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In Search of the Perfect Crystal Ball for Ta Urothelial Cancer

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Urothelial cancer (UC), with its characteristic polychronotropism and wide spectrum of virulence, has long presented a therapeutic challenge for urologists. Although the majority of UCs are non-muscle invasive, up to 70% recur, and although only 2% of Ta G1–2 and 10–15% of Ta G3 cancers progress, those patients who do progress have a guarded prognosis despite radical cystectomy. For any given clinical Ta cancer, being able to determine the propensity for subsequent recurrence and progression confers a tremendous benefit in terms of customizing the intensity of surveillance and in terms of whether to institute preventative measures such as intravesical immuno- or chemotherapy, whether to use adjunctive diagnostic and staging measures, and whether to plan definitive ablative treatment. A reliable, practical, and accurate “crystal ball” for Ta UC has significant implications in terms of health care economics and patient survival.

Through the decades, there have been many efforts to define predictive factors for propensity of non-muscle-invasive disease to recur and to progress. Based on earlier retrospective observational studies, the most commonly accepted clinical (histologic and morphologic) parameters for predicting recurrence include tumor grade, multiplicity, and tumor diameter [1]. For prediction of progression, lamina propria invasion, high-grade (G3) disease, multiple or frequent recurrence, multifocality, presence of carcinoma in situ (CIS), presence of tumor at the first cystoscopy at 3 mo, and prostatic urethral involvement are reliable features. Although they can be regarded as primitive and perhaps naïve compared to the current state of technology, retrospective correlative studies on cellular and nuclear characteristics 2–3 decades ago improved our understanding of UC tumor biology and natural history and helped set the stage for more sophisticated investigations in subsequent decades.

Cell-surface antigens identified as predictors of progression included, among others, ABH(O) [2] and Thomsen-

Friedenreich antigens [3]. Tumors positive for ABH antigen had a statistically significant lower recurrence rate than those negative for the antigen. DNA ploidy of bladder tumors analyzed by flow cytometry [4] showed a fairly strong relationship between aneuploid tumors (compared to their diploid counterparts) and subsequent aggressive clinical behavior in terms of recurrences and progression to muscle-invasive and/or metastatic disease.

Fradet et al devised a panel of monoclonal antibodies to characterize UCs based on the presence of certain cell-surface glycoproteins (T138, T43) identified as being associated with high-grade and clinically aggressive behavior [5]. The group performed simultaneous multiparameter flow cytometric measurements of DNA and surface antigens to predict bladder cancer (BCa) progression. Their pioneering ideas and technology have since been applied to other tumor sites. Over the years, many other potential markers have been proposed and evaluated. Among the recent promising putative markers are cell-cycle-related proteins (eg, p53, p16, p21, p27, pRb), proliferation markers (eg, Ki 67, survivin), and oncogene products (eg, FGFR3). In particular, FGFR3 has garnered attention recently as being useful in risk stratification of high-grade non-muscle invasive UCs [6].

Another approach to predict the subsequent clinical course of UC involves efforts to improve our ability to detect early or preclinical UCs via urine cytology and adjunctive techniques with cystoscopy such as the use of hexamino-levulinate fluorescence [7] in place of standard white light cystoscopy. Strictly speaking, these techniques are pre-emptive rather than predictive because they facilitate identification and treatment of preclinical cancers and often elusive CIS in a more timely fashion, presumably with better long-term outcome.

Combined retrospective analyses of various databases have been performed for non-muscle-invasive UCs. Anal-

gous to the Partin's tables and Kattan nomograms for prostate cancer, the European Organization for Research and Treatment of Cancer (EORTC) risk calculators ("Recurrence Calculator" and "Progression Calculator") assist the clinician in the prediction of likelihood of recurrence and progression when presented with a patient diagnosed with Ta or T1 BCa [8]. Sylvester et al [8], in their seminal paper, analyzed close to 2600 patients from seven EORTC clinical trials on these patient populations and categorized risk groups as low, intermediate, or high. Other collaborative efforts from national and international consortiums and intergroup studies have provided additional data for validation of such clinical tools. One caveat for users of such prediction nomograms is that their sensitivities and specificities are imperfect in that patients are assigned risk categories based on a number of clinical characteristics. Individual patient management requires and deserves individual independent considerations.

