available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

*Referring to the article published on pp. 200–206 of this issue*

# Limited Upstaging in Luminal Subtype Tumors: Ready for Clinical Practice?

*Joshua J. Meeks* [a,*], *David J. McConkey* [b]

[a] *Department of Urology and Biochemistry and Molecular Genetics, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA;* [b] *Department of Urology, Greenberg Bladder Cancer Institute, Johns Hopkins University, Baltimore, MD, USA*

In this issue of *European Urology*, Lotan et al. [1] provide evidence for a potentially important clinical application of mRNA expression-based tumor subtyping in patients with stage I and stage II bladder cancers. The goal of the study was to use paraffin-embedded transurethral resection (TUR) samples from multiple sites across the USA and apply the GenomeDx Decipher GSC single-patient classifier to determine whether rates of upstaging varied according to subtype [2]. The authors found that luminal T1 and T2 cancers were associated with lower rates of upstaging (34%) than were tumors assigned to the other three molecular subtypes (51%; $p = 0.02$), which almost certainly contributed to a significant difference in cancer-specific mortality for patients with luminal cancers. The results are consistent with other data demonstrating that luminal bladder cancers are less clinically aggressive than cancers belonging to the other subtypes, and they suggest that nonluminal cancers should be managed more aggressively [3,4]. Coupled with other recent work demonstrating that essentially all of the clinical benefit from neoadjuvant chemotherapy occurs in patients with basal cancers [2], the data lend further support to the conclusion that patients with luminal cancers might be managed more conservatively.

The authors should be congratulated on an impressive amount of work: assembly of a cohort of 258 real-world T1 and T2 TURs across multiple sites, with molecular analysis and biostatistical comparison to clinical outcomes, requires significant effort and collaboration. Compared to The Cancer Genome Atlas (TCGA), for which only very high-quality flash-frozen tissue was collected from a limited number of sites, these formalin-fixed, paraffin-embedded (FFPE) samples were obtained during routine clinical care. In FFPE samples the RNA is severely more degraded, making the findings more applicable to clinical practice. Importantly, the authors point out that no patients received chemotherapy and that 34% of organ-confined luminal tumors on TUR were pT3+ and an equivalent percentage (21% vs 26%) had node-positive cancer that could have been eradicated by systemic therapy. Overall, it also appears that tumor subtyping is not a strong predictive biomarker for surgical (or chemotherapy) efficacy, and the next steps in precision oncology will include determining how to apply these and other genomic biomarkers in the clinic.

Decipher is a locked-down test that is already available for clinical application, and it therefore has high practical value. However, the data in Fig. 1 [1] show that the Decipher subtype calls are not all that similar to those generated by two other high-profile subtyping strategies (TCGA and the Global Consensus subtypes) [5]. Therefore, the other subtyping strategies may provide complementary information, and there is more work to be done to define the various biological mechanisms that control subtype membership. Furthermore, recent studies have challenged the notion that tumor subtype membership is an intrinsic, stable property of a given tumor [2]. Therefore, subtype calls made on TUR specimens could be completely different from those produced from tumors (or metastases) collected at cystectomy. The authors should consider carrying out this experiment as a means of directly addressing this question, particularly because none of the patients received neoadjuvant chemotherapy, which can strongly affect post-treatment subtype calls.

DOI of original article: https://doi.org/10.1016/j.eururo.2019.04.036.
* Corresponding author. Department of Urology and Biochemistry and Molecular Genetics, Northwestern University, 676 North St. Clair, Chicago, IL 60611, USA. Tel. +1 312 3638959.
E-mail address: joshuajmeeks@gmail.com (J.J. Meeks).

https://doi.org/10.1016/j.eururo.2019.05.025
0302-2838/Published by Elsevier B.V. on behalf of European Association of Urology.

What message can we take from the results reported by Lotan et al? We can appreciate that stage I and II luminal tumors have a better prognosis compared to nonluminal subtypes. We agree with the authors that we do not have sufficient data to suggest that patients with luminal tumors should avoid neoadjuvant chemotherapy, given that many of these cancers are downstaged by therapy. What remains unresolved is the predictive value of tumor subtype. Before application to clinical care, it will be important to identify the molecular mechanisms that drive upstaging and nodal metastasis, and whether they vary by subtype. Despite a proposed application across MIBCs, we do not have enough evidence yet to treat a patient with MIBC differently according to whether their tumor belongs to a basal or luminal subtype. Yet the findings of Lotan et al and the earlier work might support the evaluation of less toxic (and potentially more efficacious) new FGFR inhibitors such as erdafitinib given that luminal papillary tumors are enriched with activating *FGFR3* mutations and fusions, and FGFR3 pathway gene expression [4,6]. These patients may benefit from early precision targeting.

***Conflicts of interest:*** The authors have nothing to disclose.

## References

[1] Lotan Y, Boorjian SA, Zhang J, et al. Molecular subtyping of clinically localized urothelial carcinoma reveals lower rates of pathological upstaging at radical cystectomy among luminal tumors. Eur Urol 2019;76:200–6.

[2] Seiler R, Ashab HAD, Erho N, et al. Impact of molecular subtypes in muscle-invasive bladder cancer on predicting response and survival after neoadjuvant chemotherapy. Eur Urol 2017;72:544–54.

[3] Choi W, Ochoa A, McConkey DJ, et al. Genetic alterations in the molecular subtypes of bladder cancer: illustration in The Cancer Genome Atlas dataset. Eur Urol 2017;72:354–65.

[4] Robertson AG, Kim J, Al-Ahmadie H, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell 2017;171, 540–56.e25.

[5] Kamoun A, de Reyniès A, Allory Y. The consensus molecular classification of muscle-invasive bladder cancer. bioRxiv 2019. http://dx.doi.org/10.1101/488460.

[6] US Food and Drug Administration. FDA approves first targeted therapy for metastatic bladder cancer. www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-metastatic-bladder-cancer.