Differences in the expression heterogeneity of ADC-related markers between primary tumors and metastatic lymph nodes in advanced urothelial cancers.

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Background: The booming development of antibody–drug conjugates (ADCs), which represent a novel, effective and low-toxicity therapeutic approach, has dramatically improved clinical outcomes in urothelial cancers, especially those with advanced disease. However, previous studies focused less on the targeted genes expression pattern and heterogeneity in metastatic tissues, which are more critical to inhibit tumor progression. Here, we aimed to explore the expression of potential ADC-related genes, including HER2, HER3, Nectin4 and Trop2 in advanced urothelial cancers between primary tumors and metastatic lymph nodes (mLN) in pairs. **Methods:** A large cohort of 306 urothelial cancer patients (292 patients, pN+), including 65 renal pelvis, 38 ureter, 179 bladder and 24 urethral cancer patients (10 patients, pN+), from SYSUCC was enrolled. Paraffin-embedded primary tumors and corresponding mLN sections were subjected to immunohistochemistry (IHC) to detect ADC-related gene expression. HER2 IHC scores of 2/3+ were defined as high expression as previously described. HER3, Nectin4 and Trop2 were evaluated by H-scores (range 0-300, rank 0 to 3+) multiplied by the extent and intensity of the staining, and H-scores >15 were considered positive. **Results:** A total of 74.8% of advanced urothelial cancer patients were HER2 positive (1-3+), and 49.4% had high HER2 expression. High HER2 expression was detected in 33.8%, 42.2%, 56.5% and 50% of renal pelvis, ureter, bladder and urethral primary tumors, respectively. The rate of high HER2 expression in mLNs slightly decreased to 30.1%, 41.7%, 51.9% and 50%, and the concordance rate of HER2 expression between primary and mLNs was 71.9%. Similarly, 27.7%, 42.1%, 52%, and 66.7% of primary tumors were positive for HER3 expression; 72.3%, 89.5%, 77.7%, and 87.5% were positive for Nectin4; and 89.2%, 94.7%, 83.2%, and 95.8% were positive for Trop2 in renal pelvis, ureter, bladder and urethral cancers, respectively. Overall, 71.9%, 50.7%, and 65.3% of patients had consistent expression of HER3, Nectin4 and Trop2 in mLNs, respectively. Survival analysis indicated that the overexpression of HER2, HER3 and Trop2 in advanced urothelial cancers was associated with poor OS (p=0.001, 0.025 and 0.022, respectively). More importantly, we found that patients with higher HER2 expression in mLNs at primary sites had a worse prognosis (p=0.006). **Conclusions:** We first investigated the heterogeneity of ADC-related marker expression in primary urothelial tumors and mLNs in a large single cohort, especially in patients who underwent radical lymphadenectomy. Therapy targeting HER2-ADCs might show better homogeneity in advanced disease, but it is more recommended to detect IHC staining both in primary and metastatic tissues if possible. Research Sponsor: Natural Science Foundation of Guangdong Province, China.