



Editorial – referring to the article published on pp. 728–739 of this issue

## The Importance of the Quantification of the Extent of Cancer in Prostatic Biopsies in Prediction of Biochemical Recurrence: A Global Perspective

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Biochemical recurrence (BCR) after definitive therapy for localized prostate cancer represents an important surrogate end point and heralds metastatic progression and possibly cancer-specific mortality. At 20 yr after radical prostatectomy (RP), as much as 41% of patients demonstrate BCR [1]. Of those with BCR, 10 yr after BCR diagnosis, 25% progress to distant metastases and 11% die of prostate cancer (PCa). Although only a proportion of individuals with BCR will progress to clinically meaningful end points, BCR represents a worrisome finding to both patients and clinicians.

Several variables have been examined with respect to their ability to predict BCR after definitive therapy. After RP, pretreatment prostate-specific antigen (PSA), clinical stage, and biopsy Gleason patterns represent the standard predictors. The ability of these variables to predict BCR is substantially improved when they are combined within multivariable models. Kattan and colleagues were the first to apply these variables within a prognostic nomogram that quantified the individual probability of BCR after prostatectomy [2]. These three variables were 79% accurate in predicting BCR at 5 yr after RP in the original 1998 nomogram ( $n = 168$ ) and 77% accurate in predicting BCR at 10 yr after RP within an updated 2006 version of the nomogram [2,3]. In an

attempt to improve accuracy, Stephenson and colleagues added the number of positive and negative cores to PSA, clinical stage, and biopsy Gleason [3]. Consideration of information from biopsy cores resulted in a 2% accuracy gain when the nomogram was externally validated within a North American cohort ( $n = 1545$ ). Interestingly, a systematic analysis of the information contained within the number and/or percentage of positive cores was recently assessed by Briganti et al within a European cohort ( $n = 1783$ ) [4]. Their assessment indicated that the number of cores can increase the accuracy of BCR predictions by 1.1% versus 0.9% when the percentage of positive cores is used versus 1.1% when both fields are included in prognostic models [4]. Taken together, the North American and the European data confirm the value of the information that quantifies the amount of cancer within biopsy cores. Harnden et al have concluded that the percentage of cancer in biopsy cores might represent the most informative coding scheme for information contained within biopsy cores [5].

Despite its added value, a 1–2% accuracy gain from consideration of biopsy cores is insufficient to improve the accuracy of BCR predictions in a clinically meaningful fashion. Therefore, information from biopsy cores should ideally complement

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other informative predictors of BCR. Shariat and colleagues have recently reported on several highly informative biomarkers capable of predicting BCR. For example, the addition of plasminogen activator inhibitor 1 increased the accuracy of BCR predictions by up to 10.3% [6]. The inclusion of a panel of 11 biomarkers improved the accuracy of BCR predictions by 14.6% [7]. The consideration of transforming growth factor  $\beta$ -1 and interleukin 6 soluble receptor improved the accuracy of BCR predictions by as much as 16.8% [8]. The reports of Stephenson et al [3], Briganti et al [4], and Harnden et al [5] indicate that information from biopsy cores is valuable; however, the added value of biomarkers is 10-fold more valuable than the information derived from biopsy cores [6-8]. Consequently, investigators should continue exploring the information regarding the risk of BCR or other pertinent end points related to the natural history of prostate cancer that might be extracted from biomarkers as well as from clinical and histopathologic sources.

As we demonstrated in the above examples, neither biopsy core-derived information nor information extracted from biomarkers can provide 100% accurate predictions. Residual sources of error account for a misclassification rate of 15-25% when BCR or other end points are examined. Should this error rate discourage clinicians from relying on multivariable predictor and prognostic tools? The answer is a definitive no. Although predictive and prognostic tools are not perfect, their ability to foretell the outcome of interest exceeds that of expert clinicians in a substantial and statistically significant fashion. For example, clinician experts at Memorial Sloan-Kettering Cancer Center were 54% accurate in predicting lymph node metastases versus 72% for nomogram-based predictions [9]. Similarly, clinicians were, on average, 68% accurate in predicting life expectancy of PCa patients treated with either RP or radiation therapy versus 84.3% for a nomogram predicting the same outcome [10,11]. Of various predictive models, nomograms recently emerged as the preferred format when the opinions of North American urologists were polled [12].

Despite the established benefit of various multivariable models in prediction of BCR and other prostate cancer end points, skepticism may be encountered when their implementation into routine clinical practice is suggested. Lack of prospectively proven benefit in patient outcomes is commonly used as an argument against the use of predictive and prognostic models. At initial glance, clinicians who are accustomed to randomized

prospective trials that quantify the benefits and detriments of a standard of care to that of a novel molecule tend to agree with absence of data supporting the usefulness of nomograms in clinical practice. A randomized prospective evaluation of nomogram-based decision making versus standard-of-care (clinician-based) decision making is, however, neither practically nor ethically possible. First, ethical considerations would not allow the randomization of patients to management that is purely based on information technology. Second, nomograms and other predictive or prognostic tools are merely meant to assist the clinician in decision making. In that regard, they provide the clinician with a probability of a given end point, say BCR. When the nomogram states that the patient is 80% likely to experience a BCR after RP, the clinician may, for example, decide to (1) do nothing, (2) increase the frequency of follow-up, (3) initiate adjuvant radiotherapy, or (4) start androgen deprivation. Although the nomogram-derived prediction of elevated risk of BCR prompts the clinician to select one of the four treatment options, it is entirely dependent on the clinician's preference which of the choices is selected. It is, therefore, impossible to objectively test the effect of nomograms on health outcomes, since clinician choices remain the decisive factors in diagnostic and/or therapeutic decision making.

In summary, BCR represents an important clinical end point. The prediction of BCR is more accurate with the information derived from biopsy cores; however, the accuracy of BCR predictions, even when biopsy cores are considered, is not perfect. As a result, models that rely on biomarkers along with clinical and pathologic predictors of BCR should be considered when diagnostic or therapeutic choices are required. Despite the superiority of these models to predictions of expert clinicians, clinicians ultimately decide on the type and timing of diagnostic and/or therapeutic interventions. Thus, the impact of nomograms on health outcomes cannot be tested in a head-to-head fashion.

**Conflicts of interest:** The authors have nothing to disclose.

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