Gleason 6 Cancer Is Still Cancer

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Source:

Drs. Lepor and Donin[1] pose the sensible question of whether Gleason grade 3+3 (score = 6) prostate cancer possesses life-threatening potential—and even whether it is “cancer.” A few points need to be emphasized or clarified.

In the final two-thirds of their article, starting with the section “How Reliable Is Our Detection of Gleason 6 Disease?” the authors repeatedly emphasize the constraints in risk stratification of prostate cancer by “random systematic biopsies.” They seemingly refer to the widely used 6- or 12-site biopsy approach, which by its inherent sampling variation identifies Gleason score 6 (G6) cancer in many patients who also have undetected cancer of a higher Gleason score. They conclude that G6 cancer may be more effectively stratified in the future by determining which cases coexist with higher-grade cancer.

Nevertheless, they neglect to mention that at some medical centers the future is now. For men with low-volume G6 cancers in 1 to 3 cores of an initial biopsy and for men with persistent increases in prostate-specific antigen (PSA) levels and negative biopsies, template-guided, transperineal mapping biopsy (TPMB) is currently the best choice for patient care.[2] This procedure samples 60 to 120 cores (depending on prostate volume) in the x, y, and z axes (with the proximal end of the core inked for orientation), which allows the creation of whole three-dimensional in vivo reconstructions of the prostate gland. These three-dimensional maps perfectly correlate with “gold standard” prostatectomy results, including tumor location, size, and Gleason grading.[2] Thus, previously undetected cancers with high Gleason scores can be accurately identified, and patients can receive the most appropriate therapy. In addition, men with G6 cancer in more than a few cores or a high tumor burden, which puts them at increased risk for progression,[3] usually meet the criteria for more radical therapies.

Another increasingly popular approach to the stratification of G6 cancer is to perform molecular studies such as PTEN detection by fluorescence in situ hybridization or by immunostaining.[4] Loss of PTEN expression occurs in about one-third of prostate cancers and portends an adverse outcome, particularly if there is concomitant ERG overexpression.[5] Commercial tests such as Oncotype Dx and Prolaris are gaining recognition as ways to stratify G6 cancer, allowing the use of conservative treatment alternatives such as targeted focal therapy with partial cryoablation of the prostate,[6] hormone therapy only, and watchful waiting.

As pathologists, we appreciate that Gleason grading is an oversimplification that reduces a continuum of disparate architectural cancer patterns to a few numbers (3, 4, and 5). Furthermore, pathologists’ subjectivity blurs the boundary between G6 and Gleason score 7 cancers. The only difference between these scores is the fusion of tumor glands, and even expert uropathologists can disagree on the recognition of definite fusion. In one study, the agreement of pathologists with the consensus Gleason score was 78%, and overall interobserver agreement had a kappa of 0.54.[7] Further molecular evidence that Gleason grade 3 cancer is distinctly different from Gleason grade 4 (G4) cancer is still lacking.

G4 cancer likewise warrants further stratification because it includes a broad variety of architectural configurations, such as fused small glands and papillary, glomeruloid, and cribriform glands. Using precise digital image analysis, we can distinguish barely fused from extensively fused small glands, and can identify cribriform glands with more or less cellularity; even differences in size, shape, and lumen spacing correlate with different clinical outcomes.[8] Those patients with any cribriform or similar large-gland pattern of G4 cancer have significantly worse outcomes than those who have G4 cancer with fused small glands.[9,10] The adverse outcome is most pronounced if the sum of cribriform areas exceeds 25 μL in whole mounts of totally submitted prostatectomy specimens.[9] Finally, Drs. Lepor and Donin conflate the terms high-grade prostatic intraepithelial neoplasia...
(HGPIN) and atypical small acinar proliferation (ASAP) as being suggestive of but not diagnostic of malignancy, citing the coexistence of both with cancer, as if both were precursors. It is not fair to equate the association of these two entities with cancer to the association of G6 disease with higher-grade cancer and ask, “Where do we draw the line?” Yes, HGPIN is a precursor, and 75% of HGPIN foci show topographic abutment to cancer. ASAP, however, is not a cancer precursor by itself but a heterogeneous diagnostic category representing findings that fall short of the minimal diagnostic criteria for cancer. It comprises both marginally sampled cancer lesions and mimics of cancer (eg, atrophy, atypical basal cells, and outpouchings of HGPIN). Yet, ASAP carries a 40% to 50% predictive value for cancer on repeat biopsy, about double that of HGPIN.

The authors conclude by expressing the hope that most true G6 cancer will no longer be diagnosed or treated, and asserting that such cancer should not be labeled as “cancer.” In a recent study, men with G6 cancer were classified as “low risk” or “very low risk” based on number and percentage of core involvement and serum PSA level; those at low risk had a 21.8% risk of Gleason score upgrade and a 23.1% risk of non–organ-confined cancer. Even for those at very low risk, the percentages were still considerable: 13.1% and 8.5%, respectively. The authors also admit in the section on laboratory evidence that the data on the progression of pure G6 cancer to a higher grade remain mixed and contradictory. Thus, as long as there is any risk of progression, G6 cancer cannot be equated to just a precursor lesion, and the emphasis should remain on screening patients with serum PSA measurement, contrary to the recommendation of the US Preventive Services Task Force (which was based on questionable interpretation of a few trials).

Although overdiagnosis of prostate cancer is not a problem, awareness of its overtreatment is growing. Therefore, we should continue to diagnose G6 cancer but use a more comprehensive approach to prostatic sampling, including TPMB, and we should expand the range of options for its clinical management on the basis of risk, with targeted focal therapy and watchful waiting among the possibilities. In conclusion, we agree that some G6 cancers can be relegated to the status of a toothless lion, but many cases are not innocuous. G6 still merits a cancer diagnosis, and patients should have access to the broadest possible array of options.

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References:


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