Title

Gleason score 3+3=6 prostatic adenocarcinoma is not benign and the current debate is unhelpful to clinicians and patients

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Authors

Samaratunga, Hemamali

Egevad, Lars

Yaxley, John

et al.

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Comment

Low-grade prostate cancer should still be labelled cancer

Kenneth A. Iczkowski[1], Mariel Molina[1], Lars Egevad[2], David G. Bostwick[3], Geert J.L.H. van Leenders[4], Francisco G. La Rosa[5], Theodorus van der Kwast[6], Daniel M. Berney[7], Andrew J. Evans[8], Thomas M. Wheeler[9], Katia R.M. Leite[10], Hemamali Samaratunga[11], John Srigley[12], Murali Varma[13], Toyonori Tsuzuki[14], Marshall Scott Lucia[5], Elward David Crawford[15], Richard G. Harris[16], Philip Stricker[17], Nathan Lawrentschuk[18], Henry H. Woo[19], Neil E. Fleshner[20], Neal D. Shore[21], John Yaxley[22], Ola Bratt[23], Peter Wiklund[24,25], Matthew Roberts[26], Liang Cheng[27] and Brett Delahunt[28]

[1]Department of Pathology, Medical College of Wisconsin, Milwaukee, WI, [3]Bostwick Laboratories, a division of Poplar Healthcare, Orlando, FL, [5]Department of Pathology, University of Colorado Anschutz Medical Campus, Aurora, CO, [9]Department of Pathology & Immunology, Baylor College of Medicine, Houston, TX, [15]Department of Urology, University of California San Diego, San Diego, CA, [16]UroPartners, Melrose Park, IL, [21]Atlantic Urology Clinics, Myrtle Beach, NC, [25]Department of Urology, Icahn School of Medicine, Mount Sinai, NY, [27]Department of Pathology and Laboratory Medicine, Indiana University, Indianapolis, IN, USA, [2]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, [23]Department of Urology and Clinical Cancer Epidemiology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenberg, Gothenberg, [24]Department of Molecular Medicine and Surgery, Section of Urology, Karolinska Institutet, Solna, Sweden, [4]Department of Pathology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [6]Laboratory Medicine Program, University Health Network and Princess Margaret Cancer Center, [12]Department of Laboratory Medicine and Pathobiology and [20]Division of Urology, University of Toronto, Toronto, [8]Department of Pathology, Mackenzie Health, Richmond Hill, ON, Canada, [7]Department of Pathology, Barts Health NHS TRUST, London, [13]Department of Cellular Pathology, University Hospital of Wales, Cardiff, UK, [10]Urology Department, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil, [11]Department of Pathology, University of Queensland School of Medicine, and Aquesta Uropathology, Toowong, [22]Wesley Medical Center, Auchenflower, [26]Department of Urology, Royal Brisbane and Women's Hospital, Brisbane, QLD, [17]Department of Urology, St. Vincent's Private Hospital and Clinic, [18]Urology Department of the Royal Melbourne Hospital and University of Melbourne, Melbourne, Vic., [19]College of Health and Medicine, Australian National University and SAN Prostate Centre of Excellence, Sydney Adventist Hospital, Sydney, NSW, Australia, [14]Department of Surgical Pathology, Aichi Medical University Hospital, Nagakute, Japan and [28]Pathology and Molecular Medicine, University of Otago, Wellington, New Zealand

In a pair of recent articles [1,2], Eggener et al. revived the decade-old argument, which we refuted previously [3], that Gleason score 3 + 3 = 6 (GS6; International Society of Urological Pathology [ISUP] Grade Group 1) prostatic adenocarcinoma should no longer be labelled cancer.

As members and allies of the ISUP, we disagree. The ISUP President (K.A.I.) surveyed the ISUP membership in May 2022 as to whether they: endorsed designating 3 + 3 = 6 as cancer; favoured renaming; opposed sending a written opinion; or were unsure. Of 314 respondents, 278 (89%) endorsed retaining GS6 as cancer vs 7% who favoured renaming (Appendix S1). These percentages were 90% and 6%, respectively, for academic pathologists, and 95% and 4%, respectively, for non-academic pathologists.

