Brief Correspondence

Addition of Prostate Volume and Prostate-specific Antigen Density to Memorial Sloan Kettering Cancer Center Prostate Cancer Nomograms

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Abstract

Prostate-specific antigen (PSA) density is an established prognostic marker for prostate cancer. We investigated whether the inclusion of PSA density or prostate volume in the Memorial Sloan Kettering Cancer Center nomograms improves the prediction of biochemical recurrence (BCR) after radical prostatectomy (RP). Among the 11,725 men included, 2,140 developed BCR. Neither PSA density nor prostate volume was associated with BCR when added to either the pre-RP or post-RP model (all p values > 0.10) and changes in the C index were very small (largest change, 0.002). The results were robust to exclusion of outlying prostate volumes and restriction to patients treated after 2005. There is no justification for adding prostate volume or PSA density to BCR nomograms.

Patient summary: Addition of prostate volume or prostate-specific antigen density to Memorial Sloan Kettering Cancer Center prediction schemes did not improve the prediction of recurrence of prostate cancer after removal of the prostate.

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predicting adverse pathology among those undergoing RP [4]. We thus investigated the value of adding prostate volume or PSA density to the three MSKCC models for BCR after RP.

Our cohort consisted of men who underwent RP at MSKCC between June 15, 1988 and March 31, 2020 and had preoperative PSA and preoperative prostate volume measurements available (n = 11,725). Clinical stage before RP was assessed via digital rectal examination. A total of 0.4% of patients received adjuvant radiation. PSA was assessed at 6–12 wk postoperatively, every 6 mo for 5 yr, and annually thereafter. Our goal was to assess whether the addition of prostate volume or PSA density improved the performance of the standard MSKCC models. We used the same covariates as the previously described preoperative and postoperative MSKCC models. However, since these models were built from a cohort that includes patients with unknown prostate volumes, we refitted the models using the same covariates on a subset of the original cohort for which volume data were available. We then created two additional models by adding either prostate volume or PSA density to the existing covariates, including nonlinear terms using cubic splines with knots at the tertiles.

Weibull parametric survival models were used for the outcome of time to BCR and included all specified covariates. These models were weighted by surgery year. Weights were calculated as the inverse of the square root of the number of years between a patient’s surgery and the latest surgery year (2020) plus one. A concordance index was calculated as a metric of predictive value. Two sensitivity analyses were conducted; one excluded patients with outlying prostate volumes (<10 ml or >200 ml), while the other only included patients treated in 2006 or later to account for stage shift and updated Gleason grading. All analyses were conducted using R v4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Among the 11,725 men in the analysis, 2140 developed BCR. Median follow-up for men without BCR was 2.9 yr, with 3057 men followed for more than 5 yr without BCR. Patient and disease characteristics are provided in the Supplementary material (Supplementary Table 1).

The results are shown in Table 1. In brief, prostate volume and PSA density were not independently associated with BCR when added to the nomograms and therefore did not result in a relevant increase in the C index, with increases of no greater than 0.001 and 0.002, respectively. Results were similar in sensitivity analyses excluding outlying volumes or patients treated before 2006 (Supplementary Table 2), with no relevant increases in discrimination associated with the additional markers.

In 2002, Freedland et al [5] reported that PSA density was an independent predictor of BCR. Moreover, in their multivariable analysis, PSA was not an independent predictor of BCR when PSA density was added. Subsequent studies compared the accuracy of predictive models when either PSA density or PSA was included and found that those using PSA density did not achieve higher C indices than those using PSA [6,7]. These results supported the hypothesis that PSA rather than PSA density should be used in predictive models. However, no studies to date have assessed whether adding PSA density to models that currently include PSA improves their predictive accuracy. In our analysis, we found that adding PSA density provides no benefit to three widely used predictive models.

Previous investigations of prostate volume in predictive models show mixed results. Moschini et al [2] demonstrated that addition of prostate volume to a model for BCR after RP slightly improved the discrimination (from 0.654 to 0.673) in a cohort of 5637 men; this improvement was even greater in a subanalysis of only men with intermediate risk (from 0.628 to 0.675) [2]. However, Ito et al [8] found that addition of prostate volume resulted in a negligible improvement in the C index of the postoperative MSKCC nomogram (from 0.863 to 0.865) for a cohort of 1261 patients. Our findings confirm those of Ito et al in a larger cohort and for the preoperative MSKCC nomograms as well. The ability of prostate volume to improve discrimination in predictive models may be partly related to the accuracy of the base model under investigation. In the context of contemporary models that already achieve high predictive accuracy, we find that prostate volume provides no additional benefit.

The major limitation of our study is that prostate volume, and therefore calculation of PSA density, was measured via transrectal ultrasound for the vast majority of patients. It is possible that magnetic resonance imaging would more accurately assess prostate volume and, accordingly, add to the BCR prediction models. Inclusion of patients with prostate volume measured via magnetic resonance imaging, although a minority of the cohort, may have also introduced heterogeneity.

In conclusion, addition of prostate volume or PSA density to the three MSKCC nomograms failed to improve the predictive accuracy for BCR after RP. These variables should not be considered in patient counseling regarding the risk of recurrence.

Table 1 – Value of adding prostate volume or PSA density to the existing Memorial Sloan Kettering Cancer Center prediction models

| Model                  | Base model | Plus prostate volume | Plus PSA density |
|------------------------|------------|----------------------|------------------|
|                        | C index    | p value              | C index          | p value          | C index |
| Preoperative           | 0.798      | 0.4                  | 0.799            | 0.10             | 0.800  |
| Preoperative with core data | 0.802    | 0.5                  | 0.803            | 0.2              | 0.804  |
| Postoperative          | 0.843      | 0.9                  | 0.843            | 0.6              | 0.843  |

PSA = prostate-specific antigen.
* The p value is from the Wald test of prostate volume or PSA density as nonlinear terms in the multivariable model.
Author contributions: Andrew J. Vickers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical analysis: Vertosick, Vickers.
Obtaining funding: Hu.
Administrative, technical, or material support: Hu, Vickers.
Supervision: Hu, Vickers.
Other: None.

Financial disclosures: Jim C. Hu certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: Jim C. Hu receives research support from the Frederick J. and Theresa Dow Wallace Fund of the New York Community Trust and salary support from grants NIHRO1 CA241758, PCORICER-2019C1-15682, and CER-2019C2-17372. The sponsors played no direct role in the study. MSKCC investigators are supported by P50 CA092629 and P30 CA008748 and the Sidney Kimmel Center for Prostate and Urologic Cancers.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.euros.2021.06.002.

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