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EDITORIAL

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The end of "very low risk" in localized prostate cancer?

The guidelines of the National Comprehensive Cancer Network added the very low-risk (VLR) group for localized prostate cancer (PC) in 2010[1] and shortly thereafter, this risk group was included in the American Urological Association guidelines.[2] The characteristics that define this risk group are similar to those criteria that Dr. Epstein presented in 1994,[3] bearing in mind that the standard biopsy template has changed since that time, increasing from 6 to 12 cores. Additional changes to the number of cores included an expansion of the concept of insignificant PC and an update of the Gleason staging system.[4] This VLR group must present the following characteristics: PSA < 10 ng/ml, Grade Group 1, less than 34% of positive biopsy cores positive, no core with more than 50% cancer, PSA density less than 0.15 ng/ml/cc and clinical stage T1c or T2a depending on the guideline used.

Characteristics required for VLR classification are complex—and thus difficult to achieve accurately due to several considerations. Three areas of inconsistency include: (1) calculating percentage of involved cores; (2) determining how to "count" number of cores obtained; and (3) obtaining a precise measurement of prostate volume, and thus PSA density. Given these inconsistencies, the utility of VLR classification in contemporary practice should be explored.

Regarding the first area of inconsistency, understanding the percentage cores compromised by tumor can differ based on pathologist evaluation. In cores with two separate tumor areas, pathologists lack consensus regarding how to "count" the area framed between regions with tumor. While some pathologists interpret this as a tumor-free zone, others interpret this portion as one with malignancy potential, thus "counting" it within the total percentage of the sample compromised by tumor.[5] Another area of controversy is measurement of the core length. Core length of the biopsy sample can vary from 1 to 2 cm in length depending on the type of biopsy needle used and can also vary in core length among samples obtained from the same needle.

Regarding the second area of inconsistency, cores obtained from targeted biopsies represent a dilemma in how to "count" these, given they are taken from the same location, with two or more cores typically obtained from each target. The International Society of Urological Pathology of 2019[6] consensus presents two scenarios. The first scenario involves target samples taken in areas within the twelve systematic sample regions. In this case, the sample with the highest grade should be reported and not added as an additional core to the 12 planned sites. The second scenario involves target samples taken outside of the 12 regions. In this case, the core with the highest grade is again reported, but this time, is added as an additional core to the 12 performed. With these recommendations in mind, some points remain unclear. For example, is a patient with three cores of systemic positive biopsies plus an extra positive target biopsy (four different areas in the prostate) considered VRL even fulfilling all the characteristic of this risk group?

Another challenging classification scenario is when a patient has an additional positive target area, with two or three positive cores (not a single one) all within a single target lesion with a percentage less than 50% on the positive cores. Does this patient classify as VRL considering that greater tumor volume implies greater risk? In these given cases, both patients fall within the definition of VLR but may vary based on outcomes.[7] In the Genitourinary Pathology Society[8] survey, there was an equal split between grading approaches, 49% grading each individual positive core sampled from an magnetic resonance imaging (MRI)-targeted area separately versus 51% using the average grade of all positive cores from a given target. This survey concluded that, when multiple undesignated cores were taken from a single MRI-targeted lesion, an overall grade is given as if all cores involved were a single core. When different scores are found in the standard and in the MRI-targeted biopsy, a global score must be given. Clearly, differences exist with regard to definitions from two prominent GU Pathology Societies.

With regard to the third and final area of inconsistency for VLR disease classification, prostate volume contributes to misclassification of risk due to inaccurate measurement, and thus, inaccurate PSA density.[1,2] With regard to accurate prostate volume measurement, digital rectal examination was replaced by a more precise measurement, such as transrectal ultrasound (TRUS) that demonstrated adequate correlation with pathological samples using planimetric techniques which calculates volume via ellipsoid formula.[9] Nevertheless, the exact reference points of the measured limits are rarely provided in the images to ensure overall reproducibility. Furthermore, measurement depends on the experience of the examiner. Most studies performed with TRUS underestimate the global pathological measurement of size by weight,[10–12] although this may be due to the inclusion of seminal vesicles, vas deferens and periprostatic tissue in the weight of the pathological samples. In addition, if the biopsy has been performed in another healthcare center, the measurement may not be available.

Currently, the most accurate measurement of prostate volume is performed with mpMRI, which is now indicated before the initial prostate biopsy[13] by the European Association of Urology guidelines, although not all patients undergo this procedure. However, even mpMRI is not 100% accurate, as the coefficient used to calculate volume is debated. While the PIRADS v2 classification uses the coefficient of 0.52 to calculate prostate volume, other Diagnostic

Imaging Specialists have opted for other coefficients, such as 0.65 and 0.66, believing these to be more accurate.[14] In fact, the last update of the PIRADS classification (2019 PIRADS v2.1) included changes in the calculated measurements for prostate volume. The midaxial plane is recommended for this measurement in PI-RADS v2, while the midsagittal plane is recommended in PI-RADS v2.1.[15] Prostate volume can be calculated even more accurately when planimetry is applied.[16] Furthermore, a new technique (Biproximate) was proposed which uses more precise and reproducible reference points as an alternative to measuring the ellipsoid volume.[17] Given that PSA density is a function of volume, PSA density is therefore not obtained with precision, and may vary depending on which method or technique is used.

After highlighting three areas of inconsistency which influence risk classification: (1) calculating percentage of involved cores; (2) determining how to "count" number of cores obtained; and (3) obtaining a precise measurement of prostate volume, and thus PSA density; several considerations exist. First and foremost, accurate classification of a patient as VLR is challenging given that 50% of tumors misclassified as VLR were in fact tumors on the anterior prostate not sampled due to the biopsy technique, which generally omits the transition and anterior sampling of the prostate.[18,19] Patients with tumors in the anterior area of the prostate generally have fewer positive and less involved nuclei, which can be misclassified using standard techniques and often better evaluated with mpMRI and transperineal biopsies.[20–22] Small-volume, high-grade tumors in the peripheral area may also be missed using standard techniques, and sometimes not identified by mpMRI due to their size.[23]

The utility and purpose of risk groups should be to facilitate and guide therapeutic decisions according to the prognosis they represent. The definition of "VLR" in PC was used by some institutions such as John Hopkins to define those patients who could be selected for active surveillance. However, in recent years these stricter and less inclusive criteria have been relaxed, allowing more patients to be included in an active surveillance program. Currently, patients are included beyond the percentage of samples compromised by the tumor in each core and T2a patients are accepted in selected cases,[24] rendering the utility of VLR risk classification less relevant. The association of VLR as clinically insignificant PC also lacks consensus. Among articles which use the term "clinically nonsignificant PC," only some take into account the VLR group whereas in most cases, the term "clinically insignificant" is related to a low Gleason Grade Group and a low PSA.[25]

As our understanding and management of PC continues to evolve, so must our definitions of risk groups. Several areas of measurement outlined in this commentary highlight the inconsistencies and challenges when defining these groups, particularly among those with VLR disease. Given the inability to consistently measure and define the criteria set forth in the VLR group, this classification loses meaning in our daily clinical practice.

In conclusion, given the evolution and greater use of new diagnostic methods such as imaging studies, genetic tests, and new generation biomarkers that predict the chances of diagnosing a clinically significant PC, we believe that future risk group classification should account for these nuances such that we can definitively and consistently classify patients based on prognosis using the best available evidence we have today.

CONFLICT OF INTERESTS

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