Reply by Authors: We agree with the points highlighted by Mynbaev et al. We wish to emphasize that most of the recurrences observed were due to hematogeneous spread, thus advancing the hypothesis that the cancerous cells spread through the venous system rather than in the peritoneal cavity as a consequence of bladder pedicle squeezing in the Batson plexus. We want to stress the need for further studies exploring the effect of pneumoperitoneum on urothelial cancer dissemination, challenging the adequacy of minimally invasive surgery in the management of such a lethal disease.

Re: Consensus Guidelines for Reporting Prostate Cancer Gleason Grade


To the Editors: It was with some surprise that we read the Commentary by the editors of the International Journal of Radiation Oncology, Biology and Physics; Urology; Urologic Oncology; BJU International; European Urology; and The Journal of Urology® regarding the recently defined grading system for prostate cancer.1–6 For clarification the Commentary published in The Journal of Urology is titled “Stage Grouping,” which would appear to be an error.

In the Commentary it was noted that the modifications to the Gleason grading systems have been endorsed by the International Society of Urological Pathology (ISUP). In reality this is not the case. The consensus conference held in Chicago on November 1, 2014 was convened under the auspices of the ISUP but the attendees were selected and, unlike other ISUP consensus conferences, attendance was not open to the full membership of the society. The modifications to the Gleason grading system published in the American Journal of Surgical Pathology have never been formally endorsed by either the Council or the membership of the ISUP. What has been discussed is the terminology that has been applied to the grading system and the ISUP Council has unanimously endorsed the name ISUP Grade as the meeting was coordinated under the auspices of the ISUP.

The Commentary refers to the new system as Grade Groups rather than ISUP Grade. This terminology appears in the latest edition of the World Health Organization (WHO) classification.7 However, it should be noted that this was not adopted by consensus but, rather, was a stop-gap measure proposed by the chair of the WHO Prostate Cancer Committee. While the final sentence of the definitive grading paper is “The new grading system and the terminology Grade Groups 1-5,” has also been accepted for volume 8 of the 4th edition of the WHO series on histological and genetic typing of human tumors,7 the phrase and the terminology “Grade Groups 1-5” were added to the proof of the article without the knowledge of at least some of the authors. As such, this statement is not endorsed by the ISUP. It should be noted that the term Grade Group is entirely inappropriate as the new grading system is a combination of Gleason scores and Gleason grades, and indeed is primarily score based.

Interestingly, there has been much debate in the pathology literature concerning the terminology and content of the new grading system, and it is clear that the grading system requires modification. We have recently outlined some of these concerns regarding grading terminology and criteria elsewhere, including a commentary in BJU International,8–11 although this appears to have been overlooked by the authors of the Commentary. Such is our concern that we have made recommendations regarding a re-working of the system.9–11

Over the years the ISUP has endorsed recommendations regarding issues relating to prostate and renal cancer reporting.12,13 However, these have never been the subject of a directive in the literature with respect to their implementation. We believe to do so is inappropriate and this has the effect of stifling academic debate. No such encouragement/requirement in relation to prostate cancer grading has appeared in the pathology literature and we believe that this is
entirely appropriate. Free debate is the lifeblood of science and this should be actively promoted.

Respectfully,

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Reply by Anthony Zietman, Eric Klein, Michael J. Droller, Prokar Dasgupta, James Catto and Joseph A. Smith, Jr.: We thank the authors for their Letter and hope to provide some clarification from the perspective of the 6 journal editors. The Gleason system has endured because it aligns with clinical outcomes but it is awkward for patients and physicians alike. It is misleading as it starts at 6, does not discriminate between the combinations that compose Gleason 7 and does not clearly show the emerging prognostic distinctions among the high grade cancers. This has created an obstacle not only to treating patients, but also in the consistency of scientific reporting. This is particularly true when assessing patient suitability for active surveillance and also with the nuanced treatments for higher grade tumors. The conference at which the new
system was proposed was attended by several of us. The naming of the system was a contentious issue and is not yet fully resolved, as emphasized by the Letter, but there was little disagreement among participants about its value or validity.

As editors and as practitioners caring for patients with prostate cancer, we believe that the new system for grouping of Gleason grade has clinical and pragmatic merit. Accordingly, we have encouraged our authors to use the new grouping in submitted manuscripts. This should help provide clarity, and better comparative assessment of outcomes and treatment results. Nevertheless, we recognize that little in scientific publishing is static, and ongoing study and novel analyses will likely result in further modifications. The exact name used for the system, while important for reference and consistency, is not within our purview to decide, and we await wider discussion in the prostate cancer community, particularly among the pathologists, for a final consensus on that issue.

Re: The NLRP3 Inflammasome Mediates Inflammation Produced by Bladder Outlet Obstruction


To the Editor: The authors report that the NLRP3 inflammasome is involved in the induction of inflammation and bladder dysfunction secondary to bladder outlet obstruction (BOO). The pathogenesis of bladder wall remodeling caused by BOO may be started by bladder inflammation. But based on several reports, the historical view is that it is caused by bladder ischemia, oxidative stress or mechanical stimuli.1–3 Hughes et al provide a new direction for further research on the pathogenesis of bladder outlet obstruction.

However, the NLRP3 inflammasome is also involved in cystitis.4 Urinary tract infections including cystitis are common complications of BOO.5 Meanwhile, in our recent work we found that 2 mice with BOO suffered from pyuria. Infectious cystitis may have increased bias in the research of Hughes et al. Therefore, we would like to know whether they found urinary tract infections or even pyuria in animals with BOO.

Respectfully,

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Reply by Authors: Activation of NLRP3 likely does not function independently of the well established roles of ischemia and oxidative stress (and perhaps mechanical stimuli), but rather may be triggered by them. Indeed, reactive oxygen species are thought to be the central activator of NLRP3 in response to a wide variety of stimuli in many different tissues that mount innate immune responses.6 Thus, we champion the idea that NLRP3 functions as a central processing unit,7 integrating the input from these various pathways and triggering an inflammatory response.

Regarding the possible influence of infectious cystitis in our BOO studies, some pathogen associated molecular patterns (such as lipopolysaccharide) are indeed known to activate NLRP3, and we have shown that this activation occurs in the urothelium.4 In these studies we did not test directly for bacteria in the urine or for pyuria (which may also occur through sterile mechanisms8), but did not see any obvious signs such as cloudy urine or clinical signs of infection. Thus, we cannot rule out a contributory action, although we believe it would likely have a minor role in these short-term (12-day) studies. Nevertheless, prophylactic antibiotics would be a useful addition to our protocol, particularly for more long-term studies.