Preface

# Genetics and biomarker in bladder cancer for optimized clinical decision-making and improved outcomes

Urothelial carcinoma is the second most common urological malignancy after prostate cancer and with approximately estimated 79,000 newly diagnosed cases and 16,800 deaths in the United States in 2017 a significant burden of morbidity and mortality (1). With over 90% of all cases, the vast majority of urothelial carcinomas are located in the urinary bladder. Frequently updated national and international clinical guidelines summarize the best evidence for diagnostic and therapeutic pathways to optimally treat our patients with urothelial carcinoma of the bladder (UCB). At a first glace, it feels we are progressing since survival rates significantly improved over the past decades—over half of all UCB patients surviving their disease for more than ten years compared to only a third in the 1970s (2). However, despite many advances in the diagnostic and therapeutic management, imaging modalities as well as local and systemic chemotherapy, still about half of all UCB cancer patients with muscle invasive disease will develop metastasis and subsequently die from their disease (3,4). Treatment strategies and outcomes are fundamentally different according to the disease stage of UCB. At initial presentation, the majority of patients have non-muscle invasive bladder cancer (NMIBC) (5) and bladder preserving local treatment represents the standard of care. Approximately a quarter of patients, however, have muscle-invasive bladder cancer (MIBC) or advanced UBC at initial presentation and another 25% of patients with NMIBC will progress to MIBC during their course of disease (6). Radical cystectomy and urinary diversion with or without perioperative systemic chemotherapy is the gold standard treatment for patients with MIBC (7). Due to the very complex underlying genetics with a tremendous heterogeneity and variability between different individual UCBs, the natural UCB history of NMIBC, MIBC and metastatic UCB, respectively, is highly variable. In different solid cancer entities, such as breast or lung cancer, systemic and targeted therapies address the genetically heterogeneity by pretreatment biomarker testing. Beyond that, decision-making on multimodal therapy, treatment sequence as well as serial therapy monitoring has also been established based on biomarker analyses in such cancers (8). Despite the fact that the genetic heterogeneity of UCB ranks highest among all cancers (9,10), in contrast biomarker-guided decision-making has not progressed from bench- to bedside in UCB. Albeit several promising findings are available, there is a lot of room for improvement and a great deal of work needs to be done.

This special issue of *Translational Andrology and Urology* (*TAU*), therefore, is focused on "genetics and biomarker in bladder cancer for optimized clinical decision-making and improved outcomes". As editor, I strove to present a current, state-of-the-art and global perspective of the genetically heterogeneity in UCB as well as different approaches, possibilities and implications of biomarkers in UCB for current and future clinical decision-making, management and research. Established national and international experts as well as rising stars were invited to contribute to this comprising and timely subject of major importance for our daily practice and future clinical trial design. Due to the overwhelming response, it is my pleasure, to present a fantastic collection of outstanding articles covering the entire field in genetics and biomarkers from NMIBC to metastatic UCB including original articles, insightful updates, comprehensive reviews, opinions and perspectives.

NMIBC is a disease characterized by a significant risk of disease recurrence and a considerable risk of disease progression to MIBC (6). Particularly, patients with high-risk tumor features represent a non-negligible NMIBC subgroup that has a substantial burden for both endpoints during the course of disease. Scoring systems based on standard clinico-pathologic variables remain imperfect for optimal outcome prediction (11), and thus often fail identifying candidates who may be cured by early more invasive treatment approaches. Biomarker, which may reflect the genetically heterogeneity and stability of an individual tumor, therefore may represent an optimal adjunct in clinical decision-making and patient guidance. In their original report, Dr. Vetterlein and colleagues from University Medical Center Hamburg-Eppendorf investigated the value of routine biomarkers in bladder tumors invading the submucosal tissue (pT1 NMIBC).

