Editorial

Trimodality therapy in variant urothelial carcinoma: choose wisely

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Trimodality bladder-sparing therapy with maximal transurethral resection (TUR) followed by combined chemoradiation is an alternative to neoadjuvant chemotherapy followed by radical cystectomy (RC) in optimally selected patients treated in expert multidisciplinary centers. Little has been studied regarding the impact of variant urothelial histology when utilizing a trimodality therapy (TMT) approach. Investigators from Boston, Massachusetts retrospectively reviewed their long-term experience with this approach. With the caveats of the retrospective nature of the study and limited numbers across a long time period, no significant differences in outcome were described in those with variant *vs.* pure urothelial carcinoma (UC) histology. Previously described clinical prognostic indicators were validated in this patient population. Additional genomic and transcriptomic analyses are warranted.

Treatment of muscle invasive bladder cancer (MIBC), which can present either *de novo* or after progression despite treatment of non-muscle invasive disease, represents an area of great challenge and opportunity for preventing metastases and improving cure rates.

The current guidelines for stage cT2-T4aN0M0 support the use of neoadjuvant cisplatin-based chemotherapy followed by RC (1,2). However, a multidisciplinary approach involving the combination of maximal TUR, and combined chemoradiotherapy (CRT) is an alternative in selected patients (1,2). Despite lack of reported randomized data, this approach, described as TMT is utilized either for highly selected patients aiming at bladder preservation or for patients unfit for RC (1,2), based upon several prospective and retrospective studies. In optimally selected patients, overall complete response (CR) rate of 78%, local relapse rate of 28%, and 21% requirement for salvage cystectomy, can be achieved based on results of a recent metaanalysis (3). Although there are no head-to-head comparisons with RC or RC plus chemotherapy, the 5-year overall survival (OS) rates may be comparable (57% *vs.* 52% *vs.* 53%, respectively) (3).

Approximately 90% of bladder cancers originate from transformation of normal urothelium and are classified as UC. However, the existence of tumor heterogeneity as well as the recognition of UC's ability to differentiate (or de-differentiate) into different phenotypes have led to characterization of several variants of UC (VUC) (4). Squamous, glandular, micropapillary and sarcomatoid differentiation are the most frequently observed (4). Identification of variant histology has been challenging as no common definition has been used among studies, and the term refers to any bladder cancer with features other than pure UC (PUC), often including mixed forms (4). This is further complicated by the frequent lack of recognition of variant histology, particularly among community pathologists, and also the lack of concordance between TUR and RC specimens, with a sensitivity of TUR in detecting VUC as low as 39% (5). In addition, the extent of differentiation has not been accounted for in several retrospective studies which explored the impact of VUC on survival and their responsiveness to treatment modalities. Presence of more than 80% classic UC pattern on RC was reported as a favorable prognosticator in one of the first reported cohorts (6), while presence

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of >2 non-conventional differentiation patterns on RC predicted lymph node (LN) involvement (7). A lower cut-off of 30% was used in another cohort to quantitate VUC squamous or/and glandular differentiation, without any significant impact on survival after RC (8). Others observed a significant association of variant histology with worse cancer-specific survival only at a higher extent of the former (>60% or >70%), but its effect was weak when adjusted for established prognostic factors, including grade, stage, LN status and surgical margins (9).

The presence of VUC has important implications for treatment as well. In a recent retrospective study, mixed VUC tumors inclusive of additional variant histologies (small cell, micropapillary, sarcomatoid, nested, lymphoepithelioma-like, and plasmacytoid) had 11 times lower odds of pT0 after cisplatin-based neoadjuvant chemotherapy (NAC), with authors discussing a potential benefit from upfront RC (10). However, a secondary analysis of the prospective randomized Southwest Oncology Group (SWOG)-led S8710 trial of neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) followed by RC versus RC alone in locally advanced UC patients revealed a superior pT0 downstaging and a survival benefit from chemotherapy in patients with squamous and glandular differentiation (11).

Few studies have explored the effect of VUC with TMT. The study entitled "*Clinical outcomes of patients with histologic variants of urothelial cancer treated with trimodality bladder-sparing therapy*" by Krasnow *et al.*, recently published in *European Urology Journal*, addressed, for the first time, the role of TMT in outcomes of VUC patients (12). The authors of this retrospective study investigated the 5-yr and 10-yr disease-specific and OS of 303 patients with MIBC treated with TMT. No significant differences were found between the subgroup of 66 (22%) patients with VUC and the rest PUC population. In addition, there were no differences in the rate of CR or salvage cystectomy (12).

These findings are not surprising given that the great majority of VUC patients had squamous and glandular differentiation (50/66, 76%), therefore poor prognostic histologies including sarcomatoid, plasmacytoid and neuroendocrine were underrepresented. It has been clearly shown that recurrence-free and OS do not differ between UC patients with squamous or/and glandular differentiation and PUC patients (13). Further, the presence of mixed but not pure variants is not associated with worse rates of recurrence and OS (14).

