Editorial

Improving outcome and prognosis prediction in non-muscle invasive bladder cancer using a gene expression score

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Bladder cancer is the ninth most common malignancy worldwide considering both genders and approximately 75% of the patients are initially diagnosed with non-muscle invasive bladder cancer (NMIBC) (1,2). About 10–20% of the patients will suffer from progression to muscle-invasive disease (2-4). Due to long-term follow-up regimen with cystoscopies over many years, bladder cancer carries the highest cost among cancers per patient from diagnosis to death (5).

NMIBC is stratified into three risk groups according to clinical (diameter, focality) and pathological [stage, grade, concomitant carcinoma *in situ* (Cis) criteria] (2). This is the basis for treatment decision and follow-up strategy. To predict recurrence and progression of NMIBC, the European Organization for Research and Treatment of Cancer (EORTC) developed a score (EORTC score) (4). To improve this limited clinicopathological risk calculator, various molecular markers have been investigated in the meantime.

Tumor heterogeneity has been investigated on in different cancer types, with bladder cancer emerging as one of the most heterogeneous tumors with multiple mutations. These studies have mainly analyzed muscle-invasive bladder cancer (MIBC) and found distinct subtypes based on molecular characteristics (6-9). This results in major clinical relevance, since it has been observed that tumors of the same clinical and histopathological characteristics show different progression and survival rates. The molecular classifications between the studies on MIBC differ and to date no consistent taxonomy for molecular classes of MIBC has been found (10).

For NMIBC various single markers or combinations of markers that predict progression have been investigated on immunohistochemically or genetically (11-16). More recently Hedegaard *et al.* could show in a multicenter prospective trial that NMIBC can also be divided in distinct molecular subgroups with distinct biological behavior that differs from those subgroups found in MIBC (17). Luminal subtype, reflected by high KRT20 expression is associated with a higher risk for progression, which could be proven in another NMIBC cohort of solely pT1 bladder cancer (18). In MIBC, the basal subtype is the more intrinsic aggressive tumor, which implies different molecular subgroups for MIBC and NMIBC and demands to investigate those entities by their own (7,10). Evaluation and validation of prognostic and predictive molecular markers or subtypes is still highly needed to improve prediction of prognosis and selection of a tailored therapeutic strategy.

In a recently published multicenter prospective trial, Dyrskjøt *et al.* validated a 12-gene score for improving prediction of progression to muscle-invasive disease in a large cohort of NMIBC (19). They could include 750 patients prospectively and prove that a previously described and established 12-gene score (17) was of high significance in predicting progression to MIBC ($P<0.001$ in multivariable analysis) (19). Furthermore, combining the well-established

risk-score EORTC with the novel 12-gene score even improved the predictive accuracy (19). The 12-gene score was able to detect a "highest" risk group in the EORTC high risk group (score >6), whereas no significant difference could be found for the intermediate risk group (19). These highest risk patients might benefit from early cystectomy, which of course would need to be proven in a prospective clinical trial.

The progression rate in the study at hand was rather low with 5% of the 750 patients suffering from progression to muscle-invasive disease (19). Progression rates of 10–20% for NMIBC have been described, with up to 30% for T1G3 tumors (2-4,20). The low progression rate in this study might be due to the mean follow-up time of 28 months and more likely due to the pathologic and clinical characteristics of the cohort. The highest ranked parameters of the EORTC score were less represented with 11% of the tumors staged pT1, 41% high grade tumors, 15% with diameter ≥3 cm and 14% CIS, which explains the low number of muscle-invasive progressions. Nevertheless, even with low progression rates, this 12-gene score proved to be of clinical relevance in improving outcome prediction.

The measurements were performed at one center from fresh frozen (FF) tissue, which is not the standard of processing the TUR tissue. However, the authors could show in a small group of 52 paired FF and formalin-fixed paraffin-embedded (FFPE) tissues that this evaluation also works with FFPE tissues (19). The major advantage of an RT-qPCR approach is the objective and investigator-independent quantification, since it has been shown for staging and grading of NMIBC, that the inter-observer variability is rather high with conformity levels of 50–60% (2). Though, the RT-qPCR assessment is also not devoid of technique-inherent weaknesses. Small tumors or low percentage of tumor tissue in the investigated tissue as well as low amount of RNA results in invalid measurements, which were exclusion criteria in the study of Dyrskjøt *et al.* (19). Since the measurements were performed at one site, it would be necessary to reevaluate the findings in different sites with different devices before implication into clinical routine use.

To conclude, the addition of this novel 12-gene score to the established EORTC score could improve prediction of prognosis, especially by identifying patients at highest risk of progression within the EORTC high risk group. This could lead to a stricter follow-up or to support decision-making for early cystectomy in these patients.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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