Editorial Commentary

How to guide the selection of patients for trimodality therapy: the case for tumor immune and stromal signature

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Bladder cancer (BCa) is the 7th most common cancer in men, with an estimated 81,190 new cases and 17,240 deaths in 2018 in the USA (1). Radical cystectomy (RC) with cisplatin-based neoadjuvant chemotherapy (NAC) is the standard of care for the management of muscle-invasive BCa (MIBC). In recent years, bladder-preserving strategies combining bladder tumor transurethral resection (TURB) with radiotherapy and concurrent radio-sensitizing chemotherapy, also known as trimodal therapy (TMT), have shown similar results and reduced morbidity as compared to RC in selected MIBC patients (2,3). As a result, current guidelines now recommend both RC and TMT as effective treatment options for MIBC (4-7). TMT is underutilized by most practitioners (8), mostly because of the difficulty in identifying appropriate patients that might benefit from this treatment. Therefore, the identification of molecular biomarkers that can predict TMT outcomes to guide its selection as a therapeutic choice is of utmost importance.

Efstathiou *et al.* (9) investigated the impact of molecular subtyping, immune and stromal infiltration on the outcomes after TMT or NAC and RC for MIBC. They found that, in the TMT group, increased tumor immune infiltration and IFN-γ signalling was associated with improved cancer-specific survival. This was not the case for the NAC/RC population. On the contrary, a stromal signature was associated with worse survival in the NAC/RC group, but not in the TMT group. Authors suggested a potential use for transcriptional profiling to guide the selection of patients who will benefit most from TMT.

Authors should be commended for the innovation and significance of their findings. Our increasing knowledge of the molecular and genomic features of BCa and their integration into clinical diagnostics pipelines denote the focus toward tailored approaches in MIBC.

Several tumor-related factors (T stage, hydronephrosis, carcinoma in situ) and treatment-related factors (TURB quality and complete response to induction chemotherapy or chemoradiation) have been associated with survival outcomes after TMT (3,10). Nonetheless, typical clinicopathological characteristics are often inadequate to predict survival outcomes or direct treatment choice. The discovery and validation of genomic biomarkers that predict response to various BCa treatments could be essential to guide tailored therapies based on a tumor's molecular features (11).

In the recent literature, several studies have investigated biomarkers associated with radio/chemo outcomes and prognosis of TMT such as apoptosis-related biomarkers, cell proliferation-related biomarkers, receptor tyrosine kinases, DNA damage response-related biomarkers, hypoxia-related biomarkers, molecular subtypes, and immune checkpoint biomarkers (12). Very little is known about that role of the immune and stromal tumor infiltration as predictors for TMT outcomes.

In the metastatic BCa setting tumor infiltration by immune cells has been associated with response to immune

checkpoint inhibitors (13,14), but the role of tumor immune characteristics on response to TMT has been scantly evaluated. Efstathiou *et al.* (9) found that TMT-treated tumors with higher expression of genes associated with T-cell activation and IFN-γ signalling had better survival outcomes as compared with tumors with a lower signature score. This was not the case for patients treated with RC. Immune cells infiltration in BCa tissue before TMT may provide a more appropriate environment in which radiation can stimulate immune-mediated tumor killing through various mechanisms such as antigen release, chemokine secretion, or recruiting new immune cells (15,16).

Additionally, the presence of fibroblasts in BCa has been linked with a T-cell exclusion phenotype and different grade of response to systemic therapy (13). Authors showed that high expression of a stromal signature was associated with worse survival after cystectomy, but not in the TMT cohort, suggesting that radiation could alter the treatment-resistant phenotype associated with stromal infiltration.

Activating T cell therapy has shown impressive results in various tumors, including BCa (17,18). This strategy aims to emancipate the immune system from the suppressive signals secreted by the tumor and promotes the identification of cancer cells as targets for killing (11). Given the association between radiation and immune activation, it is reasonable to speculate that a tumor immune infiltrate may be associated with an improved response to TMT.

Although Efstathiou *et al.* (9) have performed a brilliant analysis to explore predictive factors for TMT outcomes, some limitations should be recognized.

NAC and induction chemotherapy regimens were different among protocols (yet primary cisplatin-based) (3,19). Since pathological and survival outcomes are different according to NAC regimes, the variability among study protocols might impact on oncologic outcomes for TMT and NAC/RC patients (20).

Smoking should always be taken into consideration when dealing with MIBC, as recent findings have revealed it might promote mechanisms of resistance to cisplatin-based chemotherapy in BCa patients. Pathologic response to cisplatin-based NAC was significantly affected by smoking status and smoking quantity in MIBC patients (21).

Baseline characteristics of patients were not balanced between groups, potentially affecting survival patterns. Moreover, rates of non-urothelial or mixed histologies and carcinoma *in situ* at TURB were not reported.

Authors used a narrow range of RT dosed among protocols (approximately between 64–65 Gy). It would be of great interest to investigate the effect of RT dose-escalation in TMT considering the emerging role of image-guided treatment and intensity-modulated RT that are characterized by improved target localization and reduced side effects.

In conclusion, it is crystal clear that precision medicine will play a predominant role in the management of MIBC in the next future, changing our focus from prognostication to prediction, with the need to elaborate modern classification systems that will take into account the nature of bladder cancer from a biological rather than histopathological perspective. Despite the continuous investigation of predictive biomarkers for guiding MIBC treatment choice, their integration into daily clinical practice requires strong validation in prospective clinical trials. While waiting for the results of ongoing clinical trials of TMT with or without PD-L1 inhibitors (e.g., SWOG/NRG 1806) that might further elucidate the association between immune infiltrate and radiation response, the study by Efstathiou *et al.* (9) deserves a prominent place in the current literature for the identification of immune and stromal tumor characteristics as biomarkers to guide the use of TMT.

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None.

Footnote

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

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