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Predictive Biomarkers for Muscle-invasive Bladder Cancer: The Search for the Holy Grail Continues

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Patients diagnosed with muscle-invasive bladder cancer (MIBC) suitable for radical treatment have an unenviable choice between radical cystectomy (RC) with a neobladder or urostomy, and trimodal therapy (TMT) based on maximal transurethral resection of bladder tumour followed by radical radiotherapy given with a radiosensitiser, usually chemotherapy, and cystoscopic surveillance. The available evidence shows no advantage for one or other approach in terms of survival outcomes [1,2]. Toxicity and patient experience differ greatly and the choice is currently made according to patient and clinician perception and preference, with many still regarding nonsurgical treatment as less effective in the face of contrary evidence. Against this background the prospect of a robust, readily available biomarker to aid patient selection is a highly attractive proposition. Biomarkers for bladder cancer have a long history, with decades of publications of small retrospective cohorts identifying yet another biomarker. Few have undergone rigorous clinical validation and there is no biomarker in routine clinical practice to stratify patients for TMT or surgery.

The paper by the Boston group published in this issue of *European Urology* [3] describes yet another approach by identifying differing immune profiles predicting for prognosis in MIBC. Immunotherapy has long been important in the management of high-grade non-muscle-invasive bladder cancer (NIMBC) and carcinoma in situ [4]. However, the past few years have seen a revolution in the management of metastatic solid tumours with the recognition that checkpoint inhibitors, molecules that themselves inhibit immune function enabling proliferation of tumour cells, have significant activity. In bladder cancer the most promising results are with drugs targeting PD-1 and PD-L1. Proof of principle has been demonstrated in trials showing significant gains in metastatic bladder cancer with atezolizumab, nivolumab, and pembrolizumab [4].

Attempts to relate the activity of the immune system to prognosis in MIBC are not new. It has been shown that absolute lymphocyte count, a simple surrogate for immune response, is associated with survival in a cohort of patients receiving bladder-conserving therapy [5]. In a series of 72 patients treated with TMT, overexpression of PD-L1 was both independently associated with locoregional relapse and prognostic for both disease-specific survival (DSS) and overall survival (OS) [6]. Preclinical data showed that in vitro irradiation of urothelial cancer cells increased PD-L1 expression and the radioresistance of in vivo bladder cancer models could be reversed by anti-PD-L1 drugs [6].

It is therefore rational to explore potential biomarkers of immune response in bladder cancer on the basis of the preclinical evidence of association between radiation response and immune activity within the tumour. Efstathiou and colleagues chose to evaluate tumour and stromal infiltrates by profiling whole-transcriptome gene expression in two retrospective cohorts, the first comprising 475 patients receiving TMT at a single institution and the second, 223 patients undergoing RC with neoadjuvant chemotherapy (NAC). Mature follow-up data censored at 5 yr were available for both cohorts. Ultimately, whole-transcriptome expression profiles were available for only 136 TMT patients and 223 NAC + RC patients. The reasons for the substantial dropout rate from the TMT cohort are not

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given, which raises concern over selection bias, whether conscious or unconscious. The authors acknowledge that the TMT and NAC + RC cohorts are unbalanced, with a higher median age, larger proportion of males, and lower T stages in the TMT cohort. Gene profiling allowed classification by molecular subtypes: luminal, luminal-infiltrated, basal, and claudin-low. While others have shown worse outcome with the luminal subtype, this was not seen in the TMT cohort. In the NAC + RC cohort, DSS was worse for those with claudin-low tumours. It has been shown that this subgroup has an inferior response to NAC + RC, which may be of relevance.

Two signatures reflecting immune infiltration were analysed: CD8 T-cell infiltrate and *IFN* gene expression. Both showed a positive association with DSS in the TMT group, independent of molecular subtype, but no association was seen in the NAC + RC cohort. However, in a multivariate model including clinical prognostic factors, only *IFN* gene expression remained an independent factor for DSS in the TMT cohort. This analysis divided gene expression into quartiles and compared the lower quartile with the rest, rather than simple dichotomisation of the data. It is not clear what exploratory analyses were undertaken with regard to the chosen cutoff or whether this was defined a priori.

Stromal infiltration was assessed using a predefined gene signature comprising nine genes commonly expressed in fibroblasts or myofibroblasts. Once again the expression levels were divided into quartiles, but for this analysis the upper quartile was compared with the rest. The reasons for this difference compared to the immune profiles are not clear. Stromal infiltration expression was not associated with outcome in the TMT cohort, but high stromal infiltration expression was associated with worse DSS and OS in the NAC + RC group ($n = 16$).

This is not the first report of a relationship between T-cell infiltration, stromal cell activity, and outcome in MIBC. A study using The Cancer Genome Atlas (TCGA) urothelial cancer data set comprising 408 RC samples explored the association between tumour-infiltrating T-cell abundance (ITA) and epithelial-mesenchymal transition (EMT)-related gene expression and outcome [7]. EMT has been associated with enhanced capacity for invasion and metastases, and in this study predicted worse OS. While ITA alone did not predict outcome, combination with EMT gene expression led to a highly significant prognostic biomarker, whereby good prognosis was associated with high ITA and low EMT, and poor prognosis with low ITA and high EMT in both the TCGA data set and a data set from the CheckMate 275 trial of nivolumab in metastatic bladder cancer.

Clearly, there is a complex association between immune activity in the tumour microenvironment and prognosis in bladder cancer. In principle, immune activation imparts a better outcome, while stromal gene activity can be adverse. However, despite the sophisticated use of gene expression profiles neither the Boston study nor the TCGA study have shown a positive impact of gene expression reflecting T-cell infiltration in either TMT or RC cohorts. It is of course unlikely that a single gene expression parameter will be the biomarker that is so sorely needed in the clinical setting. The TCGA group performed the more rigorous study by moving towards the use of a panel of genes reflecting both good and poor prognosis. It is unfortunate that the Boston group did not carry out analyses for combined T-cell, *IFN*, and stromal signatures. To have validated the TCGA signatures would have been a step forward and would have been a first among patients treated with TMT. Unfortunately, as it stands this paper does not move the field forward or change practice, but adds to the number of small retrospective cohort studies awaiting further validation.

Conflicts of interest: The authors have nothing to disclose.

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