Prediction tools in non-muscle invasive bladder cancer

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Abstract: Non-muscle invasive bladder cancer (BCa) is the second most common genitourinary malignancy, burdened by high rates of recurrence and progression. Urologist are encouraged to stratify patients on the bases of recurrence and progression risks in order to define the best therapeutic approach and follow-up scheme. For these reasons, the aim of the present non-systematic review was to assess the literature on prediction tools in non-muscle invasive BCa. Currently, the most widely used tools remain the European Organization for Research and Treatment of Cancer (EORTC) and the Club Urologico Espanol de Tratamiento Oncologico (CUETO) risk tables, which are based on clinicopathologic features. Recent external validations, therefore, reported their low accuracy, probably related to the lack of the role of re-transurethral resection (TURBT), early instillations, chemotherapy and complete BCG schedules in the studies included to asses these scores. More recently several immunological, biochemical and genetics biomarkers have been tested by themselves and in combination with clinicopathologic features, and many of them resulted related with risk of recurrence and progression. Future perspectives will presumably include the update of EORTC and CUETO scores with newest guidelines' recommendations and their integration with biomarkers.

Keywords: Bladder cancer (BCa); non-muscle invasive; NMIBC; tools; progression; recurrence

Introduction

Bladder cancer (BCa) is the second most common genitourinary malignancy with 81,190 estimated new diagnosis in 2018 in the United States only (1). Approximately 75–85% of all patients with BCa present at diagnosis a non-muscle invasive BCa (2). Therefore, this condition is very heterogeneous, and it is burdened by variable but high rates of short- and long-term recurrence and progression. Given the availability of several therapeutic options such as surveillance after resection, single instillations, intravesical therapy with chemo- or immunotherapeutic agents and

early cystectomy, a risk-based therapeutic approach should be always applied by urologists to propose the most efficient treatment for each case. Moreover, despite the clinical similar characteristics of diseases, the response to intravesical chemotherapy is variable and the follow-up should be always targeted on the risk of recurrence and progression.

Finding clinical, pathological and molecular features seems to be more and more necessary for stratifying patients in groups with different prognosis, and consequently to help urologist in the decision making of non-muscle invasive BCa. This review highlights the current available tools to predict risk of recurrence and progression in non-muscle invasive BCa.

Evidence acquisition

We searched the Medline/PubMed databases for the comprehensive information on the prediction tools in non-muscle invasive BCa. The terms used for the search included "bladder cancer", "non-muscle invasive", "NMIBC", "BCa", "tools", "prediction", "predictors", "recurrence", "progression", "clinical", "molecular", "biochemical".

Clinical predictors

European Organization for Research and Treatment of Cancer (EORTC) and Club Urologico Espanol de Tratamiento Oncologico (CUETO) risk tables

In 2006, EORTC proposed risk assessment tables to predict short- and long-term recurrence and progression in non-muscle invasive BCa and currently this is the most frequently applied and validated model (3). Data of 2,596 patients with Ta and T1 neoplasms, included in seven EORTC randomized studies between January 1979 and September 1989, were analyzed. This tables are founded on clinical/pathologic characteristics which showed the strongest association with outcomes. These variables included tumor stage, grade [World Health Organization (WHO) 1973] (4), number of tumors, size of tumors, presence of concomitant carcinoma in situ (CIS) and previous disease recurrence. A multivariable analysis was built to assess a weight score for each factor. The recurrence risk-table includes a score from 0 to 17 whereas the progression score is from 0 to 23, and patients were divided in four prognostic groups. However, 21% of the patients included in these studies have not been treated with intravesical therapy and patients who received Bacillus Calmette Guerin (BCG, 7%) have been treated with induction course but not with maintenance.

On the contrary, the Club Urologico Espanol de Tratamiento Oncologico (CUETO) proposed risk-assessment tables to predict short- and long-term risk of recurrence and progression specifically for patients treated with BCG. The results were based on analyses on 1,062 patients who received BCG instillations: the scoring system was calculated with a score from 0 to 16 and from 0 to 14 for recurrence and progression, respectively. It was based of seven variables which include age, gender, prior recurrence, number of tumors, tumor stage and grade, and presence of concomitant CIS. Patients were classified into four groups by score.

