, gaps, and future directions in detecting indolent PCa. We explain why the optimal diagnosis of indolent PCa, defined as low-volume well-differentiated acinar neoplasm with invasive histologic features that do not spread outside the prostate, become symptomatic, or shorten a patient's life if left untreated requires coordination among clinicians, radiologists, and pathologists rather than by pathologists alone. We also show why clinically insignificant PCa and indolent PCa, although they considerably overlap, do not necessarily mean the same entity.

In a totally examined radical prostatectomy (RP), GG1 PCa has exceptionally excellent outcomes. In RPs harboring pure GG1 PCa, metastasis to lymph nodes and distant sites and cancer-specific death do not occur. Extraprostatic extension is uncommon (up to 6%) while seminal vesicle invasion is rare (0.03%).

Most incidentally detected PCa in cystoprostatectomy specimens are GG1 and are likely clinically insignificant. Using the Epstein's criteria, most (81–90%) incidental PCa in cystoprostatectomy series are clinically insignificant [1].

Non-index tumors in the multifocal PCa setting typically meet the clinically insignificant PCa criteria. Most PCas are multifocal tumors comprising the index and secondary non-index lesions. In multifocal PCa, tumor volume, GG, and pathological stage were almost invariably defined by the index lesion whereas, 87% and 99% non-index satellite foci are <0.5 cm and GG1 respectively [2]. The clinically insignificant PCa criteria capture many indolent PCas; however, the same criteria also encompass early-phase non-indolent PCas that subsequently may progress during active surveillance (AS) and would receive definitive treatment. Therefore, not all clinically insignificant PCas are indolent PCas.

A subset of GG1 PCa in NBX is upgraded to a higher grade in RP. Despite the combination of MRI-targeted and systematic biopsies, substantial upgrading at RP still occurs in 22% to 27% of biopsy GG1 PCa due to sampling error or potential progression [3 , 4].

Reclassification from GG1 PCa during AS may represent a previously unsampled higher-grade component, progression of the same tumor, or de novo higher-grade cancer . Longitudinal biopsy sampling has shown shared clonality of the preceding low-grade PCa and subsequent high-grade PCa. Reclassification to higher-grade PCa may occur due to prior under-sampling of the higher-grade component of the same tumor, temporal grade progression [5], and the phylogenies

of localized PCa [6] or due to sampling of a clonally unrelated tumor, including a new onset higher grade tumor, given the multifocal nature of PCa [7]. The very low mortality from PCa for men in multiple series of AS is the result of having both indolent PCas and preemptively treated non-indolent PCas in the cohort, the latter identified through reclassification. Distinction between indolent and non-indolent GG1 PCas in biopsies before reclassification is not possible.

A very small subset of GG1 PCa at NBX is associated with PCa-specific mortality. In a Danish population-based study of an unselected cohort of men with untreated GG1 PCa, PCa-specific mortality at 15 years was 14% [8]. Even if the mortality rate likely would be much smaller as no central pathology review ensuring purity of GG1 PCa was conducted, death can occur using AS criteria or a “clinically insignificant” definition.

Higher interobserver variation occurs in diagnosing a subset of the GP4. This variation may be reduced by ensuring novel and structured quality improvement processes in an anatomic pathology laboratory. Interobserver agreement for grading PCa is substantial, however, discrepancies especially for certain GP4 architectures has been high.

A subset of GG1 PCa harbors molecular alterations present in higher-grade and aggressive PCa . Molecular studies of GP3 and GP4 tumors that are in proximity often show evidence of a clonal relationship, and GP3 regions that are part of larger GG3 and GG4 PCa show an increased incidence of molecular changes such as PTEN loss, 8p loss, and 8q24 MYC gain than that detected in GP3 lesions from GG1 PCa [9]. PTEN loss and germline mutations in ATM and BRCA1/2 have been associated with grade reclassification in AS for PCa [10 , 11].

Racial disparities are likely to contribute to biological diversity in PCa . Although most PCa-associated genes in European American men have been detected in Black men, there is differential expression of some genes, which may explain the higher aggressiveness of PCa in Black men.

A contemporary “histopathological definition” that captures (does not define) the majority of indolent PCa would include GG1, no equivocal GP3/GP4, no cribriform PCa [Cribriform GP4/intraductal carcinoma (IDC-P)], and no stromal desmoplasia (“stromogenic” PCa). This histopathological definition must be combined with other multidisciplinary factors to optimally identify indolent PCa.

Stringent selection and monitoring criteria for enrollment help reduce biopsy grade reclassification during AS. In a contemporary AS cohort of 1818 men with stringent selection and monitoring criteria, the 5-, 10-, and 15-yr cumulative incidence of biopsy grade reclassification was 21%, 30%, and 32%, respectively. Older age, self-reported ancestry, PSA density, and increased cancer volume were significantly associated with grade reclassification while men who had mpMRI before enrollment had a lower incidence of grade reclassification [12].

Novel biopsy approaches may help reduce clinically insignificant PCa detection. The combination of lesion-targeted and systematic sampling has been shown to improve the detection of csPCa. Interestingly, csPCa is often found in a perilesional radius, while systemic biopsies far from the lesion are least likely to reveal csPCa [13].

Determining PCa aggressiveness in biopsy mapped to a particular prostate location holds great promise for more informed clinical decision-making. The development of multifocal PCa is debated, and two models have been proposed, one theorizes that an initially transformed PCa spreads to multiple locations, while the other suggests that each PCa foci arise independently and aggressive and non-aggressive cancer foci co-exist[14]. Consequently, the index tumor may not always be representative of PCa behavior. DNA methylation changes occur concordantly with tumor aggressiveness and therefore may be used to inform therapeutic approaches [14].

Tissue-based Genomic Classifier tests help refine PCa risk stratification. Numerous molecular biomarkers have been developed to improve risk stratification but few have undergone extensive validation. These biomarkers are generally modeled to distinguish biologically aggressive tumors. Specifically, no tissue-based biomarker or test can positively identify indolent PCa, especially in vivo tumors with very long latency. Biopsy sampling can also significantly influence the test result particularly if the portion of the PCa that exhibits molecular alterations associated with aggressive disease is not sampled. Multicancer early detection test may help reducing overdiagnosis of indolent PCa by preferentially detecting high-grade PCa in the intended use population (age 50–79) [15].