Ehdaie and Theodorescu recently published an excellent overview of the current state of prognostic markers for BCa, rendering the clinician better equipped to partake in the all-important translational studies [9]. One such study is the article by Birkhahn et al [10], who employed real-time reverse transcriptase-polymerase chain reaction to retrospectively determine the genetic expression profile of a series of patients with initial presentation of Ta T2/3 UCs. The patients were retrospectively selected based on their subsequent clinical course: no recurrence, recurrence without progression, and progression to CIS or invasive disease. The genetic profiles of tumors with the different outcomes were analyzed, yielding potentially predictive information on tumor recurrence and progression. Based on theoretical considerations involving pathways essential for carcinogenesis and tumor invasion, selection of the genes for the study from the Kyoto Encyclopedia of Genes and Genomes was logical and intuitive. The major pathways and their respective defects thereof include apoptosis, cell-cycle regulation, signal transduction (including the mitogen-activated protein kinase [MAPK] pathway), angiogenesis, and cellular adhesion and invasion.

Results from this study indicated cyclin D3 (CCND3), a cell-cycle-regulation gene and the Harvey rat sarcoma viral oncogene homolog (HRAS) of the MAPK signaling pathway may predict recurrence [10]. For prediction of progression, genes involving vascular endothelial growth factor A signaling and tumor angiogenesis (VEGF and VEGFR2), apoptosis (BIRC5/survivin), and cell-cycle regulation (E2F1) as well as HRAS are implicated. Although these results are preliminary and involve only a small cohort of subjects, the study design was insightful and the investigators have addressed the majority of confounding issues. One concern was the possible presence of concomitant CIS and the role CIS may play in tumor progression in this cohort, thereby affecting the outcome of the genetic profile, although the gene panel used in this study did not significantly overlap with those implicated in CIS. Nevertheless, the multivariable modeling results from this study can be rationalized with the current understanding of urothelial carcinogenesis and

behavior and are certainly compelling and merit validation with a larger cohort in a prospective manner.

As with all such studies involving data from retrospective correlation of histopathology and clinical outcome, the one-time "snapshot" does not reflect or capture the effects of time and promoting factors on tumor recurrence and progression. Prospective studies employing a panel of prognostic genes would be very useful, especially if the study cohort can serially provide samples from subsequent recurrent tumors for profiling. The practicality of routine genetic expression profiling for any given tumor has been questioned by some; however, technological advances have enabled researchers to perform previously laborious and seemingly impossible tasks. The ideal biomarker for Ta BCa, or a panel of markers, should be easily accessible, reproducible, and cost effective, with high sensitivity and specificity. With further technological refinement and improved understanding of the molecular mechanisms and pathways of UC carcinogenesis and progression, the perfect crystal ball for Ta BCa may eventually become a reality.

Conflicts of interest: The author has nothing to disclose.

References

- [1] Oosterlinck W, Lobel B, Jakse G, et al. Guidelines on bladder cancer. *Eur Urol* 2002;41:105–12.
- [2] Das G, Buxton NJ, Stewart PA, et al. Prognostic significance of ABH antigenicity of mucosal biopsies in superficial bladder cancer. *J Urol* 1986;136:1194–6.
- [3] Langkilde NC. T-antigens in primary non-invasive and superficially invasive human urinary bladder tumors: the correlation to tumor recurrence and tumor progression. A mini-review. *Scand J Urol Nephrol Suppl* 1995;172:45–9.
- [4] Chin JL, Huben RP, Nava E, et al. Flow cytometric analysis of DNA content in human bladder tumours and irrigation fluids. *Cancer* 1985;56:1677–81.
- [5] Fradet Y, Tardif M, Bourget L, et al. Clinical cancer progression in urinary bladder tumors evaluated by multiparameter flow cytometry with monoclonal antibodies. *Cancer Res* 1990;50:432–7.
- [6] Burger M, van der Aa MNM, van Oers JMM, et al. Prediction of progression of non-muscle invasive bladder cancer by WHO 1973 and 2004 grading and by *FGFR3* mutation status: a prospective study. *Eur Urol* 2008;54:835–44.
- [7] Mynderse L, Stenzl A, Denzinger S, et al. Hexaminolevulinat fluorescence cystoscopy improves detection and resection of papillary bladder cancer lesions and reduces early recurrences. *J Urol* 2009;181(Suppl):689.
- [8] Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49:466–77.
- [9] Ehdaie B, Theodorescu D. Predicting tumor outcomes in urothelial bladder carcinoma: turning pathways into clinical biomarkers or prognosis. *Expert Rev Anticancer Ther* 2008;8:1103–10.
- [10] Birkhahn M, Mitra AP, Williams AJ, et al. Predicting recurrence and progression of noninvasive papillary bladder cancer at initial presentation based on quantitative gene expression profiles. *Eur Urol* 2010;57:12–20.

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