NMIBC Risk Calculators
How Useful Are They for the Practicing Urologist and How Can Their Clinical Utility Be Improved?

Rianne J.M. Lammers, MD[a], Richard J. Sylvester, ScD[b], Cheryl T. Lee, MD[c], J. Alfred Witjes, MD, PhD[a,*]

KEYWORDS

• Non-muscle invasive bladder cancer • EORTC • Risk table • Prognostic model

KEY POINTS

- The natural history of non-muscle invasive bladder cancer in individual patients can be unpredictable.
- Although there are known clinical and molecular factors associated with tumor recurrence and progression, it is challenging to reconcile these data during a typical patient encounter within a busy clinic.
- Prognostic models, such as risk tables and nomograms, aim to facilitate risk stratification, patient counseling, and treatment decision making.
- There are many prognostic models available for non-muscle invasive bladder cancer, but they are not commonly used in daily practice because of their complexity and limited usefulness in treatment decision making.
- To make prognostic models more useful, the focus should be on the clinical implications of the model for the patient, such as by focusing on negative and positive predictive value, rather than *P* values, sensitivity, and specificity. The net benefit of the model should be compared with the standard model by means of classification tables and decision analytic techniques to test its additional clinical value.
- Biomarkers do not have sufficient additional value, and markers undergoing investigation should first stand the test of time.
- Ultimately, even good models will not be translated into clinical practice unless they can be integrated into the standard clinical workflow.

BACKGROUND

Overall, bladder cancer (BC) is the seventh most common malignancy in men and the 17th in women.[1] The incidence increases with age and is highest at 50 to 70 years of age. Eighty percent of patients with BC are men.[2] Important risk factors are chemical and environmental exposures, such as smoking and aromatic amines, and chronic irritation.[3,4] In the Western world,

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[a] Department of Urology, Radboud University Medical Centre, Geert Grooteplein Zuid 10 (659), P.O. Box 9101, Nijmegen 6500 HB, The Netherlands; [b] Department of Biostatistics, EORTC Headquarters, 83 Avenue E. Mounier, Brussels 1200, Belgium; [c] Department of Urology, University of Michigan, 7303 CCGC, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0946, USA
* Corresponding author.
E-mail address: f.witjes@uro.umcn.nl

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more than 90% of BC are urothelial carcinomas or transitional cell carcinoma.[5]

On average, 70% of patients with BC present with non-muscle invasive BC (NMIBC) and the remainder with muscle-invasive disease (MIBC). In the non-muscle invasive group, approximately 70% present as Ta lesions (noninvasive papillary carcinoma), 20% as T1 lesions (invasion into subepithelial connective tissue), and 10% as carcinoma in situ (CIS or Tis lesions; high-grade noninvasive flat tumor).[6] For grading, both the World Health Organization's (WHO) 1973 and the WHO's 2004 classifications are advised. The WHO's 1973 grading system recognizes 3 groups: grade 1 to 3. The WHO's 2004 classification defines 4 groups of papillary lesions: urothelial papilloma (benign), papillary urothelial neoplasm of low malignant potential, low-grade papillary urothelial carcinoma, and high-grade papillary urothelial carcinoma.[7] For staging, the TNM classification is used.[8]

Another way to stratify patients is by prognostic factors and, thus, outcome. The European Organization for Research and Treatment of Cancer (EORTC) developed a prognostic model for recurrence and progression for patients with NMIBC,[9] which the authors discuss in this article. Other prognostic models with applications in urological practice have been created recently using other techniques: nomograms, neuro-fuzzy models, and artificial neural networks (ANN).

The most well-known prognostic model is the risk table, which divides patients into risk groups based on their score. It gives the probability of an event (recurrence, progression) for patients within a given risk group. It assumes that all patients within a given risk group have a similar prognosis; however, the choice of cutoff values when stratifying patients into groups is somewhat artificial. It is unlikely that all patients within a given group will have the same prognosis, and patients with similar scores who fall into different risk groups might not have different prognoses. Furthermore, when one variable is missing, it is not possible to calculate the probabilities. Nevertheless, risk tables can easily identify the very low- and very high-risk patients.

A nomogram is a graphical device that is used to calculate an individual patient's probability of an event based on a multivariable model with their specific prognostic factors and, hence, gives a more individualized risk calculation. Nomograms are based on a (continuous) score, whereas risk tables subdivide patients into different categories based on their score. They provide a more individualized probability of the event of interest, and software is usually developed to make them easy to use. Because the nomogram probabilities come directly from the multivariable model, it is important that the model is well calibrated, that is, it has an excellent goodness of fit. Otherwise, the probabilities provided by the model will be incorrect. However, when one of the variables is missing for a patient, the nomogram cannot be used for that patient. As mentioned by Hernandez and colleagues,[10] nomograms are usually developed with very large series, and it has to be determined if they are applicable to lower-volume centers.

More advanced prognostic models are neuro-fuzzy models and ANN. The latter is a mathematical model based on a biologic neural network. It can handle complex relationships between input and output and can find patterns in the data. ANN are adaptive systems that can change their structure during the learning phase. A neuro-fuzzy model is a combination of an ANN and fuzzy logistics, which is a form of logistics that can handle reasoning. Because there is little experience in NMIBC with these models, they are not discussed further.

In the next paragraphs, the advantages and disadvantages of the most well-known prognostic model, the EORTC risk tables, are discussed. Then, several other NMIBC prognostic models are described; the authors discuss the lack of use of prognostic models in the daily urological practice. Finally, the authors provide a future perspective on prognostic models: how should we develop and use prognostic models for patients with NMIBC?

EORTC RISK TABLES

Development of the EORTC Risk Tables

In 2006, Sylvester and colleagues[9] published the EORTC scoring system for NMIBC. They combined individual patient data of 2596 patients from 7 EORTC trials (inclusion period: January 1979–September 1989). The aim was to provide simple tables that would allow urologists to easily calculate the probability of recurrence and progression after transurethral resection of the bladder tumor (TURBT) for patients with NMIBC. The most appropriate adjuvant treatment after TURBT and the frequency of follow-up can then be determined in an individual patient based on their prognosis. Data on patient and tumor characteristics and the endpoints of time to first recurrence and time to progression to MIBC were merged. The most important variables were then determined by regression models. Patients were divided into 4 risk groups for both recurrence and progression according to their total score. Probabilities of recurrence and progression at 1 year