



# Prognostic impact of tumor infiltrating lymphocytes in bladder urothelial carcinoma

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As the presence of tumor-infiltrating lymphocytes (TILs) may indicate a cell-mediated immune response against cancer cells, many studies have vigorously assessed presence of TILs as a potential prognostic factor in various types of cancers, including bladder cancer. Interestingly, previous studies have reported that the prognostic impact of TILs on bladder cancer varies depending on the status of the underlying bladder cancer and subpopulations of TILs. In cases of non-muscle-invasive bladder cancer (NMIBC), increased densities of several TIL subpopulations, including cluster of differentiation 3+ (CD3+), CD4+, and CD8+ T lymphocytes, were associated with worse recurrence and survival (1,2). In contrast, high densities of CD3+ and CD8+ TIL subpopulations were usually related to favorable survival outcomes in muscle-invasive bladder cancer (MIBC); however, high levels of other markers of positive immune cells (FOXP3 for regulatory T cells and CD68 for macrophages) among CD3+ or CD8+ T lymphocytes suggested unfavorable prognoses in MIBC (3-6). This correlation between high TIL densities and favorable survival outcomes was also identified in metastatic bladder cancer patients receiving platinum-based chemotherapy (7).

In the current study that involved T1 high-grade bladder cancer patients, stromal TILs did not provide any significant prognostic information with regards to survival outcomes,

including recurrence-free survival, progression-free survival, cancer-specific survival, and overall survival; however, stromal TILs are highly expressed in the T1b substage and variant histologies, indicating the association between the adaptive immune response and tumor progression. In the present study, the lack of prognostic significance of TILs may be due to several causes. First, the prognostic role of TILs may differ depending on the region in which they are measured. Generally, in bladder cancer, high density of intra-tumoral TILs tend to show better clinical outcomes (4,8), but high density of stromal TILs may be associated with worse survival outcomes (9). Second, the present study did not classify TILs into subpopulations according to specific immune markers (i.e., CD3+, CD4+, and CD8+). As mentioned earlier, the prognostic significance of TILs may be more evident when they are analyzed according to subpopulations (1-6).

Since the introduction of systemic immunotherapy, which restores anti-tumor immunity by blocking the immune checkpoints [i.e., programmed death 1 (PD-1), programmed death ligand 1 (PD-L1)], in treatment of bladder cancer, TILs have gained considerable interest as an attractive target for immunotherapy. The prognostic impact of TILs on clinical outcomes has been investigated with regards to PD-L1 expression but with inconsistent results

(4,9). In conclusion, a consensus has not yet been reached about the prognostic value of TILs in bladder cancer. Considering the retrospective designs and small sample sizes of previous studies (1-9), further well-designed prospective studies with large sample sizes will be required to confirm the role of TILs as a significant predictor of prognosis in bladder cancer. Furthermore, high-level evidence regarding the prognostic value of TILs can be obtained by conducting a meta-analysis that incorporates all relevant studies.

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### Footnote

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

### References

1. Krpina K, Babarović E, Jonjić N. Correlation of tumor-infiltrating lymphocytes with bladder cancer recurrence in patients with solitary low-grade urothelial carcinoma. *Virchows Arch* 2015;467:443-8.
2. Zhang Q, Hao C, Cheng G, et al. High CD4<sup>+</sup> T cell density is associated with poor prognosis in patients with non-muscle-invasive bladder cancer. *Int J Clin Exp Pathol* 2015;8:11510-6.
3. Sjö Dahl G, Lövgren K, Lauss M, et al. Infiltration of CD3<sup>+</sup> and CD68<sup>+</sup> cells in bladder cancer is subtype specific and affects the outcome of patients with muscle-invasive tumors. *Urol Oncol* 2014;32:791-7.
4. Faraj SF, Munari E, Guner G, et al. Assessment of tumoral PD-L1 expression and intratumoral CD8<sup>+</sup> T cells in urothelial carcinoma. *Urology* 2015;85:703.e1-6.
5. Horn T, Laus J, Seitz AK, et al. The prognostic effect of tumour-infiltrating lymphocytic subpopulations in bladder cancer. *World J Urol* 2016;34:181-7.
6. Yu A, Mansure JJ, Solanki S, et al. Presence of lymphocytic infiltrate cytotoxic T lymphocyte CD3<sup>+</sup>, CD8<sup>+</sup>, and immunoscore as prognostic marker in patients after radical cystectomy. *PLoS One* 2018;13:e0205746.
7. Huang HS, Su HY, Li PH, et al. Prognostic impact of tumor infiltrating lymphocytes on patients with metastatic urothelial carcinoma receiving platinum based chemotherapy. *Sci Rep* 2018;8:7485.
8. Wang B, Wu S, Zeng H, et al. CD103<sup>+</sup> Tumor Infiltrating Lymphocytes Predict a Favorable Prognosis in Urothelial Cell Carcinoma of the Bladder. *J Urol* 2015;194:556-62.
9. Wang B, Pan W, Yang M, et al. Programmed death ligand-1 is associated with tumor infiltrating lymphocytes and poorer survival in urothelial cell carcinoma of the bladder. *Cancer Sci* 2019;110:489-98.

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