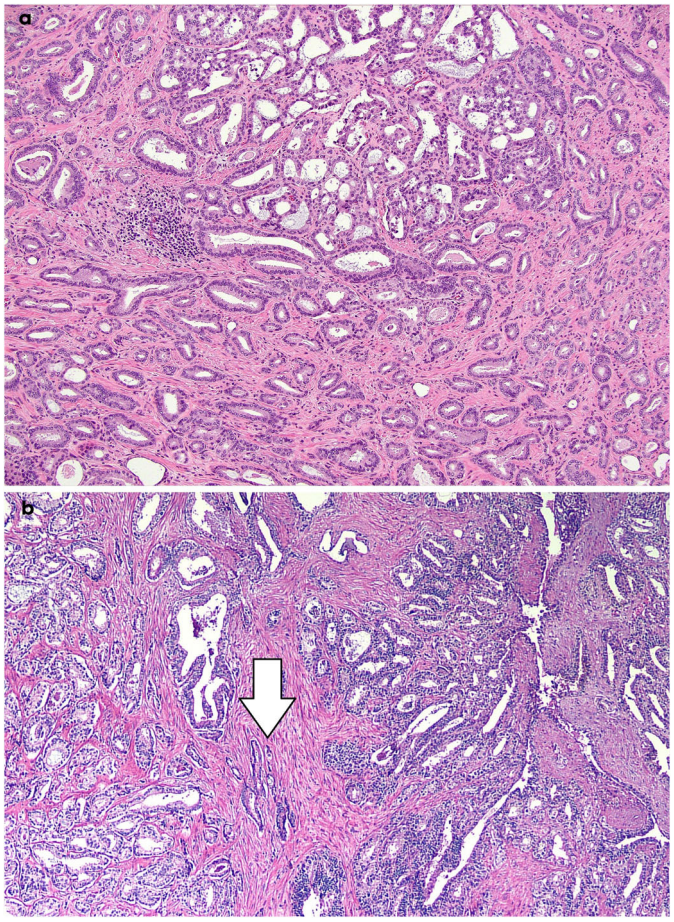
Gleason score 6 cancer heretofore constituted 50% of new diagnoses in the United States, but its incidence on first biopsy in a large uropathology practice in Australia recently decreased to 10% (H.S., pers. comm.) probably because of that practice's frequent prostate-specific membrane antigen positron emission tomography imaging for evaluation of elevated PSA. TRUS biopsies are prone to sampling error, resulting in upgrading at radical prostatectomy. As the emphasis on active surveillance has enabled some men either to forgo or delay treatment over the past two decades, the rates of GS6 cancer at prostatectomy have fallen to 8.3% to 10%. Prostate carcinoma age-adjusted deaths dropped 1.5% per year for a decade. Would a cosmetic renaming of GS6 cancer accelerate this success?

Eggener et al. [1], in their figure 1, depict a timeline with examples of lesions from other organ systems now relabelled as non-cancer. Commencing in 1998, these include bladder papillary urothelial neoplasm of low malignant potential (PUN-LMP), cervical squamous intraepithelial lesion, thyroid non-invasive follicular thyroid neoplasm with papillary-like nuclear features, and breast ductal carcinoma *in situ*. This argument is spurious as all the lesions cited are *in situ*, lacking invasion of parent tissues, which is an essential diagnostic carcinoma feature possessed by GS6 cancer. These lesions have been reclassified based on new knowledge, and they are confirmed after complete excision, unlike the needle

sampling of prostate cancer which carries significant risk of unsampled higher-grade tumour detectable by repeat sampling or a transperineal approach (mapping biopsies).

Gleason score 6 cancer lacks basal cells and basement membrane that constrain invasion, splits prostatic stromal fibres, and often demonstrates perineural invasion. Gleason grade 3 tumour forms 'a continuum of interconnecting tubules' with higher-grade cancer, according to a three-dimensional histoarchitectural study [4], producing interspersion with higher-grade tumour at prostatectomy (Fig. 1). GS6 cancer does not have, as asserted, 'an inability to invade local structures' [2] for it can invade extraprostatic adipose tissue or spread into the seminal vesicles (Fig. 1). Eggener et al. contend that GS6 cancer has low-grade cellular changes, but its cells usually manifest nuclear enlargement and macronucleoli just like higher-grade tumours. This also raises the logical and medicolegal dilemma of whether

Fig. 1 (**A**) Island of Gleason 4 tumour with cribriform pattern (top centre), in a sea of Gleason 3 tumour at prostatectomy (10× objective). Because of sampling variation, this had been Gleason score (GS)6 cancer on needle biopsy. (**B**) Invasion of GS6 carcinoma (solid arrow) into the seminal vesicle epithelium and its muscularis (10× objective).



