Editorial

Understanding risk and refining surveillance following tumor resection for low grade non-muscle invasive bladder cancer

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Breaking clinical dogma can be difficult, particularly when the practice in question is easy and billable (i.e., routine office cystoscopy for surveillance of bladder cancer). von Landenberg and colleagues provide an organized, multi-institutional study examining the conditional recurrence and progression-free survival (PFS) of TaG1 non-muscle invasive bladder cancer (NMIBC) to help clinicians better individualize patient care (1). Perhaps this data may help reduce dogmatic and unnecessary procedures and tests every three months for all NMIBC patients regardless of risk. Despite guideline recommendations and increasing focus on risk-aligned surveillance, implementation can be quite challenging in busy clinical practices (2-4). Given that more than 70% of all bladder cancers are NMIBC and many patients live a long time with their disease (i.e., median survival for patients with NMIBC is over 9 years) (5), the clinical utility of the authors' conclusions is quite meaningful.

In this retrospective study, the authors performed a conditional-survival analysis of recurrence-free survival (RFS) and PFS in a cohort of 1,245 TaG1 NMIBC patients. The data suggests that RFS rates improve the further from transurethral resection of TaG1 bladder tumor (TURBT) while PFS rates remain similar over time. These findings were consistent when comparing low and intermediate-risk disease. The results suggest that treatment (including immediate postoperative instillation of chemotherapy) and increasing years of RFS following TURBT impacts recurrence while progression is driven mainly by tumor biology. The impact of prognostic features of recurrence such as age, sex, immediate postoperative instillation of chemotherapy, tumor size ≥3 cm, multifocality and prior recurrence decreased over time.

The results described are not surprising. Intuitively, the more time elapsed from bladder tumor resection without recurrence, the less likely a patient is to relapse. Furthermore, RFS and PFS are more favorable if the features of the disease and the patient characteristics are known to be associated with improved outcomes (e.g., tumor size <3 cm, solitary tumor). What makes this analysis unique is the conditional-survival calculation over time and the applicability of the results (6). There is now broad international consensus that risk-adapted surveillance should be a priority across the spectrum of NMIBC cases (7-11). Yet, there is significant variation in the care of NMIBC patients among urologists resulting in over-treatment in low-risk patients with unnecessary cystoscopies and increased costs; and under-treatment in high-risk patients leading to delays in diagnosis and treatment (12-16). As such, this study provides further evidence to support the use of risk-aligned and individualized surveillance for patients with intermediate-risk NMIBC.

Although the authors have taken an important step towards the optimization of surveillance strategies, it is prudent to recognize the overall heterogeneity of NMIBC and question whether further refinement is possible.

There is considerable difference in management between patients with true low-risk *vs.* high-risk disease. However, the heterogeneity of intermediate-risk NMIBC is well described (17,18). The EAU guidelines, as opposed to AUA guidelines, do not specify the intermediate-risk group, stating that all tumors that are not low or high-risk qualify (2,3). Therefore intermediate-risk tumors include histologically-confirmed multiple and/or recurrent low-grade Ta tumors. The nuances between AUA and EAU guidelines do have clinical implications. Kamat and colleagues (18) previously described a sub-stratification of intermediate-risk NMIBC patients according to the number of risk factors present (e.g., multiple tumors, tumor size >3 cm, recurrence within 1 year and frequent recurrence within 1 year) and placed patients into detailed groups (i.e., no risk factors = favorable-intermediate, 1–2 risk factors = true intermediate and ≥3 risk factors = unfavorable-intermediate). The authors suggested treating favorable-intermediate similar to low-risk and unfavorable-intermediate as high-risk patients (18). Additionally, this stratification of intermediate-risk patients was suggested for consideration in the design of future clinical trials (17). In the setting of the results presented by von Landenberg *et al.* (1), intermediate-risk patients were included in the conditional survival analysis without characterizing the details according to the aforementioned intermediate-risk stratification. Therefore, the study may actually over estimate the number of patients with intermediate-risk disease who could have been considered high-risk and excluded from the study. The clinical implication is that recurrence and progression rates quoted in this manuscript may be over-reported.

In summary, patients with low-risk NMIBC and intermediate-risk NMIBC with ≤2 risk factors have improved RFS and stable PFS over time. Clinicians should strive to tailor risk-aligned plans to individual patient and tumor characteristics remaining optimistic that future studies will further impact strategies to personalize bladder cancer management and surveillance.

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None.

Footnote

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

References

1. von Landenberg N, Aziz A, von Rundstedt FC, et al. Conditional analyses of recurrence and progression in patients with TaG1 non-muscle-invasive bladder cancer. Urol Oncol 2018;36:238.e19-238.e27.
2. Babjuk M, Bohle A, Burger M, et al. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol 2017;71:447-61.
3. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol 2016;196:1021-9.
4. Schroeck FR, Smith N, Shelton JB. Implementing risk-aligned bladder cancer surveillance care. Urol Oncol 2018;36:257-64.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
6. Leitner CV, Ederer IA, de Martino M, et al. Dynamic Prognostication Using Conditional Recurrence and Progression Estimates for Patients with Nonmuscle Invasive Bladder Cancer. J Urol 2016;196:46-51.
7. Brausi M, Witjes JA, Lamm D, et al. A review of current guidelines and best practice recommendations for the management of nonmuscle invasive bladder cancer by the International Bladder Cancer Group. J Urol 2011;186:2158-67.
8. Kassouf W, Traboulsi SL, Schmitz-Drager B, et al. Follow-up in non-muscle-invasive bladder cancer-International Bladder Cancer Network recommendations. Urol Oncol 2016;34:460-8.
9. Nieder AM, Brausi M, Lamm D, et al. Management of stage T1 tumors of the bladder: International Consensus Panel. Urology 2005;66:108-25.
10. Oosterlinck W, Solsona E, Akaza H, et al. Low-grade Ta (noninvasive) urothelial carcinoma of the bladder. Urology 2005;66:75-89.
11. Sylvester RJ, van der Meijden A, Witjes JA, et al. High-grade Ta urothelial carcinoma and carcinoma in situ of the bladder. Urology 2005;66:90-107.
12. Hollingsworth JM, Zhang Y, Krein SL, et al. Understanding the variation in treatment intensity among patients with early stage bladder cancer. Cancer 2010;116:3587-94.
13. Chamie K, Saigal CS, Lai J, et al. Compliance with guidelines for patients with bladder cancer: variation in the delivery of care. Cancer 2011;117:5392-401.
14. Koo K, Zubkoff L, Sirovich BE, et al. The Burden of Cystoscopic Bladder Cancer Surveillance: Anxiety,

Discomfort, and Patient Preferences for Decision Making. Urology 2017;108:122-8.
15. Pruthi RS, Baldwin N, Bhalani V, et al. Conservative management of low risk superficial bladder tumors. J Urol 2008;179:87-90; discussion 90.
16. Kulkarni GS, Urbach DR, Austin PC, et al. Longer wait times increase overall mortality in patients with bladder cancer. J Urol 2009;182:1318-24.
17. Kamat AM, Sylvester RJ, Bohle A, et al. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations from the International Bladder Cancer Group. J Clin Oncol 2016;34:1935-44.
18. Kamat AM, Witjes JA, Brausi M, et al. Defining and treating the spectrum of intermediate risk nonmuscle invasive bladder cancer. J Urol 2014;192:305-15.

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