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## Platinum Priority – Editorial and Reply from Authors

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# How Well Can You Actually Predict Which Non–Muscle-Invasive Bladder Cancer Patients Will Progress?

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In 2006, the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Group published risk tables that provide the probabilities that a patient with stage Ta T1 bladder cancer will recur or progress to muscle invasion after transurethral resection of bladder tumor (TURBT). The tables are based on six different disease characteristics: number of tumors, tumor size, prior recurrence rate, T category, histologic grade, and presence of concomitant carcinoma in situ [1]. The European Association of Urology (EAU) has subsequently adopted these tables in its treatment guidelines, dividing non–muscle-invasive bladder cancer (NMIBC) patients into low-, intermediate-, and high-risk groups for recurrence and for progression and then tailoring the treatment according to these risk groups [2].

The seven studies included in the EORTC risk tables randomized a total of >2500 patients and had a maximum follow-up of almost 15 yr. However, certain limitations of these tables were already acknowledged in the original publication [1]. Twenty-two percent of the patients were randomized to receive no intravesical treatment after TURBT, 72% were randomized to intravesical chemotherapy, and 6% were randomized to intravesical bacillus Calmette–Guérin (BCG) but without maintenance. Because these studies included patients randomized between January 1979 and September 1989, patients were not always treated in accordance with the current EAU guidelines [2]. In particular, no high-risk patients had a second TURBT shortly after the initial resection and none received maintenance BCG. In addition, less than one-quarter of the patients received an immediate instillation after TURBT. Fluorescence cystoscopy/TURBT was not yet available at that time. Consequently, many patients were undertreated according to today's guidelines.

For these reasons, the recurrence and progression rates reported in the EORTC risk tables are likely to be higher than those that would be encountered in current-day clinical practice, especially in the high-risk patients for whom maintenance BCG has been found to be effective in reducing the risks of both recurrence and progression [2]. External validation of the EORTC risk tables is necessary to determine their applicability in current-day clinical practice.

Only a few papers attempting to validate the EORTC risk tables have been published. Van Rhijn et al [3] successfully validated the EORTC risk scores in 230 Dutch patients with primary NMIBC who were diagnosed between 1983 and 2000. Limitations of this validation include the heterogeneity of the different adjuvant intravesical treatments used, the treatment of patients not necessarily in accordance with the current EAU guidelines due to patients' dates of diagnosis, the small sample size, the restriction to primary patients, and the fact that no patients at high risk of recurrence were included. Nevertheless, this paper provides the first real external validation of the EORTC risk tables.

More recently, a cohort of 592 Japanese patients treated from 2004 to 2006, half of whom received no intravesical treatment after TURBT, has been used to try to validate the EORTC risk scores for recurrence. More than 90% of the patients were classified as intermediate risk, so its usefulness is limited. However, a difference in time to recurrence was found between the two EORTC intermediate-risk-score groups [4].

In a Spanish study of 417 Ta T1 patients treated between 1998 and 2008, the majority of whom had a single tumor (70%) or a Ta tumor (58%), two-thirds of the patients received only a single instillation of mitomycin C. The authors found probabilities of recurrence and progression

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that were more or less similar to those published by the EORTC, and they concluded that the EORTC risk tables accurately predicted the clinical course of their patients [5]. The validation of progression, however, is limited by the fact that only 34 patients progressed.

One of the most important limitations of the EORTC risk tables is that only 6% of the patients received induction BCG and none received maintenance. The Club Urológico Español De Tratamiento Oncológico (CUETO) study published in this issue is the first to attempt a validation of the EORTC risk tables in a large series of patients treated with BCG [6]. Included in the analysis were 1062 patients who were to receive 12 instillations of BCG over 5–6 mo between February 1990 and May 1999. Several important conclusions can be drawn from this study. The EORTC risk tables were still able to successfully divide the CUETO patients into four risk groups for both recurrence and progression. For the patients with the best and worst prognoses, there was a smaller separation between curves for time to recurrence and time to progression, except for recurrence at 5 yr. In contrast, the EORTC risk tables overestimated the risk of recurrence in all recurrence risk groups. For progression, the EORTC risk tables overestimated the risk of progression in the high-risk patients, especially at 5 yr. Thus although the EORTC risk tables provided adequate discrimination between patients with different prognoses, their calibration was poor.

The fact that the EORTC risk tables overestimated the probabilities of recurrence and progression is not surprising because it is consistent with the increased efficacy of BCG, which was used in the CUETO studies but not in those of the EORTC. However, the overestimation using the EORTC risk tables might have been even more extreme if recent changes in clinical practice that are likely to further reduce the risks of recurrence and progression had been used in the CUETO studies. These changes include fluorescence cystoscopy/TURBT, a second TURBT, an immediate instillation of chemotherapy after TURBT, and 3 yr of maintenance BCG.

Long-term follow-up is not available for patients treated according to the current EAU guidelines, so the degree by which the EORTC and CUETO scoring systems overestimate the risks of recurrence and progression in current clinical practice is unknown. Long-term follow-up is needed, but by the time it is available, treatment practices may have already changed, thus making it difficult to validate new scoring systems for use in current-day clinical practice.

One would like to use the EORTC and CUETO scoring systems to be able to accurately predict which patients will progress to muscle-invasive disease, but the positive predictive value (PPV) of both scoring systems is extremely poor. Using a cut-off score of  $\geq 7$  as the definition of high risk of progression, in the EORTC series, 64% of the patients who progressed were classified as high risk (sensitivity), 94% of the non-high-risk patients did not progress (negative predictive value [NPV]), and only 21% of the patients classified as high risk for progression actually progressed (PPV).

