Title: Diagnostic Potential of Radiological Apical Tumor Involvement

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Abstract:

We commend Veerman *et al.* for investigating the diagnostic performance of radiological apical tumor involvement (radATI) in preoperative prostate magnetic resonance imaging (MRI) and its impact on clinical outcomes in patients with localized prostate cancer. This retrospective study evaluated the diagnostic accuracy of MRI to detect pathological ATI (pathATI) in robot-assisted radical prostatectomy specimens. They found patients with radATI more likely to develop biochemical recurrence (BCR), $p = 0.003$, and have apical positive surgical margins (APSM), $p = 0.004$.

We believe that the author's acknowledgement of the relationship between tumor location and cancer risk is an important step in the classification of prostate cancer. An important question that is under addressed is, what is it about apical tumors that carry additional risk? Higher rates of PSM due to incomplete surgical excision may contribute to increased recurrence risk in the apex. If this is the case, surgical management must be tailored by a tumor location-based risk assessment.

The literature suggests that a single APSM may be clinically insignificant for long-term outcomes. Conversely the authors also recommend radATI be treated with reduced apical nerve sparing to avoid APSM. We believe this approach may lead to overtreatment in the presence of an otherwise good prognosis.

We believe the extent of APSMs upon diagnosis would be an interesting topic for further investigation. The authors may also wish to perform multivariable analysis for the effect of radATI on BCR. We believe MRI may play a critical role in enhancing diagnosis and prognostication of prostate cancer.

Letter to the Editor:

We commend Veerman *et al.* for investigating the diagnostic performance of radiological apical tumor involvement (radATI) in preoperative prostate MRI and its impact on clinical outcomes in patients with localized prostate cancer (1). This retrospective study evaluated the diagnostic accuracy of MRI to detect pathological ATI (pathATI) in robot-assisted radical prostatectomy specimens. They found 2/56 (4%) of patients without radATI developed a biochemical recurrence (BCR) compared to 25/120 (21%) patients with radATI ($p = 0.003$). Multivariate analysis found patients with radATI more likely to have apical positive surgical margins (APSM) ($p = 0.004$). These findings have implications in predicting and potentially improving prostate cancer outcomes and further investigation of certain areas in this field would be valuable.

We believe that the author's acknowledgement of the relationship between tumor location and cancer risk is an important step in the classification of prostate cancer. Tumor location has already been widely recognized as a risk component in breast and lung cancer, with increasing evidence indicating a similar rationale could be applied in the prostate (2). An important question that is under addressed is, what is it about apical tumors that carry additional risk? Variation in tumor microenvironment may result in morphological differences influenced by tumor location. Microenvironments can have asymmetric differences in vascularity based on the cell-type composition in that region. Tumor microenvironment markers have already been employed for stratification of risk of recurrence of prostate cancer (3). Additionally, higher rates of PSM due to incomplete surgical excision may contribute to increased recurrence risk in the apex. If this is the case, surgical management must be tailored by a tumor location-based risk assessment. RadATI detection of APSM, together with modifications in surgical techniques to reduce APSM may be necessary, as well as deploying adjuvant treatments to eliminate APSM. In addition, taxonomy may be warranted in categorizing apical tumors based on morphology, volume, and grade. We look forward to seeing further progress in the understanding the significance of prostate tumor location.

The literature suggests that a single APSM may be clinically insignificant for long-term outcomes (4,5). A study by Wadhwa *et al*. found that APSMs lead to less BCR than PSM in other areas (6). Conversely the authors also recommend radATI be treated with reduced apical nerve sparing to avoid APSM. We believe this approach may lead to overtreatment of radATI in the presence of an otherwise good prognosis. However, it is important to acknowledge the psychological distress PSM may have on patients, warranting the need for further treatment. In addition, Wadhwa's study has several limitations, such as the dataset details including any surgical technique, rather than focusing on specimens from robot-assisted surgery. Wadhwa also lacked important prognostic factors, such as tumor grade and amount of tumor at the margin.

We believe the extent of APSMs is a key prognostic factor and is found to be an independent predictor of BCR (7). Only extensive PSMs seem to significantly increase the risk of BCR, while focal APSMs have little effect. Most tumors in Veerman's study were clinically suspicious (63% with a PI-RADS 5) but the extensiveness was unknown. Consideration of the extent of PSM upon diagnosis would be an

interesting topic for further investigation. The authors may also wish to perform multivariable analysis for the effect of radATI on BCR.

The potential of MRI to predict ATI is encouraging, however, future study may benefit from focus on the points highlighted here. We believe MRI may play a critical diagnostic and prognostic role for prostate cancer. Integrating MRI with other diagnostic techniques such as PSMA PET-CT, micro-ultrasound and PCA3 biomarkers could form a powerful toolkit in enhancing prognostication.

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