Editorial

Building bridges in urothelial carcinoma to face common challenges

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Urothelial carcinoma of the bladder (UCB) and upper tract (UTUC) are now established as two distinct entities with differences in anatomical, biological and molecular characteristics. Indeed, specific clinical guidelines have been produced for each of them to guide clinicians (1-3). Despite their status of "disparate twins", UCB and UTUC still share similar controversies, issues/challenges. Among other are the role of new imaging and endoscopic techniques, integration of biomarkers in clinical practice, indication and risk management to allow organ-sparing treatment, impact of systemic treatment, and surgery in metastatic disease. Indeed, lessons learned from one entity may be of value for the other, giving physicians the opportunity to improve patient care in urothelial carcinoma (UC) accross all sub-entities.

Over 30 years of continuous improvement in endoscopy has led to significant advances in the identification and management of UC. New technologies such as photodynamic diagnosis, narrow band imaging and high definition digital endoscope may help even further improve diagnosis and characterization of UC (4-6). However, despite these technological advances, current limitations of transuretral resection of the bladder (TURB) or endoscopic biopsy still yield to limited samples, precluding optimal staging and grading in addition to failing to ensure complete tumor removal. Staging with multi detector computed tomography as well as all other imaging techniques also suffers from limited accuracy (7,8). To overcome the limitations of pathological assessment from TURB or biopsy and those of current imaging, new modalities of evaluation have been developed such as endoluminal ultrasound and optical coherence tomography (9-11). Preliminary reports suggest multiparametric MRI, especially ADC, may also have a role for staging and grading the tumor (12,13). New instrumental methods have been also tested to improve TURB such as en bloc trans-urethral resection (14), while new baskets may improve the quality of biopsy or the completeness of tumor removal in UTUC (15,16). Taken together, all these efforts show that modern imaging and novel endoscopic modalities will play a central role in the diagnosis, risk stratification and treatment of UC.

UC is a complex biological disease with a highly variable behavior. We reckon that despite these improvements in technology, we will not reach the full potential of progress. Fortunately, basic research and collaborative efforts have led to a better knowledge and growing understanding of the natural history and biological pathways involved in the tumorigenesis, as well as progression/metastasis of UC. For example, the role of variant histology and lymphovascular invasion in UCB is becoming a key ingredient in care decision making (17,18). High-throughput analysis methods such as proteomics, metabolomics and genomics have already contributed to the identification of promising prognostic/predictive biomarkers in both UCB and UTUC (19,20). These biomarkers may help identify patients who are more likely to harbour aggressive disease and benefit from multimodal treatment and close follow-up. The combination of such biomarkers to capture a complex biological pathway may increase their performance (21). However, there are still many challenges to face before integrating these biomarkers in daily clinical practice. Integration of biomarkers requires stepwise quality criteria that most biomarkers have not yet reached (22,23). Among the limitations that preclude their widespread use, the lack of reproducibility and reliability of their

assessment is probably the biggest hurdle. There is no doubt that harmonization of the measurement techniques and eventual multicentric validation of their performance are still mandatory steps before widespread use of the most promising biomarkers. Furthermore, most of the current tissue biomarkers have been assessed on radical nephro-ureterectomy (RNU) and radical cystectomy (RC) specimens. Therefore, to confirm the predictive/prognostic value of these biomarkers in the pre-operative setting, their validation on TURB specimen or in small tissue samples obtained with ureteroscopic biopsy is mandatory. Such studies have been recently proposed in UCB but are still awaited in UTUC (24). Recent multi-institutional collaborative efforts are attempting to close this gap. Development and validation of new prognostic/predictive models that include biomarkers and new imaging modalities represent the most likely road to success. Such models may help physicians propose a risk-stratified clinical decision making regarding intravesical and upper tract instillation, radical versus organ-sparing surgery, and peri-operative chemotherapy.

Indeed, RC and RNU still remain the standard treatment for the majority of UTUC and invasive or very high risk UCB, respectively (25). However, these treatments should be delivered as the best treatment at the right time for the right patient. In the last decades, organ-preserving therapies have been developed as alternatives to radical surgery in both diseases. In invasive UCB, different organ-preserving treatments have been proposed such as partial cystectomy, radical transurethral resection, radiation therapy, chemotherapy and trimodal therapy (TMT) that combines these three latter modalities. In UTUC, kidney-sparing procedures such as distal ureterectomy, percutaneous approach or more recently ureteroscopic management have been proposed to preserve renal function. These organ preserving therapies were initially limited to imperative indications. However, TMT in UCB, distal ureterectomy and endoscopic treatment in UTUC have shifted to elective indications for well selected patients to minimize toxicity while preserving similar oncologic outcomes to radical treatment (26). Oncological outcomes of these different treatment modalities are mostly based on studies that suffer from retrospective design, selection bias and short follow-up. Prospective studies with longer follow-up are still necessary both in UTUC and UCB to confirm the results of these alternative therapies and assess their niche in the treatment repertoire of these diseases.

A survival benefit of systemic neoadjuvant chemotherapy before RC in localized UCB has been demonstrated with high level of evidence (27). Despite this benefit, only a minority of patients undergo neoadjuvant chemotherapy nowadays (28). Conversely, while adjuvant chemotherapy failed to demonstrate any significant survival benefit, adjuvant chemotherapy has been widely adopted in advanced or lymph node positive UCB (29). Therefore, further trials that will accrue the requisite number of patients are necessary to confirm the role of peri-operative chemotherapy in UCB and justify its use in routine. In UTUC, there is no level 1 evidence to support a role for chemotherapy in non-metastatic disease both in pre and post-operative settings. One randomized controlled phase 3 trial, the Peri-Operative chemotherapy versus sUrveillance in upper Tract urothelial cancer (POUT) trial, is ongoing to assess the value of adjuvant cisplatin-based chemotherapy versus surveillance in patients undergoing RNU for UTUC (30). However, prospective trials are still lacking and further efforts are mandatory to help physicians define the place of perioperative chemotherapy. The neoadjuvant setting makes in this disease especially sense since most patients will experience renal function loss after RNU, becoming ineligible for adjuvant chemotherapy (31).

Similar challenges lie ahead in metastatic UCB and UTUC. Most metastatic patients with UC and normal renal function will undergo cisplatin based combination chemotherapy. However, in both diseases, all patients will invariably experience disease progression within 2 years and die from their disease. In the light of these disappointing results, uro-oncologists have high expectations from immunotherapy. However, physicians should not only pin their hopes on new drug therapies, but should also focus on the role of local treatment in metastatic setting. In prostate cancer, for example, recent evidence suggests that metastatic patients may benefit from cyto-reductive local surgery as part of a multimodal approach to lower the tumor burden, thereby improving outcomes (32). However, In UC, little to none is known in this regard. In metastatic UCB, first results of a retrospective study that asked US national database warrant further investigations in prospective trials on the feasibility, morbidity and oncological outcomes of local treatment in UCB, but also in UTUC (33).

Many years of intense collaborative efforts in basic and clinical research coupled with technological innovations has significantly improved management in UCB and UTUC. However, current issues and the low level of evidence in various aspects of patient care warrant further intensification of collaborations between researchers, radiation oncologist, engineers, urologist, oncologist and patients to propose

ambitious research programs to achieve a breakthrough in this tenacious disease.

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Footnote

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 an 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 is a consultant for Astellas, Ipsen, Janssen; and he is speaker for Janssen, Sanofi, Novartis, Takeda.

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