In the CUETO series, application of the EORTC scoring system yielded a sensitivity of 88% and an NPV of 95% but a PPV of only 17%. Use of the CUETO model for progression with the authors' own patients (using a cut-off of  $\geq 7$  to

define high-risk patients) yielded a sensitivity of 60%, an NPV of 92%, and a PPV of only 24% [7]. Although both the EORTC and the CUETO scoring systems can accurately predict which patients will not progress to muscle-invasive disease (NPVs  $>90\%$ ), neither scoring system can accurately identify which patients will actually progress (PPVs  $<25\%$ ).

It is clear that the accurate identification of which NMIBC patients will actually progress to muscle-invasive disease is a major problem. The PPV of current models is woefully inadequate. Molecular markers have been proposed as a way of providing new, potentially important information related to the biology of the disease and patient prognosis, eventually leading to the development of more effective, individualized patient therapies [8]. However, to determine the true value of a new molecular marker or gene expression classifier, it is not sufficient to show that, by itself, it is significantly related to the outcome of interest. It also is not sufficient to show that it is statistically significant in a multivariate model including the classical clinical and pathologic factors or even that it is more significant than these other factors in the multivariate model. To be useful in the clinic, one must ask the more stringent and difficult question of whether the addition of molecular markers and gene expression profiling to currently existing prognostic models based on clinical and pathologic factors actually increases their predictive accuracy and, more specifically, their PPV [9].

There is now evidence that the molecular grade based on FGFR3 mutation and MIB-1 expression increases the predictive accuracy of the EORTC risk scores for progression [3]. Likewise, the expression signature of E2F1 and its associated genes appears to increase the predictive accuracy of various clinical and pathologic factors related to progression [10]. However in neither case do we know their effect on the PPV, namely, whether we can more accurately predict which patients will progress to muscle-invasive disease.

Because of the poor prognosis of NMIBC patients who develop muscle-invasive disease, the identification of those factors that will significantly increase our ability to identify, at an early stage, the patients who will indeed progress should be a top research priority.

**Conflicts of interest:** The author has nothing to disclose.

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## Platinum Priority

### Reply from Authors re: Richard J. Sylvester. How Well Can You Actually Predict Which Non-Muscle-Invasive Bladder Cancer Patients Will Progress? *Eur Urol* 2011; 60:431–3

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In 2006, Sylvester et al. reported a simple scoring system (used in the European Association of Urology guidelines) based on universally assessed clinical and pathologic factors that allow urologists to easily predict the risk of short-term and long-term recurrence and progression to muscle-invasive disease [1]. However, the information provided for the seven trials included in the European Organisation for Research and Treatment of Cancer (EORTC) studies, which are the bases of the EORTC tables, could be incomplete, and consequently, many patients might be undertreated according to today's guidelines [2].

The management of bladder cancer appears to have plenty of variability at different levels of the process. In recent years, new factors have contributed to improving our knowledge of non-muscle-invasive bladder cancer (NMIBC). Evidence is emerging that a substantial number of early recurrences are caused by residual cancer due to incomplete resection rather than true recurrence of NMIBC [3]. Efforts should be directed towards improving the completeness of the resection. In this way, the roles of repeated transurethral resection of the bladder (reTURB) in T1 disease [4] and fluorescent light cystoscopy, which increases the sensitivity for the diagnosis of associated carcinoma in situ and multiple small papillary tumours [5], have been established. The introduction of the new-grade 2004 classification and lamina propria invasion microsta-

ging (T1a/b/c) [6] would also contribute to better definition of tumours, with improved estimation of the probabilities of recurrence and progression.

Another important limitation of the EORTC tables is that <10% of patients were treated with bacillus Calmette-Guérin (BCG) and no maintenance regimen was administered. A significant percentage of patients in the EORTC trials had low tumour risks; therefore, intravesical treatment mainly consisted of chemotherapy with 21.6% of patients that did not receive intravesical instillations. Although attempts at validation of the EORTC tables have been published, validation of the EORTC risk tables still had not been reported in a large cohort of patients [7]. The reported Club Urológico Español de Tratamiento Oncológico (CUETO) series is composed of patients with intermediate- and high-risk tumours treated with intravesical BCG. Although more aggressive tumours were included in our trials, better results were obtained in our patients with BCG than those reported in the EORTC series. In this way, in 2009, the CUETO tables were developed with a similar structure to the EORTC tables but were adapted for patients treated with BCG [8]. Recently, the CUETO tables have been validated for recurrence in a series of 718 patients treated with BCG and interferon- $\alpha$  [9]. The finding of lower risks observed using the CUETO tables has been confirmed in the present paper reporting validation of the EORTC tables in patients treated with BCG [7]. However, most of the limitations reported in the EORTC series are also present in the CUETO series (eg, old staging and grading methods, reTURB not performed).

Moreover, the accurate identification of which NMIBC patients will actually progress to muscle-invasive disease is a major problem. Although both the EORTC and the CUETO scoring systems can accurately predict which patients will not progress (negative predictive values >90%), neither scoring system can accurately identify which patients will actually progress (positive predictive values <25%) [2]. A small proportion of patients in the group of cases with the highest scores suffered progression to muscle-invasive disease in both the EORTC and the CUETO series but was not adequately identified. In these patients, early cystectomy might have been indicated. However, despite the large

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