External validations of EORTC and CUETO risk tables

Several studies have been performed to externally validate these two scoring systems. Xylinas et al. (5) evaluated their efficacy on 4,689 patients, founding that both risk tables overestimate disease recurrence and progression. Same result was reported by Fernandez-Gomez et al. (6), who found that the EORTC score overestimates the risk of recurrence and progression in patients treated with BCG. Moreover, when the EORTC data have been applied to the CUETO model, an underestimation of the risk of recurrence in low-risk patients and an overestimation of the risk of progression in high risk patients have been found (7). A multicenter European study was performed to external validate both EORTC and CUETO scores an found a poor ability of discrimination for recurrence and moderate for progression (8). Given the results of these studies, and especially the overestimation found when external data were applied to these two scores, it has been demonstrated that the EORTC and CUETO models are valid tools, but they probably need to be updated and recalculated with other variables such as the performance of re-transurethral resection (TURBT), early instillations, chemotherapy, complete BCG schedules and 2004 WHO grading classification system.

Other risk tables

Before the development of EORTC and CUETO risk scores other models of risk-stratification were proposed. In 1989 the British Medical Research Council (9) found variables related to the risk of recurrence in patients with primary superficial BCa: patients were stratified into 3 groups based on the result on the endoscopic evaluation at 3 months follow up and the presence of multifocal/monofocal disease at the initial TURBT. Later, Millán-Rodríguez et al. (10) found several factors related to the risk of recurrence and progression in 1,529 patients with a new diagnosis of non-muscle invasive BCa and they stratified the population in 3 risk-groups based in number of tumors, grade and stage.

Other clinical predictors

Several studies have shown the relationship between anemia and poor oncological outcomes in patients with BCa treated with radical cystectomy (11,12). More recently this factor was studied in patients with non-muscle invasive diseases (13)

and was found as well associated with increased recurrence and progression. Similar result was reported for the neutrophil-to-lymphocyte ratio (NLR).

Nomograms

In the last 15 years several nomograms to predict the risk of recurrence and progression were proposed. Shariat *et al.* (14) published in 2005 a nomogram developed on 2,681 patients with previous diagnosis of Ta, T1 or CIS. Each patient was evaluated with urinary cytology, cystoscopy and urinary matrix protein 22 (NMP22). In case of suspicion of BCa, patients underwent bladder biopsies. After assessing relationship between variables and recurrence with a multivariable analysis, three nomograms were developed to predict, first of all, the risk of recurrence of transitional cell carcinoma in general, secondly the risk of recurrence of Ta-T1-Tis G3 diseases and lastly the risk of recurrence of T2 tumors. Variables included in these nomograms were age, gender, NMP22 dichotomized and the result of cytology. Later Hong *et al.* (15) proposed a nomogram to predict disease recurrence in patients with newly diagnosed Ta, T1 BCa. 1,587 patients were included in this multicenter study between 1998 and 2002. Variables included in the nomograms were age, tumor size, number of tumors, grade, presence of concomitant CIS and administration of intravesical therapy. Pan *et al.* (16) developed a nomogram to predict cancer specific-and progression free survival based on age, WHO/ISUP grade, T stage and intravesical instillations. Yamada *et al.* (17) found that number of tumors, shape, grade, and administration of intravesical therapy were significantly associated with recurrence-free survival whereas tumor shape and grade with progression-free survival. Six factors were included in the nomogram predicting recurrence and three for the one predicting progression.

Biomarkers

Urinary fluorescent in situ hybridization (FISH)

UroVysion (Abbott Molecular Inc., Des Plaines, IL, USA) is a cytology-based test that uses FISH to detect cells with alteration of chromosomes. It was initially developed for BCa-detection but more recently he has been applied for predicting BCG-failure in non-muscle invasive BCa. Kamat *et al.* (18,19) published results of a prospective randomized controlled trial including more than one hundred patients submitted to FISH before and during BCG treatment,

founding that patients with positive FISH during the instillation had 3- to 5-fold increased risk of developing a recurrence compared to those with a negative FISH and 5 to 13 fold increased risk of developing progression (P<0.01). Moreover, the timing of positive FISH played an important role in prediction of failure: patients with a negative FISH result at baseline, 6 weeks, and 3 months had 8.3% recurrence rate versus 48.1% of patients with a positive test at all three analyses. The phenomenon characterized by a positive FISH test with a negative cystoscopy has been called "molecular failure".