In the study of Krasnow *et al.* (12), less than half of VUC patients had available tissue for pathology re-review, thus the effect of VUC extent on the studied outcomes is unknown. In their multivariate analysis including several clinical and pathologic variables, the authors confirmed the independent prognostic roles of age, stage, hydronephrosis and CR after induction CRT in the total cohort (12). These are in line with several reports from the same and other groups including Radiation Therapy Oncology Group (RTOG) protocols (8802, 8903, 9506, 9706, 9906, 0233) and nomograms which were developed to predict outcomes in patients undergoing TMT (15,16). Notably, the retrospective study encompassed data over a 20-year period. Though the multivariate analysis controlled for some known factors, information on the era of diagnosis/treatment was not analyzed and therefore improvements in imaging, chemotherapy and radiation, and supportive care may have had an impact.

Despite the long-term experience of TMT, only a handful of such studies have reported the inclusion of VUC and our ability to draw conclusions from direct comparisons is limited. In a German cohort study of 238 patients who underwent TMT, micropapillary was the most frequent variant histology (7%), and when extensive (≥30%) resulted in inferior survival (17). This may not be unique to TMT, as cystectomy series have reported similar results (18).

Important considerations in improving decision making on treatment of patients with variant histologies are accurate staging, and sensitivity of different VUC to non-surgical modalities including chemotherapy and radiotherapy. Patients with squamous and glandular features of any percentage have shown a significantly higher rate of pathologic downstaging after neoadjuvant chemotherapy compared to classic UC (60% *vs.* 32% respectively), supporting its use in these VUC subtypes (19). In addition, while non-squamous VUC seems to be at a higher risk of recurrence and cancer-specific mortality, there was no difference in survival between patients with pure and variant UC treated with adjuvant chemotherapy (20), implying a potential benefit of the latter even in non-squamous variants. For example, in small cell VUC which is traditionally deemed as an aggressive variant, neoadjuvant chemotherapy can significantly improve pathologic downstaging and OS compared to RC alone and is a recommended strategy (21). In contrast, micropapillary variant is associated with higher recurrence rates after RC and platinum-based adjuvant chemotherapy than that with PUC (22).

A deeper insight into biology of the disease, enabled by the increasing use of genomic analysis, has shed light into the molecular drivers and formation of a classification system reflecting the clinical and pathological features

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of UC. The Cancer Genome Atlas project identified four different molecular clusters in 131 MIBC, obtaining an integrated mRNA, micro-RNA and protein expression profiling, however with limited inclusion of VUC [40]. Cluster I displays "papillary" features and frequent mutations or amplifications in fibroblast growth factor receptor 3 (FGFR3). Cluster II lacks the papillary features and FGFR3 alterations but both clusters I and II were compared with the luminal subtype of breast cancer, based on comparable expression patterns of GATA3 and Forkhead Box A1 (FOXA1), as well as increased HER-2 and estrogen receptor beta signaling. Cluster III is known as "basal or squamous-like", showing expression of epidermal growth factor receptor (EGFR) and basal-type cytokeratins characteristic of squamous differentiation. Cluster IV is similar to cluster III, but devoid of the histologic squamous features (23).

Unfortunately data on genomic differences between different VUC is limited. In a cohort of 73 patients, with squamous VUC present in 1/3 of available specimens, three molecular subtypes were identified, in resemblance with breast cancer molecular taxonomy: (I) basal, characterized by p63 activation, short survival and enriched in squamous and sarcomatoid features; (II) luminal, with activating FGFR3 mutations; and (III) p53-like with marked resistance to platinum-based chemotherapy (24). A similar study examined 60 patients with UC among whom 12 (20%) featured micropapillary variant histology. While TMT data is lacking, one might extrapolate chemo-sensitivity from neoadjuvant chemotherapy RC series. Out of the three major molecular subtypes identified, basal tumors benefited most from neoadjuvant chemotherapy (MVAC plus bevacizumab), whereas the p53-like subtype was associated with development of bone metastases and poor outcomes, indicating chemoresistance and need for upfront surgery. The presence of FGFR and HER-2 signatures in the luminal subtype is promising for feasibility of targeted approaches (25).

Unlike PUC, studies on identification and validation of biomarkers predictive of response to TMT are lacking in VUC. Furthermore, improving techniques for better visualization and appropriate tumor specimen collection as well as standardization of a quantification system correlating with the true impact of each variant on outcomes remains a challenge. At present, there is one ongoing phase 2 study of TMT in patients with MIBC using neoadjuvant accelerated MVAC (aMVAC) followed by CRT with intensity modulated radiation therapy (IMRT) and 5-Fluorouracil (5-FU) and mitomycin C. Patients will have maximal TUR, followed by three cycles of aMVAC, repeat maximal TUR and then IMRT and 5-FU and mitomycin C, followed by a third maximal TUR (NCT02710734).

In conclusion, patient selection is of key importance to the success of TMT in both PUC and VUC patients. Optimal candidates for TMT are not just patients with co-morbidities less fit for radical surgery. Based upon the available data, including the large retrospective series published by Krasnow *et al.* (12), the presence (or absence) of VUC should not influence one's decision on a RC with/without neoadjuvant chemotherapy *vs.* TMT approach. Increasing genomic data as well as the potential use of targeted therapy or immunotherapy may be of use in the future. Clinical predictors continue to be useful in the optimal selection of patients for TMT and remain essential for maximizing clinical benefit and improving outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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