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**Editorial Comment on: HYAL-1 Hyaluronidase:
A Potential Prognostic Indicator for Progression to
Muscle Invasion and Recurrence in Bladder Cancer**

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The risk assessment for recurrence and progression in non-muscle-invasive bladder cancer (NMIBC) patients represents one of the most challenging issues in urologic oncology. In these patients, the prognostic models are mainly based on clinical predictors (stage, grade, multifocality, associated carcinoma in situ, and failure after bacillus Calmette-Guérin [BCG] treatment), since none of the many molecular markers evaluated as potential prognostic factors has found its way into routine clinical practice.

In this original contribution, Kramer and coworkers [1] evaluated the potential role of HYAL-1 hyaluronidase as a prognostic indicator for both local recurrence and progression of NMIBC after transurethral resection (TUR).

The authors, who are very well-recognized authorities in the investigation of hyaluronic acid and HYAL-1, should be congratulated for the clarity of the text, the excellent

statistical analysis, and the cautious interpretation of their results.

HYAL-1-type hyaluronidase expression was already found to be an independent prognostic indicator of prostate cancer progression [2] and was significantly associated with subsequent cancer development in patients with benign breast lesions [3].

The enzymatically active HYAL-1 production by bladder cancer cells represents a well-documented molecular determinant of tumor growth, infiltration, and angiogenesis. For bladder cancer detection, HYAL-1 expression from urine specimens was already proved to be an accurate marker, providing a higher positive predictive value when compared with urinary cytology [4,5].

In this study, bladder cancer specimens were taken by TUR from NMIBC patients, and the expression of HYAL-1 in the specimens was graded for intensity and area of staining. HYAL-1 emerged as a significantly correlated predictor with the tendency to recur, from a statistical perspective. Additionally, based on a multivariate analysis including many clinical parameters, HYAL-1 appeared to be an independent prognostic indicator for progression.

A key issue is whether HYAL-1 expression evaluation actually provides any additional advantage over the well-known and more familiar clinical prognostic factors. Based on the model adopted for this study, the answer should be

yes. HYAL-1 was the only independent prognostic indicator of progression, thus providing value above tumor grade and stage.

Another key issue concerns the reproducibility of the methods used for the evaluation of HYAL-1 expression. Since the authors showed a significant correlation between the staining scores assigned by different readers and the IP image analysis software, we can argue that adequate image software could be used adequately in future clinical practice, thus overcoming the subjective interobserver variability.

A third issue concerns the cost-effectiveness analysis, but this factor was not addressed. The present study was only retrospective, it involved only two centers, and patients included those who were treated with adjuvant therapy as well as those who were not.

To confirm whether the biomarker in question may actually play a pivotal role in routine decision making, as admitted by the authors, prospective multicenter studies should be designed. Toward this end, clinical investigations could be focused on high-risk NMIBC patients after BCG failure. These patients require an accurate tool to correctly discriminate the candidates either for early

cystectomy or for salvage second-line conservative treatment.

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