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Molecular Subtypes of Bladder Cancer: Academic Exercise or Clinical Relevance?

Lars Dyrskjøt [a,b,*]

[a] *Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark;* [b] *Department of Clinical Medicine, Aarhus University, Aarhus, Denmark*

Classification of bladder cancer into gene expression–based molecular subtypes has recently generated huge insights into tumor biology and progressed our understanding of this common disease. Work by the Lund group in this area has been pivotal, with a landmark publication in 2012 describing five molecular subtypes across the entire spectrum of bladder cancer [1]. Following this publication, a burst of publications with a focus on muscle-invasive bladder cancer (MIBC) described additional subtype classification schemes (reviewed in [2]). Importantly, the major subtypes (luminal-like and basal-like) were identified and validated across different patient cohorts. Subtypes in non-MIBC (NMIBC) has received less attention; however, in 2016 the UROMOL consortium reported the identification of three major subtypes in NMIBC with differences in outcome and biological features [3]. Currently, the most comprehensive analyses of MIBC have been described by The Cancer Genome Atlas project (TCGA) [4] and by the Lund group [5]. Both studies reported five subtypes in MIBC with significant overlap in subtype designation. Overall, a taxonomy consensus in MIBC seems to arise, and researchers behind the major publications in the field are working towards a consensus taxonomy.

However, data from the different studies have not previously been used for detailed combined reanalysis across analysis platforms. In this issue of *European Urology*, Tan et al. [6] report on an important study to delineate gene expression subtypes in bladder cancer by performing a meta-analysis of previously published data from 2411 bladder tumors encompassing both NMIBC and MIBC. The authors identified six subtypes showing significant differences in overall survival and with distinct biological features. To minimize bias arising from comparison of data from different tissue types and microarray analysis platforms, the authors applied robust normalization of data and included only data from relatively new microarray platforms. In spite of potential noise, limitations in genes detected across all platforms, and bias that may arise from normalization, the authors were able to identify subtypes with high similarity to previously published subtypes. High similarity to known subtypes is expected because the authors performed a reanalysis of published data. However, the statistical power in a meta-analysis of >2400 tumor samples may help to reduce bias and eliminate artifacts originating from analysis of smaller data sets. The analysis highlights the robustness of the known biological subtypes without having to extrapolate subtype interpretation between different patient cohorts as has been done previously. Importantly, the subtypes reported by Tan et al were reproduced in independent RNA sequencing expression data from the UROMOL study of NMIBC [3] and from the TCGA [4] and IMvigor210 [7] studies of MIBC.

It has previously been demonstrated that subtypes are associated with overall survival [1,4] and progression risk in NMIBC [3]. However, besides selecting NMIBC patients with high-risk molecular features for increased surveillance and bacillus Calmette-Guérin therapy, for example, the most important task may ultimately be to design therapeutic treatment regimens for individual patients based on the molecular features of the primary tumor. Although previous publications have demonstrated that subtypes are associated with response to chemotherapy [8] and immunotherapy [7,9], the results have shown inconsistencies between study cohorts and have lacked independent validation, and overall the treatment response correlations have not been robust and convincing for clinical use. In addition, most

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* Department of Molecular Medicine, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark. Tel. +45 78455320.
E-mail address: lars@clin.au.dk.

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published data do not originate from clinically well-annotated cohorts with high-quality therapy response data. As Tan et al performed a meta-analysis of already published data, this study unfortunately does not add new knowledge regarding subtypes and treatment response.

Tumor heterogeneity poses an additional challenge as it remains unclear how this affects subtype classifications and ultimately treatment decisions. Most subtyping studies in bladder cancer have focused on bulk tumor analysis, which gives a "consensus" subtype for each patient. However, the classifications of bulk tumors are often not robust, and there is a high likelihood that tumors could in fact belong to multiple subtypes, probably caused by tumor heterogeneity [3,8]. Previous studies have documented intratumor subtype heterogeneity whereby basal- and luminal-like subtypes were identified simultaneously in multifocal bladder cancer [10]. If basal- and luminal-like tumors respond differently to, for example, neoadjuvant chemotherapy [8], multiregional analysis of tumors may be necessary to identify all relevant treatment-informative subtypes for each patient. In addition, subtype classification may have to include metastatic tissue to compensate for subtype changes during clonal selection and tumor evolution, and to determine the actual subtype of the therapy target. The impact of tumor heterogeneity on subtype classification needs to be explored further in future studies.

In conclusion, the meta-analysis reported by Tan et al highlights important biological features of subtypes in all stages of bladder cancer and demonstrates convergence of consensus subtypes in both NMIBC and MIBC. However, we are still a long way from utilizing these subtype classifications in clinical practice. Future studies of clinically well-annotated patient cohorts may refine the subtypes further. Ideally, to make the subtypes clinically useful—and not just biologically meaningful—we probably need to analyze additional layers of molecular information to unravel the biological complexity of therapeutic response mechanisms. Optimized predictive subtypes may need to include combinations of genomics, transcriptomics, proteomics, and, for example, tissue composition of immune cell infiltrations to capture biological features associated with treatment response. Finally, clinical trial validation is needed before clinical implementation, ideally in combination with analysis of circulating tumor DNA during treatment for continuous monitoring of therapeutic efficacy.

Conflicts of interest: The author has nothing to disclose.

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