Gleason pattern 4 tumour accompanying Gleason 3 transforms the latter glands from benign to cancer. If not, then even 3 + 4 = 7 and 4 + 3 = 7 grades would need to be abolished so that grading started at 4 + 4 = 8.

The assertion that GS6 cancers should be renamed because of their excellent cure rate when excised, implies that they cannot metastasize if left untreated. Of 261 men with GS6 cancer during 1994–2002 randomly assigned to watchful waiting in the PIVOT trial, 20 (7.7%) died from prostate cancer, indicating a non-negligible risk [5].

Eggener et al. [1], discussing their timeline, state, 'When GS2-5 tumors were reclassified (to non-cancers or GS6). . ..'. This is misleading. It is acknowledged that some of what was 1 + 1 = 2 cancer in the past is the benign mimic atypical adenomatous hyperplasia; thus, we do not assign 1 + 1 = 2. Also, Gleason pattern 2 has a non-infiltrative border, a feature that cannot be assessed on needle biopsy but is assessable in radical prostatectomy (ISUP, WHO), and it certainly is cancer.

A further fallacy perpetuated by Eggener et al. is that the management of GS6 cancer could be 'similar to the current management of noncancerous prostate lesions such as high-grade prostatic intraepithelial neoplasia (PIN) and atypical small acinar proliferation (ASAP). . ..' [1]. We agree that PIN lacks metastatic potential and is appropriately treated conservatively. A comparison with 'ASAP, suspicious for but not diagnostic of cancer' is erroneous: ASAP is not a final diagnosis, but a designation employed when the pathologist is absolutely uncertain of whether a microscopic focus, which is usually minute, is marginally sampled cancer. ASAP should be re-biopsied with some urgency as high-grade cancer is commonly present.

Eggener et al. argue that reclassification of GS6 cancer would immediately lead to fewer men receiving radiation, surgery, and treatments with well-recognized side effects [1,2]. This is simply unnecessary as many patients with low-volume GS6 cancer are being managed conservatively. While the percentage of GS6 cases undergoing prostatectomy is difficult to measure directly, it can be inferred that this has declined. Large cohort studies have shown a reduction in the prevalence of GS6 cancer at prostatectomy in the United States to one-third of its prior incidence (to 10%) [6], and in Europe to one-half its prior incidence (to 8.3%) [7]. Renaming GS6 cancer as non-cancer is unlikely to mitigate overtreatment while discouraging a subset of patients from undergoing active surveillance, including multiparametric MRI and repeat biopsy.

Finally, genomic alterations have been studied among the various Gleason scores of prostate cancer, and Rubin et al. have provided a graphical representation of the chromosomal abnormalities from 426 prostate cancer cases listed as a

function of grade group [8]. There is considerable overlap of the somatic deletions and amplifications among all five grade groups. GS6 cancer somatic copy number alterations are strikingly similar to GS7. Analysis of Gleason 3 and adjacent Gleason 4 tumour foci according to whole-exome sequencing and transcriptome profiles revealed that these adjacent tumours emerged from a common precursor and thereafter evolved independently. PTEN loss and ERG overexpression superbly delineate that subset of GS6 prostate cancers most likely to be upgraded at prostatectomy.

Thus, screening for and diagnosing GS6 cancer remains at least as relevant today as in 2014 [3], given the expanded range of options for patient choice. Renaming GS6 would spuriously lower the reported incidence of prostate cancer and cause failure to diagnose, through omission or commission, not only GS6 lesions but also synchronous or subsequent high-grade cancers.

Disclosure of Interests

The authors have no competing interests to declare that are relevant to the content of this article. The authors did not receive support from any organization for the submitted work.

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Correspondence: Kenneth A. Iczkowski, Department of Pathology, Medical College of Wisconsin, 9200 W. Wisconsin Ave., Milwaukee, WI 53226, USA.

e-mail: kaiczkowski@mcw.edu

Abbreviations: ASAP, atypical small acinar proliferation; GS, Gleason score; ISUP, International Society of Urological Pathology; PIN, prostatic intraepithelial neoplasia.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Survey monkey question for ISUP membership.