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Bladder Cancer Recurrence Diagnosis Using Multiplatform Biomarker Discovery

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Abstract

Due to the high likelihood of recurrence of non-muscle invasive bladder cancer (BCa), lifelong surveillance is necessary. The use of urinary biomarkers as quick substitutes for cystoscopy in the identification of recurring bladder cancer shows promise. But no one marker can provide the necessary accuracy. The goal of this study was to choose a multiparameter panel for diagnosing BCa recurrence that included urinary biomarkers and clinical factors. Urine samples from BCa patients with recurrence and BCa patients without recurrence were analysed for potential biomarkers. A multiplexed microarray and an automated ELISA analysis platform were employed as part of a multiplatform strategy for marker quantification. The outcomes from both platforms were merged with the gathered clinical data using a multivariate statistical analysis. The optimal clinical and biomarker combination has an AUC value of 0.91, outperforming the separate factors in terms of performance. This panel includes three clinical parameters (VEGF-A, cadherin-1, IL-8, ErbB2, and IL-6), six biomarkers (IL-6, IL-8, EN2, and VEGF-A), and (number of past recurrences, number of BCG therapies, and stage at time of diagnosis). The clinical management of this condition may be impacted by the multipara meter panel's potential as a valuable noninvasive tool for BCa surveillance. It is necessary to validate the results in a different cohort.

Keywords: Bladder Cancer; Biomarker; Diagnosis; Clinical parameters; Diagnostic biomarker; Argeted metabolomics

Introduction

At a global age-standardized rate of 9.0 per 100 000 men, bladder cancer is the ninth most prevalent cancer overall and the seventh most common disease in men. Seventy-five to eighty-five percent of individuals with newly diagnosed instances of nonmuscle invasive disease (BCa) had tumours restricted to the mucosa or submucosa (Ta, carcinoma in situ (CIS), or T1 tumours). Although such tumours have a fair prognosis, there is a propensity for recurrence following initial treatment. Within 5 years, there is a 30% to 80% chance of recurrence, and 10% to 30% of these instances will develop into muscle-invasive illness [1].

Hence, follow-up is a crucial component of managing BCa patients and includes on-going monitoring for recurrence detection. The most accurate procedures for diagnosing and monitoring BCa are cystoscopy and urine cytology. Despite its excellent sensitivity, cystoscopy has a high rate of false negative results. Furthermore, it adds to the financial and psychological burden of BCa because it is an expensive, invasive, and unpleasant surgery. While urinary cytology lacks sensitivity in low-grade cancers, it has a better specificity of 85% to 100% and a high sensitivity in high-grade tumours, EAU Guidelines suggest deferring surveillance cystoscopy by 6 months show in [2, 3] (Figure 1).

New, noninvasive techniques with increased sensitivity and specificity could be very helpful for the management of patients with primary BCa diagnosis and postoperative surveillance. In these situations, urinary cancer development or metabolism products are extremely relevant, accessible, and acceptable for BCa screening. The FDA-approved BTA assays (BTA TRAK® and BTA stat® from Polymedco) and the Alere NMP22® BladderChek® Test are used for the diagnosis and monitoring of BCa in conjunction with conventional diagnostic procedures. Urine tests for diagnosis and recurrence detection have also been developed. Compared to urine cytology, which has a median sensitivity of only 35%, they produce results with enhanced sensitivity (up to 89%) [4,5].

Yet benign urological problems frequently affect these tests' specificity. They exhibit less specificity than urinary cytology: the median specificities of BTA TRAK, BTA stat, and NMP22 are 66%, 73%, and 73%, respectively, compared to 94% for urinary cytology. Urinary indicators often have a higher sensitivity but a lower specificity than urine cytology, according to a recent assessment. Evaluating the performance of 18 markers, the review also assessed marker performance in the setting of BCa surveillance with relation to the detection of recurrent bladder cancer and discovered that most markers had poorer sensitivity compared to their performance for original disease detection. Hence, single indicators cannot yet be used in any clinical surveillance programme to enable patients to have cystoscopy examinations less frequently [6, 7].

The urine test should perform well in terms of sensitivity and specificity. Using numerous markers in a multiplexed assay might offer a strategy for improving a BCa recurrence detection test since this is obviously not doable with single markers. Our team conducted a preliminary (pilot) investigation to uncover a collection of prospective biomarkers with potential therapeutic value in BCa. A molecular disease model for BCa served as the basis for the decision [8]. Following that, the potential markers' measurability, detectability, and BCa selectivity were assessed in urine samples. A five-biomarker panel (IL-8, MMP-9, VEGF-A, PTGS2, and EN2) was developed as a result of this pilot investigation, and it performed better overall than the individual

