Reply to the Letter to the Editor from Fromont

**In Response:** We thank Dr. Fromont for his letter. Whereas postprostatectomy identification of prostate cancer patients at increased risk for biochemical recurrence would allow administration of adjuvant therapy (i.e., radiotherapy or systemic therapy), preprostatectomy identification would allow to choose between treatment modalities (radical prostatectomy, conventional radiotherapy, brachytherapy, etc.) and administration of neoadjuvant therapy (1–6). Thus, accurate prediction of the probability of biochemical recurrence at each of these time points has independent merit for the management of prostate cancer patients.

It is true that, to date, no preoperative biomarker has been shown to improve the predictive accuracy of the Kattan postoperative nomogram (7, 8). This is largely because the postoperative nomogram includes pathologic features, which are more powerful predictors of prostate cancer outcomes than clinical features, which form the basis of the preoperative nomogram. Therefore, we reanalyzed our data with the aim of assessing whether the strong predictive value of preoperative levels of the nine candidate biomarkers is maintained after adjusting for the effect of postoperative features (9).

For details regarding patient population, biomarker measurement, postoperative follow-up, pathologic evaluation, and statistical methodology, please refer to our original paper (9).

Briefly, we measured preoperative plasma levels of transforming growth factor-β1, interleukin-6, interleukin-6 soluble receptor, vascular endothelial growth factor, vascular cell adhesion molecule-1, Endoglin, urokinase plasminogen activator urokinase plasminogen inhibitor-1 (PAI-1), and urokinase plasminogen receptor in 423 consecutive patients treated with radical prostatectomy for clinically localized prostate cancer. The accuracy of the multivariable models was quantified using the c-index statistic and internally validated with 200 bootstrap resamples.

The multivariable base model that comprised preoperative prostate-specific antigen, surgical margin status, extracapsular extension, seminal vesicles invasion, lymph node involvement, and pathologic Gleason sum had a c-index of 79.4% for prediction of biochemical recurrence. Addition of preoperative levels of the 9 candidate biomarkers improved the accuracy of the base model for prediction of biochemical recurrence by a statistically and prognostically significant margin (86%, P < 0.001). To our knowledge, this is the first time that preoperatively measured biomarkers have been shown to improve prediction of biochemical recurrence after adjusting for the effects of established pathologic features.

Although our results are promising, several limitations such as the sample size and short follow-up may apply to our analyses. Moreover, it is necessary to assess the association of prostate cancer patients with response to therapy as well as metastasis and survival. These limitations represent hypotheses for future studies and should prompt future research in the area of biomarkers. In general, biomarkers need to be systematically and critically evaluated by multidisciplinary groups of experts before their introduction to patient care (10, 11).

Disclosure of Potential Conflicts of Interest

S.F. Shariat is co-inventor of the U.S. Patent entitled “Methods to determine prognosis after therapy for prostate cancer.”

References

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