Other molecular biomarkers

Several biomarkers were studied as predictors of the potential response in patients with non-muscle invasive BCa treated with intravesical instillation. The most studied biomarker is p53 and several studies have analyzed its role in BCa on the basis of previous findings reporting anomalies of p53-expression in other type of neoplasms. The majority of the studies found that the overexpression of this gene was associated with progression but not with recurrence. However, as shown in a metanalysis (20), the results were conflicting, probably because of the differences in design of the study, criteria of inclusion, techniques of tissue sampling and analyses and different definition of progression, and consequently the role of p53 in BCa is still not clear. The role of retinoblastoma protein (pRb) was analyzed in patients with non-muscle invasive BCa and an altered expression of pRB was found associated with recurrence and progression after treatment with BCG alone or BCG plus interferon-alpha (IFN-alpha) (21,22). Even the level of survivin (an apoptosis inhibitor) in urine, was found associated with recurrence in patients treated with BCG or mitomycin C: the presence of urinary surviving one month after finishing intravesical instillation predicts tumor recurrence with 100% sensitivity and 78% specificity. Moreover, the specificity increases to 92% after one year from the completion of the treatment (23). Other molecules have been studied included bcl-2, E-cadherin, Ki67, CK20 and ezrin but in conclusion, none of them have been approved for the detection of recurrence or progression after intravesical instillation since the studies were very heterogenous and reported conflicting results.

Cytokines and immunological markers

Several cytokines were evaluated as predictors of response to

intravesical BCG. The most studied one is interleukin (IL)-2. It has been demonstrated that reduced levels of IL-2 are related to risk of recurrence, progression, leukocyturia and adverse events in patients treated with BCG for CIS (24). Other urinary cytokines have been found as potential predictors of response to BCG treatment, such as IL-8 and 18 (25), IL-6/10 ratio (26,27), tumor necrosis factor (TNF)-alfa (28), IL-12 (29), and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (30,31). However, cytokines' urinary concentration can be altered by urinary tract infections, inflammatory processes and systemic infections therefore there are potential pitfalls by using these molecules.

Programmed death-ligand 1 (PD-L1) is a transmembrane protein ligand which can be found on tumor cells whereas its receptor, is expressed on the surface of the T cell: their bond determines the deactivation of T cells. High levels of PD-L1 were found in BCG granulomata patients failing BCG treatment (32). However, a recent study did not find a significant association between PD-L1 positivity and outcomes in T1 high grade non-muscle-invasive BCa after BCG induction therapy (33). Therefore, HLA-G is an immune checkpoint molecule that is commonly neo-expressed by solid tumors, included BCa. Its main receptor is ILT2/CD85j and it is expressed on some T lymphocytes: the bond between the ligand and its receptor suppresses the function of natural-killer cells, dendritic cells, cytotoxic T lymphocytes, CD4$^+$ T lymphocytes and the proliferation of T cells. A recent study (34) analyzed the role of ILT2 on recurrence in non-muscle invasive BCa. This study reported a significant association between the proportion of circulating CD8$^+$ILT2$^+$ T cells and risk of recurrence. The role of other several immunological markers on prediction od recurrence and progressions have been tested (29,35-37). Studies evaluating the role of cytokines and immunological markers are summarized in *Table 1*.

Gene based biomarkers

Several studies evaluated genetic biomarkers as predictors of recurrence and progression of non-muscle invasive BCa, and these genes were tested in combination or not with clinicopathologic characteristic to assess a risk-stratification. Pichler *et al.* (35) found several genetic polymorphisms involved in BCG mechanism of action analyzing data of 204 patients who underwent BCG instillations and some of them were found related to risk of progression. Moreover, a risk-score model based on

the result of this study was built, and an area under the curve of 82% was found when these genes were added to clinicopathologic features (35). Dyrskjøt *et al.* (38) evaluated the role of 12 gene: a 12-gene progression score was built and it was found as independent prognostic factor beyond clinical and histopathological risk factors. Another study found the role of 42 genetic polymorphisms which were used to develop a risk to predict BCG response (39). Polymorphisms impairing cellular DNA damage repair (DDR) showed a significant relationship with recurrence in patients treated with BCG (40). This result was confirmed by a recent study, which showed relationship between DDR gene alterations (in particular ARID1A mutations) and the increase risk of recurrence after BCG (39). Moreover, GSTP1 and GSTO1 were found associated to recurrence in patients treated with intravesical epirubicin but not with those treated with mytomicin C (41).

