

# The landscape of genetics and biomarkers in bladder cancer

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Urothelial carcinoma of the bladder (UCB) is the second most common urological malignancy and ranking among the top ten malignancies in men and women, respectively (1). At initial presentation, the majority of patients have non muscle-invasive bladder cancer (NMIBC), but some patients have muscle-invasive UCB (MIBC) (2). The natural UCB history of both, NMIBC and MIBC, is highly variable and considerably depending based on treatment strategies. While some patients never experience disease recurrence, others experience disease progression and eventually decease of their disease (3). Despite significant improvements in the clinical management, technical accouterment, surgical techniques, perioperative management as well as introduction of modern drugs over the past decades, in general UCB outcomes have only marginally improved. Although NMIBC and MIBC derive from the identical epithelial lining, both UCB types show distinct differences in their biologically behavior.

## The clinical complexity of NMIBC

NMIBC has a high risk for disease recurrence and a considerable risk of disease progression to MIBC, while overall survival usually is only marginally restrained, if appropriate treatment is timely applied. Up to now, predicting the individual short- and long-term risk of disease recurrence and progression is mainly based on scoring systems and risk tables by either the EORTC Genito-Urinary Cancer Group or the CUETO group, respectively (4). These scoring systems particularly rely on clinical and standard histopathological parameters. According to available clinicopathological prognosticators combined with information from the risk tables, NMIBC patients are stratified in three risk groups to facilitate

treatment recommendations and follow-up monitoring (4). Indeed, different groups have investigated the reliability of the risk tables based on individual patient data with long-term outcomes and found that unfortunately the two most common prediction models exhibit a poor discrimination for both disease recurrence and progression, respectively, in NMIBC patients (5). Therefore, individualized patient-based counseling and treatment approaches are gaining enormous interest in these days, and general risk models may be past its best. Multivariable prediction models (e.g., nomograms) (6) that adjust for additional, individual information that may influence the course of disease including environmental and occupational influences (7), individual behavior such as smoking (8,9), comorbidities and their complaining drug therapies (e.g., diabetes hypercholesterinemia) (10,11), etc. may allow a more individually-tailored risk assessment and treatment decision-making, respectively. Despite these important factors may influence the biology of UCB, they do not account for the underlying genetics of each individual tumor. Genome-wide association studies, however, demonstrated the importance of genetics and several susceptibility loci associated with the UCB risk seem to be an important driver for disease outcomes (12).

## The dilemma in treatment of MIBC

MIBC usually is a highly aggressive disease. About a quarter of patients have muscle-invasive or advanced bladder cancer at initial presentation and approximately another 25% of patients with NMIBC will progress to MIBC during their course of disease (4). Radical cystectomy (RC) and urinary diversion, a complex surgical procedure with a non-negligible risk of perioperative

morbidity and complications as well as a significant influence on the patients' quality of life, still remains the gold standard procedure for MIBC treatment. In MIBC, a large number of prognostication models holding the promise of facilitating treatment decisions and outcome prediction, respectively. However, many models are missing confirmation and only a few studies have investigated the clinical utility of any given model as measured by its ability to improve clinical decision making and true outcome prognostication (6). In order to improve survival, neoadjuvant or adjuvant chemotherapy perioperatively is administered in many MIBC patients (13). There is level 1 evidence that neoadjuvant Cisplatin-based chemotherapy significantly increases the rate of pT0 disease at RC and leads a net-survival benefit of 5–8% at five years (14). In contrast, adjuvant chemotherapy in general is only administered to patients with advanced ( $\geq$  pT3) or lymph-node positive UCB after final histopathological staging. There is ongoing controversy regarding the risks and benefits of both, neoadjuvant and adjuvant chemotherapy, respectively, and whether one treatment approach may be superior over the other. Fact is, that only 12% patients with MIBC treated with RC receive neoadjuvant and only 22% of patients with advanced or lymph-node positive UCB receive adjuvant chemotherapy, respectively (14). Although the reasons for these rather low numbers are multifactorial, the mixed response of UCB to systemic chemotherapy is an important issue. In general, UCB is considered a chemotherapy sensitive disease and several different single drugs have demonstrated effectiveness (15). Combination chemotherapy regimens, however, are more effective, but still only about 50% respond to Cisplatin-based chemotherapy and another quarter of patients have stable disease (16). Again, the underlying biology and genetics are of tremendous importance for treatment efficacy in MIBC. A very recent study demonstrated the complicated, variable molecular pattern of UCB and its response to neoadjuvant chemotherapy (17). Thus, insight in the genetic and molecular structure of MIBC prior to therapy may improve prediction of response to chemotherapy and subsequently improve outcome prognostication.