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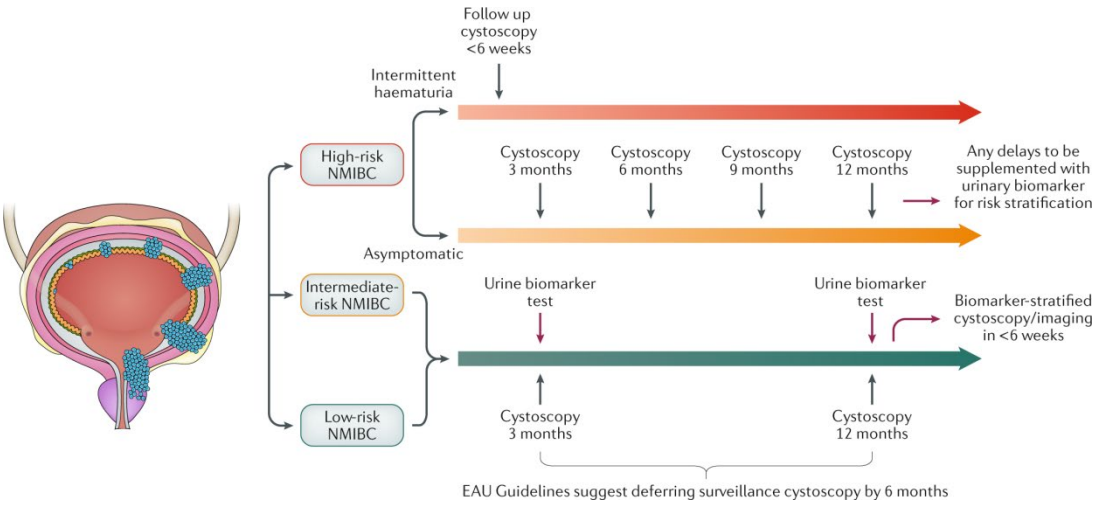

Figure 1: EAU Guidelines suggest deferring surveillance cystoscopy by 6 months.

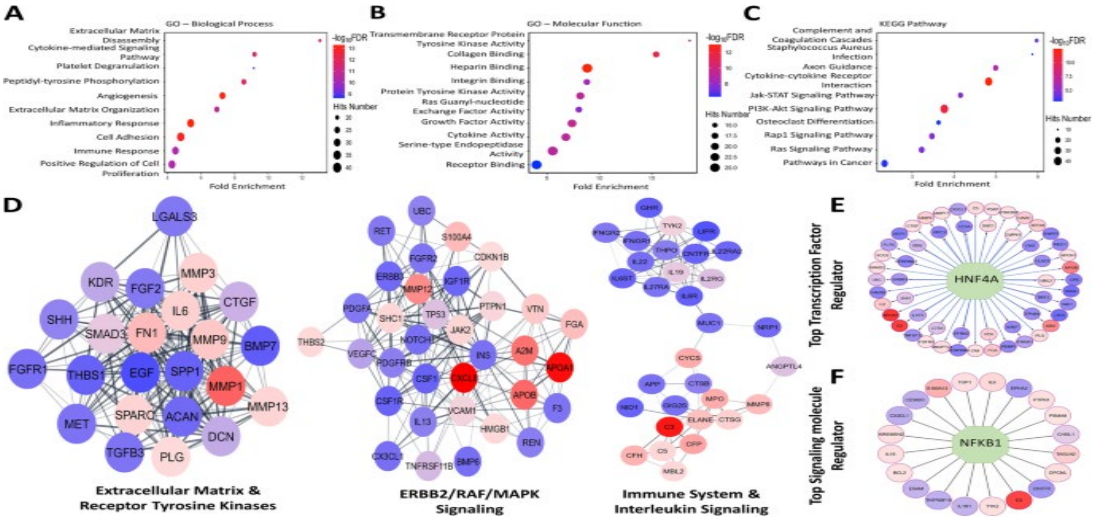

Figure 2: Biomarkers for bladder cancer diagnosis and staging.

markers. This study solely looked into the diagnostic side of de novo BCa since it compared a group of BCa patients to a group of healthy donors [9].

In this paper, we discuss a second (discovery) study which aims at identifying a marker panel for BCa recurrence diagnosis. Urine samples from BCa patients with recurrence and BCa patients without recurrence were examined for the presence of the biomarkers chosen in the pilot study as well as additional pertinent potential indicators of the molecular disease model. A multiplexed microarray (BCa chip) and an automated platform for 96-well plate ELISA analysis were used for the marker measurement. In order to identify a panel of biomarkers and clinical parameters for the diagnosis of BCa recurrence, results from both platforms were integrated with clinical parameters for a multivariate statistical analysis [10].