CUETO and EORTC risk tables in combination with biomarkers

Several markers have been integrated to EORTC and CUETO scores. The molecular grade based on fibroblast growth factor receptor 3 (FGFR3) gene mutation status and MIB-1 expression have been tested in a multicenter study which included data of 230 patients with non-muscle invasive bladder tumors (42): the addition of the molecular grade increased the accuracy of the EORTC score from 74.9% to 81.7% (P<0.001). On the contrary, the addition of five biomarkers (p21, p27, p53, KI-67, and cyclin E1) to both CUETO and EORTC scores demonstrated only a little benefit (43) and the biomarker status was not associated to recurrence and progression.

Conclusions

EORTC and CUETO score remain the most used tools to predict recurrence, progression and treatment response, in non-muscle invasive BCa. The accuracy of both scores is currently low and an update with the newest recommendation of guidelines is needed. Several immunological, genetic and molecular biomarkers have been more recently tested and have shown to have a role as tools in prediction of non-muscle invasive BCa. Future perspectives include the combination between clinical-pathological features and molecular biomarkers to facilitated and improve patient stratification.

Table 1 Summary of studies evaluating the role of cytokines and immunological markers on prediction pf recurrence and progression of non-muscle invasive bladder carcinoma

Study	Year	Design	Predictor	Sample	Stage	Intravesical therapy	Results
Cytokines							
Thalmann et al. (25)	2000	Prospective	IL-8, IL-18	Urine	Ta, T1, CIS	BCG	High level of IL-8 in the first 6 hours after BCG instillation predictor of recurrence-free survival; high level of IL-18 in the first 12 hours after BCG predictor of recurrence-free survival
Saint et al. (24)	2003	Prospective	IL-2, IL-10	Urine	Ta, T1, CIS	BCG	IL-2 overproduction predictor of higher recurrence- and progression-free survival
Ludwig et al. (30)	2004	Prospective	TRAIL	Urine	Ta, T1, CIS	BCG	Predictor of BCG response
Shintani et al. (28)	2007	Prospective	GM-CSF, TNF-alpha, G-CSF, IL-1beta, IL-8, IFN-gamma, and IL-12	Urine	Ta, T1, CIS	BCG	High level if TNF-alpha 4 h after the instillation predictor of low recurrence
Cai et al. (26)	2007	Prospective	IL-6, IL-10	Urine	Ta, T1, CIS	BCG	IL-6/10 predictor of recurrence
Kamat et al. (31)	2016	Prospective	IL-6, IL-1ra, IL-2, IL-1b, IL-8, IL-10, IL-12 (p40), IL-12 (p70), IL-18, IFN-g, TNF-α, and TRAIL	Urine	Ta, T1, CIS	BCG	CyPRIT nomogram score predictor of recurrence
Immunological markers							
Nunez-Nateras et al. (37)	2014	Retrospective	Th1 and Th2 immune response	Tissue	CIS	BCG	Pre-existing Th1 immunologic response within the tumor predictor of BCG-failure
Pichler et al. (35)	2016	Prospective	Tumor-associated macrophages (TAMs; CD68, CD163); B lymphocytes (CD20); T-lymphocyte subsets (CD3, CD4, CD8, GATA3, T-bet, FOXP3, and CD25)	Tissue	Ta, T1, CIS	BCG	CD4$^+$ and GATA3$^+$ T cells predictors of prolonged recurrence-free survival; TAMs, Tregs, and T-bet+ T cells predictors of shorter recurrence-free survival
Pichler et al. (29)	2017	Prospective	Th1 (neopterin, tryptophan, kynurenine, kynurenine-to-tryptophan ratio (KTR), IL-12, IFN-g, soluble TNF-R75 and IL-2Ra); Th2 components (IL-4, IL-10)	Blood urine tissue	Ta, T1, CIS	BCG	GATA3/T-bet ratio, neopterin, and KTR predictor of response
Chevalier et al. (36)	2017	Prospective	T cell to MDSC ratio	Urine	Ta, T1, CIS	BCG	T cell to MDSC ratio <1 predictor of lower recurrence-free survival
Wankowicz et al. (33)	2017	Prospective	PDL-1	Tissue	T1	BCG	No correlation
Desgrandchamps et al. (34)	2018	Prospective	CD8$^+$ILT2$^+$ T cells	Tissue blood	Ta, T1, CIS	BCG or chemotherapy	CD8$^+$ILT2$^+$ T cells and risk of recurrence

CIS, carcinoma in situ; BCG, bacillus Calmette-Guérin.

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Footnote

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

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