### **New horizons in metastatic UCB?**

Once UCB has spread to the lymph nodes, or distant sites, or has recurred after surgery on curative intent, outcomes are poor (18). Unfortunately, over the past decade outcomes in recurrent or metastatic UCB almost remained unchanged

and the median survival is about 14 months in patients, who are fit for Cisplatin-based systemic chemotherapy (19). Systemic chemotherapy is the standard of care in the metastatic situation with reasonable response rates in the first-line situation, and unsatisfactory results in the subsequent lines (16). However, in 2014 Powles *et al.* reported the results of a phase 1 basket study demonstrating the clinical activity of the anti-PDL1 immune checkpoint antibody Atezolizumab in metastatic UC (20). The revival of various immunotherapeutic strategies particularly recognizing the importance of T-cell inhibitory pathways has revolutionized the treatment of various solid cancers including UCB in the past few years (21). Nevertheless, the more data are accumulating, the more it becomes evident that although efficacy and safety of immunotherapy are superior compared to standard chemotherapy, still only about 20% of UCB patients respond (22). The initial excitement for immunotherapy biomarkers unfortunately has proven unfounded, as it has become clear that tumor cell expression of any immunotherapy biomarker, or the lack thereof, does not possess adequate positive or negative predictive value to dictate treatment decisions (23). The heterogeneity between the primary tumor, lymph node metastasis, and distant site metastasis as well as tumor cells in the peripheral circulation are likely being an important reason for this dilemma. The inter- and intraindividual tumor genetic variability, as demonstrated in several studies (24,25), needs to be addressed to improve treatment success and outcomes. In addition, salvage radiotherapy and resection of metastases have been assumed having potential in prolonging the survival of patients with metastatic UCB (26). However, several limitations aggravate drawing strong conclusions from the present data. Therefore it is still unclear, which patient benefits most from standard chemotherapy or which patient more individually may benefit from a multimodal treatment approach including surgery, radiotherapy and chemo-/or immunotherapy.

### **The biologically and genetically heterogeneity of UCB**

Finally, it is of utmost importance to realize that UCB is not only clinically, but particularly biologically and genetically a highly heterogeneous disease (3). In 2013, Lawrence *et al.* reported in their landmark paper the mutational heterogeneity in various cancers and found a high somatic mutation frequency in muscle-invasive bladder cancer (27). The somatic mutation frequency was

almost highest among all analyzed adult solid tumors, similar to melanoma and lung adeno- and squamous cell carcinoma. A year later The Cancer Genome Atlas (TCGA) Research Network demonstrated an integrated analysis of 131 urothelial carcinomas providing a comprehensive landscape of molecular alterations (28). The investigators found important frequently recurrent mutations in 32 genes, including multiple genes involved in cell-cycle regulation, chromatin regulation, and kinase signaling pathways, but also nine genes, which previously were not reported as significantly mutated in any cancer, yet. These seminal investigations provided tremendous novel insights into UCB cancer biology. Of foremost significance, phenotypically similar tumors may harbor completely different molecular genotypes representing the individuality of each tumor and its host (3). Differences in the molecular landscape of individual tumors probably explain in some extent the potential lack and variability of efficacy in systemic and targeted therapies. Also, the variable biological behavior with regards to aggressiveness, as well as risk of disease recurrence and progression, respectively, in phenotypically comparable tumors is probably mainly due to this molecular diversity. In consequence, individualized analyses of each tumor and its metastasis may delineate multiple potential opportunities for therapeutic intervention. In UCB three major sources (i.e., tissue, blood and urine) are available for analysis of genomic variability. A plenty of studies have demonstrated that a high heterogeneity may be present between the primary tumor and its metastasis even in an individual patient (24,25,29) representing another challenging issue in cancer therapy. Thus, to draw a thorough genetic landscape of each individual's UCB, complete analysis of the primary tumor and every single distant focus may be needed—which is not only an extraordinarily difficult goal, but also hardly realizable in daily clinical practice. Nevertheless, biomolecular predictors hold the potential to unmask individual genomic, epigenetic, transcriptomic, and proteomic alterations that may explain the variable clinical course of disease (3,30).

With regards to the many previously mentioned controversies, open questions, limited evidence and often contradictory research findings, I am very happy that in this issue of *Translational Andrology and Urology* we are focusing on genetics and biomarkers for optimizing clinical decision-making and improving outcomes in Bladder Cancer I am proud and honored that together with several leading authorities and foremost experts in the field of urothelial carcinoma and tumor biology we are discussing

exciting contemporary concepts and controversies, but also generate hypothesis and questions for future research studies. I am delighted that brilliant leaders from all over Europe dedicated to UCB research have summarized the latest evidence and also present exciting new data that may influence our clinical practice as well as may improve our patients lives.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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