

## **Disease profiling in superficial bladder cancer**

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Superficial bladder tumours are a heterogeneous tumour family characterised by its capacity to develop superficial recurrence and, in less extent, progression to muscle-invasive tumours. As a whole, from 37.2 to 72.7% of patients will develop superficial recurrence and from 2.2 to 49% progressions (table 1).

Transurethral resection is the standard treatment for these patients, but according to previous data is insufficient in a vast majority of them. Since seventies intravesical adjuvant therapies have been applied in order to reduce recurrence and to prevent or at least delay progression. Some drugs have been used as intravesical chemotherapy and, more recently, intravesical immunotherapy, essentially based on bacillus Calmette-Guerin. In randomised trials different outcome has been observed between both approaches in terms of preventing recurrence and progression as well as in term of toxicity. In this way, prognostic factors related to recurrence, progression and survival are essential for the identification patients at risk and in consequence to establish different risk groups, in order to define the most appropriate therapy strategy for each group.

On the other hand, some patients quickly develop progression regardless the therapy applied and an early cystectomy can be considered. To identify patients at high risk to develop progression is one of the important challenges for Urologists since the cause-specific survival of patients who develop progression significantly decrease compared to those in whom the tumour remains as superficial.

Since many years clinical and pathological tumour characteristics have been identified as prognostic factors in univariate analysis (table 2). However, only few of them have been established in multivariate analysis with independent value for recurrence (table 3), for progression (table 4) and for survival (table 5). However, there is no unanimous consensus in to determine which factors are the most reliable for elaborating risks groups (table 6) and each author outlines his own risk groups (table 7). Compelling different authors who define his own risk groups the EAU determine three risk groups (table 7). Regardless of different prognostic factors used in the 4 series analysed, the important issue is that all series observed no very different percentages of recurrence and progression rate in each risk group (tables 8). According to these three risk groups a basic therapy strategy can be considered (table 9).

Recently, huge amount of molecular markers have been tested as prognostic factors, mainly in univariate analysis, but few of them have shown independent prognostic value in multivariate analysis (table 10). Nevertheless, in other multivariate analysis these same variables were not significant when traditional clinical and pathological factor were also included. In summary, there is not enough evidence that currently, molecular factor can take part in our therapeutic decision-making. Only p53, which is the most promising molecular marker as predictive factor for progression, is prospectively evaluated in at least two trials. The combination of several

molecular markers once we better know the different oncological pathways involved in the progression process can open a new future for molecular prognostic factors.

One the most important and difficult issue on superficial bladder cancer is to decide the optimal timing of cystectomy. Unfortunately, initially there is no clinical or pathological factors or p53 overexpression as prognostic factors in high-risk patients that reliably predict progression. Another pathological factor analysed was the microstaging (T1a/T1b/T1c) but controversial results have been reported and there is no reliable reproducibility on the level of muscularis mucosae invasion (table 11). However, initial response to intravesical therapy seems to be a more reliable predictive factor for progression with percentages between 50 to 100% and if the pathological pattern of non response is taken into account the prediction increased up to 80-100%, being independent variable in multivariate analysis (table 12). Also the p53 overexpression after BCG failure could be another important predictive factor for progression, but there are only few series studied with small sample(table 13).

Conclusion are summarised in table 14.

### **Conclusions.**

- 1. The most useful prognostic factor for recurrence and progression are stage, grade, recurrent character, multifocality and bladder TIS associated.**
- 2. Based on these factors three risk groups can be defined in which a different therapy strategy can be considered.**
- 3. Molecular markers are new promising prognostic factors but currently are not enough reliable.**

#### **4. Clinical response can be an important predictive factor for progression and the pathological pattern or p53 overexpression can be considered as potential factor for indicating early cystectomy**

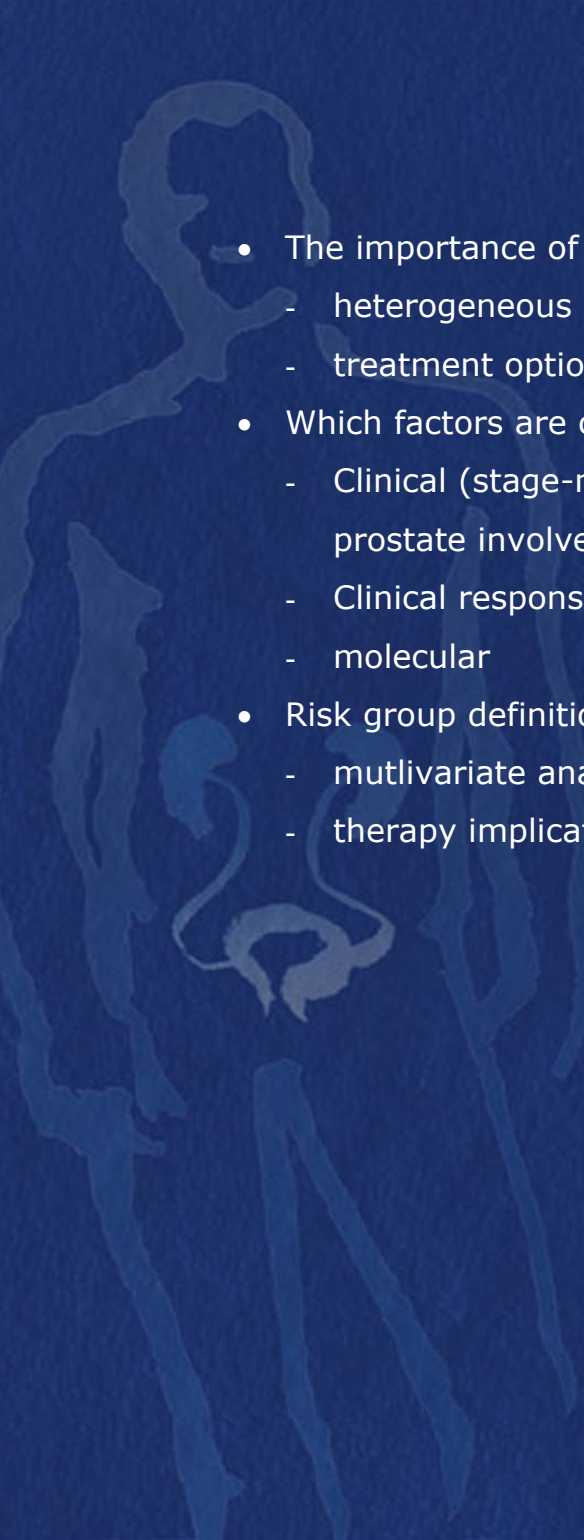
##### **Molecular prognostic factors**

Many molecular markers have been tested as prognostic factors for superficial bladder cancer. However only few of them provides prognostic information in univariate analysis and, in lesser extent, in multivariate analysis, Table x. Nevertheless, no conclusive results can be deduced since this prognostic value has not been proved in other series using the same methodology for assessment.

One of the most tested molecule has been p53 overexpression but conflictive results has also been reported in both uni and multivariate analysis. Combining evaluation of different molecules participating in pathway of growth control deserves further evaluations, such as p53 and p21 or Ki-67 and p21 expression.

The use of different antibodies, subjective in assessment and different criteria for defining normal or abnormal staining contributes to the lack of unanimity in approach.

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- The importance of prognostic factors in SBC
    - heterogeneous **behaviour**
    - treatment options
  - Which factors are clinically useful
    - Clinical (stage-microstage-, Tis, grade, multifocality, number, size, number, fre recurrence interval, prostate involvement, recurrent)
    - Clinical response
    - molecular
  - Risk group definitions
    - multivariate analysis
    - therapy implications