In UCB, urine, blood and tissue may be used as source for biomarker analyses. Intuitively, it feels reasonable to use urine for biomarker analyses, this medium is in direct contact to the tumor and thus tumor cells may be released to this source early at time of initial presence or local recurrence (12). In an elegant review, Dr. Xylinas, the leader of the Urothelial Carcinoma Group of the Young Academic Urologists (YAU) of the European Association of Urology (EAU), and some colleagues form the YAU-group report about the contemporary role and impact of urine-based biomarkers.

DNA sequencing is an indispensable method in fundamental research of normal and cancer biology. Next-generation sequencing has revolutionized biological science by reducing cost, improving turnaround time and reducing sample input requirements compared to regular qPCR and the Sanger method. Dr. Noon, a dedicated expert in bladder cancer, summarized the most contemporary evidence on next-generation sequencing in NMIBC.

Due to the aggressive nature of Muscle-invasive and advanced urothelial cancer, multimodal therapy including radical cystectomy with neoadjuvant or adjuvant systemic chemotherapy represents a standard of care in urothelial carcinoma treatment. Several important findings on systemic perioperative therapies were published in the past years. Dr. Seisen, a brilliant researcher, presents an overview of the best evidence and the state-of-the-art in perioperative chemotherapy in 2017.

One of the key challenges in improving outcomes for UCB is the heterogeneity of the disease. In the last few years a couple of landmark studies were published investigating the complicated, variable molecular pattern of UCB (9,10). Especially MIBC presents large genetic and molecular variability. Dr. Seiler, a young world-wide recognized expert in molecular UCB biology, summarizes the current knowledge and implications of genetically complexity of MIBC that need to be addressed in drug development.

Despite there is evidence that neoadjuvant and adjuvant Cisplatin-based chemotherapy may improve survival in UCB, only a limited number of patients receive these treatments. The reasons for this are obviously multifarious, but the mixed response and underlying biology are an essential clinical issue. Dr. Roghmann, an accomplished clinician-researcher, is answering the question if we have biomarkers to predict response to neoadjuvant or adjuvant chemotherapy.

In addition to this, Prof. Dr. Shariat, a world-leading authority in clinical and translational bladder cancer research, is comprehensively presenting the latest evidence on genetic determinants for chemo- and radiotherapy resistance in bladder cancer.

While urine may frequently contain epitopes and genetic material from UCB, genomic characteristics may vary between the primary tumor site and distant sites (13). Blood represents another source for liquid biopsies. Tumor cells in the peripheral circulation may not only represent an indicator for metastatic spread, but also may be used for genetic analyses investigating differences between the primary tumor site and metastases, which may be a reason for treatment failure. Dr. Riethdorf, a foremost expert in the field of circulating tumor cells, presents the state-of-art of circulating tumor cells and circulating cell-free tumor DNA in bladder cancer.

In these days, one of the most exciting findings was the response of UCB to immuno-oncologic therapies. In recent years, a large number of industry-sponsored trials were published and the introduction of PD-1/PD-L1 checkpoint inhibition changed our current treatment strategies in UCB. Dr Necchi and Dr. von Rundstedt, two brilliant medical and surgical scientists, summarize and discuss the evidence on UCB biomarker in the era of immuno-oncology.

Last but not least, the role of consolidative extirpative surgery in metastatic UCB is still unproven. In patients with clinically evident lymph node metastasis, data suggest a survival advantage for patients undergoing postchemotherapy radical cystectomy with lymphadenectomy (14). The benefit of metastasis surgery in distant metastatic UCB is unclear. Dr. Decaestecker, a great surgeon scientist, presents a perspective on this controversial topic.

Finally, Dr. Gild and Dr. Meyer, two rising stars, present a comprehensive workup of online tools for patient counseling. According to the increasing number of prognostic tools in cancer care, and the broad presence and use of the Internet in daily clinical practice, their review presents an elegant overview about the availability and accessibility of online tools.

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Michael Rink

 

**Michael Rink, MD, FEBU**

*Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

*(Email: m.rink@uke.de)*

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