

Platinum Priority

Reply from Authors re: Joseph L. Chin. In Search of the Perfect Crystal Ball for Ta Urothelial Cancer. *Eur Urol* 2010;57:21–2

Anirban P. Mitra^a, Marc Birkhahn^{a,b}, Richard J. Cote^{c,*}

^a Department of Pathology, University of Southern California, Keck School of Medicine, Los Angeles, California, USA

^b Department of Urology, University of Southern California, Keck School of Medicine, Los Angeles, California, USA

^c Department of Pathology, University of Miami, Miller School of Medicine, Miami, Florida, USA

The unrelenting quest for determinants that can predict the behavior of urothelial carcinoma (UC) has resulted in the identification of many different candidate markers over the years. Classic studies have identified morphologic, genetic, and immunologic characteristics of UC that are associated with patient outcome. More recent investigations of molecular genotypes and phenotypes have identified specific alterations in individual tumors that have shown great promise in predicting outcome and therapeutic response in UC, particularly p53, Rb, and p21 [1]. These endeavors are well summarized in the editorial by Chin [2]. Much of this work, however, has been performed in patients with invasive UC. Although there is a body of work classifying noninvasive papillary (Ta) UC into risk groups, most studies depend on histologic (tumor grade) and clinical/morphologic criteria (size, multifocality, and frequency of recurrence). More patient-specific approaches for predicting risk of recurrence and progression in Ta UC, based on molecular characteristics of tumors, have lagged far behind. As Chin points out, the ability to determine which Ta tumors will recur and progress will have a profound impact on the management of the most common form of UC.

The use of molecular markers in UC management is imminent. Although prior approaches have focused on evaluating single determinants or a few markers in combination (primarily due to technological limitations at the time), we envision significant modifications to existing approaches for the study of putative markers. Molecular alterations in tumors do not occur as isolated events but rather as part of a cascade of aberrations [3,4]. It is therefore important to consider the major pathways associated with carcinogenesis. Recent approaches have taken advantage of array-based expression technologies to examine profiles of thousands of genes and gene products [5]. While such studies have provided useful means for discovery of new markers, we have taken a hypothesis-driven approach to profile crucial alterations associated with each cancer pathway, with a particular focus on those

alterations known to be associated with UC. This pathway-driven approach to quantitatively assay molecular alterations in invasive UC tumors was done with the idea of identifying concise, robust signatures associated with outcome, and it has proven to be a powerful method [6,7]. We have now extended this approach to Ta UC in our current study [8].

Our study in *European Urology* quantified the expression levels of 24 genes that feature in relevant cellular processes in bladder and other cancer types that are associated with Kyoto Encyclopedia of Genes and Genomes pathways [8]. The choice of genes was based on previously published results and theoretical considerations regarding the candidate genes that might be most productively studied in Ta UC. The study identified *CCND3* and *HRAS* as genes that can predict recurrence and *HRAS*, *E2F1*, *BIRC5/Survivin*, *VEGFR2*, and *VEGF* as markers for progression in Ta UC at initial presentation.

The most unique aspect of this investigation was the study cohort [8]. This cohort consisted of primary tumor samples obtained at initial presentation from patients with Ta UC and without evidence of carcinoma in situ (CIS) who then proceeded to remain recurrence-free, to recur, or to progress to CIS or invasive disease. The strict inclusion criteria limited the study cohort to patients in whom (1) a minimum 5-year follow-up was available for those who did not recur or recurred but did not progress, (2) concomitant CIS was absent, and (3) no systemic or intravesical immunotherapy or chemotherapy was administered at first presentation. For patients who recurred and progressed, the median times to first clinically significant event (ie, recurrence or progression, whichever occurred earlier) were 11.3 mo and 7.4 mo, respectively. These indicate that the new tumors were indeed new events and not residual tumors from previous incomplete resection.

The tumors were graded according to the 1973 World Health Organization (WHO) grading system because many patients were diagnosed as early as 1993; thus, this group represents a historical cohort [9]. Nevertheless, it is important to note that the grading systems for Ta G2/3 tumors do not differ between the 1973 and 1999 WHO systems [10]. Moreover, the European Organization for Research and Treatment of Cancer (EORTC) risk calculators for Ta T1 bladder cancer also currently rely on the 1973 WHO grading system [11].

An important issue raised in Chin's editorial is the possible presence of concomitant CIS in the study cohort and its effects on patient outcome [2]. The possibility of concomitant CIS cannot be entirely ruled out in our cohort because biopsies were obtained under white-light cystoscopy; however, the random quadrant biopsies in all cases did not reveal any concomitant tumor of higher grade or stage [8]. Importantly, none of the significant genes identified by our study was part of any CIS-gene expression classifier [12]. This finding indicates that the identified markers are truly prognostic for recurrence and survival in

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* Corresponding author. Department of Pathology, University of Miami Miller School of Medicine, 1611 NW 12th Avenue, Miami, FL 33136, USA. Tel. +1 305 585 6103; Fax: +1 305 243 5929. E-mail address: rcote@med.miami.edu (R.J. Cote).

noninvasive papillary UC at first presentation rather than indicative of possible concomitant CIS. Indeed, the prognostic potential of these genes was far superior to current clinical criteria, including the EORTC risk calculators for Ta T1 bladder cancer [11].

The United States National Cancer Institute–Translational Research Working Group’s biospecimen-based assessment modality pathway recommends validation of promising prognostic marker panels on retrospective and prospective cohorts before being handed off for definitive clinical testing [13]. The markers identified in our study [8] have the potential to be part of a biomarker panel for prognostic prediction in Ta UC. We have already instituted broad studies to further interrogate and validate these findings. Given the pace of technology development and the fact that we have shown that only a few determinants can provide relevant information, it is likely that prognostic markers including those identified in our study will be available at reasonable costs in prefabricated multiwell or expression-chip formats for clinical reference use in the future. The high prevalence of Ta UC and the high costs associated with its management provide urgent impetus to develop panels that can predict clinical outcome at first presentation.

Conflicts of interest: The authors have nothing to disclose.

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