Materials and Methods

A bio bank with 80 samples from BCa patients was available to us. 19 markers in all were counted. The measurements of the markers were conducted on two platforms, and the outcomes were analysed statistically together with the clinical data of the patients. In the sections following, each stage of the investigation is thoroughly explained. Patients were chosen based on the following inclusion criteria: BCa diagnosis (cystoscopy and histological evidence of BCa), BCa treatment prior to sample collection visit, and absence of muscle invasive BCa in the patient's past. Recurrence-negative patients are those who don't exhibit any cystoscopy or histological signs of BCa during follow-up after de novo BCa treatment. Patients who test positive for recurrence must have cystoscopy and histological signs of BCa during follow-up following de novo BCa treatment [11].

According to usual operating protocol, first pass urine samples were taken from the chosen bladder cancer patients and spun at 150 g for 10 minutes. The supernatant was divided into 1 mL samples, frozen, and kept at a temperature of 80°C. All donors provided their informed consent before donating a sample, and the local ethics committee accepted the collection (ref. 3/LO/0739). On a monitoring visit, the samples were taken [12]. There are at least two monitoring visits available for each sample: one for the initial diagnosis and one for the moment the sample was taken. Up to four visits after sample collection and up to six additional visits between the initial diagnosis and the time of the sample have been documented. Gender, age, smoking status, date, grade, stage, recurrence, TURBT (transurethral resection of the bladder tumour), and medication use were all recorded during the monitoring

sessions (name and start date) [13].

45 samples from the initial bio bank of 80 samples could be included in the analysis, representing 27 patients who had recurrences that were negative and 18 patients who had recurrences that were positive, depending on the availability of the full set of clinical phenotype parameters and the availability of valid biomarker readouts [14].

Discussion

Because BCa recurrence is so common, surveillance is an important part of patient care. Hence, enhanced techniques for evidence-based risk assessment, which would affect surveillance strategy, could have significant clinical benefits. After transurethral resection, the European Organization for Research and Treatment of Cancer (EORTC) has created a grading system to identify the short- and long-term risks of cancer progression and recurrence [15]. Only conventional clinical and pathological predictors of outcomes are used in this grading system (tumor stage and grade, number of tumors, tumour size, concomitant CIS, and history of prior disease recurrence). The EORTC risk tables have serious flaws, and new parameters and updates could enhance the risk classification. The clinical relevance and accuracy of prognostic and prediction tools in BCa could be enhanced by biomarkers, biomarkers for bladder cancer diagnosis and staging [16] (Figure 2).

Biomarkers have only recently been included as parameters in prediction systems in a small number of studies. A panel of five cell cycle regulatory biomarkers, including cyclin E1, p53, p21, pRB, and p27, were found to increase the predictability of BCa recurrence and survival following cystectomy in patients with pTa-3N0M0 tumours. In a different study, Rosser et al. assessed the effectiveness of a 10-biomarker panel (IL-8, MMP-9, MMP-10, SERPINA1, VEGF-A, ANG, CA9, APOE, SERPINE1, and SDC1), which outperformed any single biomarker and had a higher sensitivity (79%) than urine cytology (33%) for the diagnosis of recurrent BCa [17].

In our discovery project, we assessed the possibility of various clinical and biomarker indicators for diagnosing BCa recurrence. Clinical data alone are insufficient to diagnose recurrence, according to individual parameter performance analysis. Furthermore, no one biomarker candidate performed satisfactorily on its own. We found multiple multivariable regression models by combining the clinical and molecular factors. The model with the greatest performance (Model 6) has an AUC of 0.91, outperforming the single parameters. It includes the following clinical factors and biomarker candidates that were automatically chosen (using LASSO): cadherin-1, IL-8, ErbB2, IL-6, EN2, and VEGF-A. It also includes the number of BCG treatments [18].

All of the chosen biomarkers indicate a possible role for detecting BCa recurrence, even though ties to recurrence or its mechanism have not yet been definitively demonstrated for any of them. It seems like a decent idea to combine these markers with clinical criteria in order to diagnose BCa recurrences with acceptable accuracy. A panel of this kind will enable the creation of patient-specific profiles and may significantly enhance recurrence detection [19]. Notwithstanding the potential for the development of a new BCa surveillance tool demonstrated by our findings, numerous study limitations must be taken into account. Moreover, due to strict selection criteria, the study only uses a tiny number of samples Also; the study's design only permitted evaluating the diagnosis of BCa recurrence, providing no data on the condition's prognosis. Our findings must be confirmed by a different cohort, as required [20].

Conclusions

In conclusion, because cancer is a complicated disease that cannot be detected by a single biomarker, it is anticipated that the study of a profile of biomarkers will be more effective for this purpose. Choosing biomarkers that represent early tumour growth and disease activity is still a difficulty. Our multiplatform approach enabled the evaluation of 19 urinary markers for the diagnosis of BCa recurrence, and it resulted in the selection of six markers and three clinical factors establishing a panel for patient segmentation. This multipara meter panel performed better for diagnosing BCa recurrence than any one biomarker or clinical parameter, and it may be an effective tool for BCa surveillance plans.

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Acknowledgment

None

Conflict of Interest

None

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