

Contemporary concepts and controversies in the diagnosis and management of urothelial carcinoma

Urothelial carcinoma (UC) is the fourth most common cancer in men in the Western world and the second most frequent malignancy of the urinary tract after prostate cancer. It can be located in the lower (bladder and urethra) or upper (pyelo-caliceal cavities and ureter) urinary tract. Bladder UC accounts for 90–95% of UCs, still claiming more than 52,000 lives each year in Europe (1). In the United States, there will be an estimated 76,960 new bladder UC cases and 16,390 related deaths in 2016 (2). While survival rates have improved over the past thirty years, with 50% of people surviving their disease for more than 10 years compared to only a third in the 1970s—there is still a great deal of work to be done. For example, in addition to the 5% of patients who present with metastatic disease, roughly 50% of patients with muscle invasive disease will ultimately develop distant metastases, demonstrating the lethality of the disease (3). Yet despite a prevalence and morbidity/mortality, UC has been overlooked by both decision-makers, the pharmaceutical industry, and the society in general. This lack of investment has resulted in few new treatment options being available to patients, delays in diagnosis because of the lack of awareness resulting in the current low survival rates. Current funding levels for research do, indeed, not reflect the burden, nor the complexity of the disease.

Upper tract urothelial carcinoma (UTUC) is relatively uncommon compared to bladder UC. Indeed, UTUC accounts for only 5–10% of UCs, with an estimated annual incidence in Western countries of ~2 cases per 100,000 inhabitants (4). In 17% of cases, concurrent bladder UC is present. Recurrence in the bladder occurs in 22–47% of UTUC patients. However, compared to the 15–25% of bladder UCs, 60% of UTUCs have an invasive stage at diagnosis (5). UTUC has a few specific hereditary/familial components [i.e., hereditary non-polyposis colorectal carcinoma (HNPCC) aka Lynch syndrome] as well as exposure risk factors (i.e., aristolochic acid) (6,7). In an elegant review, Dr. Roupret, a world-wide recognized pioneer in the field of UTUC, underlines the current knowledge regarding familial/hereditary UTUC and the effect of aristolochic acid on UTUC tumorigenesis and behavior.

Recently, new tools and drugs have entered the clinical world aiding the diagnosis and management of UCs based on our understanding of the biological pathways underlying tumorigenesis and progression/metastasis. While proper staging remains challenging in both diseases, the appropriate management is based on adequate risk stratification with highly variable outcomes according to selected treatment strategies. We are, indeed, seeing a revolution in the diagnosis and management of these disparate UC twins (bladder and UTUC) with the advent of novel technological and molecular breakthroughs (8-10).

This special issue addresses some of the most exiting contemporary concepts and controversies in UC. Dr. Nyirady, a leading authority in the management of UC, describes the differences between bladder and UTUC. Dr. van Rhijn, a foremost expert in the biology of UC, discusses the genetic and biological markers that could help us guide early diagnosis and clinical decision-making in urachal cancer, a specific type of bladder cancer.

One of the key challenges in improving outcomes for UC is the heterogeneity of the disease. This and the generally disappointing outcomes call for support of clinicians and patients based on the best available evidence. One of the hottest areas today is discussed by Dr. Burger, a brilliant surgeon-scientist, who unravels the secrets of the immunotherapeutic boom and its potential to change the treatment paradigm in metastatic (and possibly localized) UC.

Like all cancers, early diagnosis is currently the best approach to improve outcomes. Unfortunately, opportunities to spot UCs in a timely manner are often missed, especially in women, who have consistently lower survival rates than their male counterparts (11-13). Dr. Rink, one of the most accomplished clinician-researchers in the field of UC, addresses gender-specific differences in the management and outcomes of UC, focusing on possible hypothesis for these differences.

UC is an age-related cancer and because of aging population, an increase of UC patients seems inevitable (14-17). Dr. Soria, a rising star in the field of UC, helps us perfect the management of this frail patient population with its specific needs. Dr. Krabbe, another rising star with an admirable track record, discusses one of the biggest game changers in UC treatment algorithms, variant histology (18). Dr. Sargos, a radiation therapist with in-depth experience of UC, helps us reconsider the role of radiation therapy as an adjunct to surgery with the aim of improving local control. Dr. Bensalah, a superb surgeon-scientist who has spearheaded various collaborative projects in upper tract cancers, take inroads on the safest and most

practicable risk-stratification of UTUC to avoid over- and under-treatment of this elusive disease (19,20). Dr. Mbeutcha, a highly promising young urologist, helps us understand this disease better by synthesizing the literature on current prognostic factors and predictive tools in UTUC. Finally, Dr. Abufaraj, another exemplary young urologist, discusses the next frontier in the management of metastatic UC—the role of surgery.

Taken together, these foremost experts will inform us on the hot new data that will shape our practice of UC tomorrow. I hope this issue will delight you as it did with us while putting it together for you.

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Conflicts of Interest: SF Shariat owns or co-owns the following patents: methods to determine prognosis after therapy for prostate cancer.

Granted 2002-09-06. Methods to determine prognosis after therapy for bladder cancer. Granted 2003-06-19. Prognostic methods for patients with prostatic disease. Granted 2004-08-05. Soluble Fas: urinary marker for the detection of bladder transitional cell carcinoma. Granted 2010-07-20. He is advisory board member of Astellas, Cepheid, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanofi, Wolff. He is speaker for Astellas, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanochemia, Sanofi, Wolff. R Mathieu—Consultant: Astellas, Ipsen, Janssen; Speaker: Janssen, Sanofi, Novartis, Takeda.

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