Pretreatment Prostate-Specific Antigen Velocity and the Risk of Death From Prostate Cancer in the Individual With Low-Risk Prostate Cancer

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Evaluating the ability of a new prognostic factor to predict cancer-specific outcomes for an individual stands in contradistinction to an assessment of whether the prediction of these outcomes improves when the new prognostic factor is analyzed with a known prognostic factor in a population of men with heterogeneous cancer-based risk profiles. Specifically for the case of the individual with localized prostate cancer, several studies have shown that a prostate-specific antigen (PSA) velocity higher than 2 ng/mL/year has a clinically important impact on the risk of prostate cancer–specific mortality after either radical prostatectomy or external-beam radiation therapy if that man has otherwise favorable known prognostic factors (ie, low-risk prostate cancer with a PSA < 10 ng/mL, biopsy Gleason score 6 or lower, and clinical tumor category 1c or 2a). In those studies, cumulative incidence estimates of prostate cancer–specific mortality reached 19% as compared to more than 10-fold reduction to less than 2% by 10 years after local therapy if the pretreatment PSA velocity was greater than 2 ng/mL/year as compared with a rise in the PSA level of 2 ng/mL/year or less, respectively. However, if an individual already had a markedly elevated PSA level or a biopsy Gleason score of 7 or higher, then the impact of PSA velocity on prognosis is lessened because of the already increased risk of prostate cancer–specific mortality based on the known prognostic factors. Therefore, when making an assessment of the clinical utility of a PSA kinetic parameter in a cohort of men with newly diagnosed prostate cancer, one should look specifically at men with low-risk prostate cancer where the known prognostic factors (PSA level, biopsy Gleason score, and clinical tumor category) do not adequately distinguish the cancer–specific outcomes.

In this issue of Journal of Clinical Oncology, O’Brien et al. ask whether various PSA kinetic parameters add to the PSA level in predicting cancer-specific outcomes after radical prostatectomy. The conclusion they reach is that PSA kinetic factors are prognostic when looked at alone but do not add significantly to the PSA level in predicting cancer–specific outcomes. This is exactly what one would expect based on the distribution of cancer-based risk profiles for the men in their study. Specifically, at most 46% of the men in their study had low-risk prostate cancer as determined by their subset analysis evaluating 1,362 of 2,938 men who had a PSA lower than 10 ng/mL and Gleason score of 6 or lower, but could have had any tumor category. As a result, for the majority of the men in the current report, one would not expect significant enhancement of cancer-specific outcomes prediction based on a PSA kinetic measure because the patient’s risk of recurrence and metastatic disease is already significantly increased based on the fact that more than one half of the study cohort were men with intermediate- or high-risk disease. Moreover, as the authors note in the first paragraph of their results section, “Less than one third of our study cohort had a calculable dynamic for 2 definitions, D’Amico PSADT and D’Amico B PSAV.” As a result, fewer than 15% (one third of 46%) of the original cohort would be available to analyze the PSA velocity higher than 2 ng/mL/year metric in men with low-risk prostate cancer. In addition, based on the numbers reported in the sensitivity analyses, we would expect to observe no more than one third of 47 or approximately 16 PSA failures and one third of seven or approximately two distant failures in men with low-risk prostate cancer whose PSA velocity was calculable. Therefore, the authors’ ability to assess the clinical utility of the PSA velocity higher than 2 ng/mL/year metric using the data presented with only a handful of PSA and distant failures due to small sample of assessable men. The short median follow-up of 2.1 years after radical prostatectomy is very limited and, therefore, not reliable. In fact the authors recognize this issue and make the following statement in the results section, “however the estimates are based on very few events and the CIs around the enhancements are very wide.”

One statistical issue should be raised. Individual 95% bootstrap CIs should not be used to determine whether two C-metrics are statistically different if the metrics are calculated using a single data set. When using the same data set as in this study, C-metrics are likely to be highly correlated. Thus, 95% bootstrap CIs of the difference of two C-metrics would be a better approach to determine whether two C-metrics are statistically different because the SE of the difference may be much smaller than the individual SEs of the C-metrics. Therefore, the approach used in this study sheds some doubt on the significance of the reported differences as well as the lack of reported differences.

As a result, it is clinically important when facing the individual patient in your office with newly diagnosed prostate cancer to ask yourself two questions—is this patient’s prognosis already determined by a high PSA level, biopsy Gleason score, and/or advanced clinical
stage? — in which case the need for additional factors to counsel the patient regarding outcome is not necessary. Does the patient have low-risk prostate cancer where PSA-based kinetic parameters have been shown to be able to identify a high-risk patient despite “low-risk numbers?”

In either case, whether the answer to either question is yes, the clinical implication and relevance is that monotherapy with radical prostatectomy or radiation therapy will often not be sufficient to achieve the best cancer-specific outcomes. Therefore, counseling the patient destined for radical prostatectomy about the possible need for adjuvant radiation therapy or the patient destined for external-beam radiation therapy about the addition of hormone therapy based on benefits in cancer-specific outcomes observed in men with intermediate- and high-risk prostate cancer from prospective randomized clinical trials would be prudent.

Finally, we know that despite low-risk prostate cancer at presentation, men still die of prostate cancer. Why is this? It is due in part to undergrading of the biopsy Gleason score due to the sampling error intrinsic to prostate biopsy sampling. For this example, clues that undergrading may have occurred include the situation where more than one half of all the biopsies obtained contain Gleason 6 cancer and/or the presence of perineural invasion. It also could be due to a rapid rise in PSA (> 2 ng/mL/year) during the year before diagnosis that was unappreciated because the patient’s first and only PSA level before initiating treatment was 7.7 ng/mL. Finally, for a man who presents with palpable Gleason score 6 disease (tumor category 2a) and who is hypogonadal with a PSA level of 1.2 ng/mL, this low PSA level may not accurately represent the underlying disease extent due to a reduced ability to express PSA in this setting. Certainly additional factors remain to be determined, but in that search it is our hope that investigators will shift the mathematics toward solving the problem of outcome prediction with adequate power for the individual patient where prognostic information is lacking. By looking for a solution that improves prediction of outcome beyond pretreatment PSA alone in patients treated with radical prostatectomy.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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REFERENCES