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Risk Stratification in Superficial Bladder Cancer: Fact or Fiction

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Abstract

Non-muscle-invasive bladder cancer is a heterogeneous group of tumors with completely different oncological outcome. What is more, their oncogenesis runs along different pathways with different oncological potential. The actual EORTC- risk tables are currently the best tool for counselling patients. They do not however, take tumor biology into account and the single factors used have multiple underlying errors.

It seems possible to assess the biological behavior of urothelial carcinomas more accurately using the FISH technique. Based on previous studies patients with a diploid chromosomal pattern, or only p16 and/or chromosome 3 positivity, can be considered as low-risk for recurrence/progression, whereas patients with a chromosomal pattern including aberrations of chromosomes 7 and/or 17 should be considered as high risk. In fact, patients with a high-risk chromosomal pattern have a significantly shorter disease-free survival time and higher progression rate compared to patients with a low-risk pattern.

Patients at high risk could therefore, be treated more aggressively to prevent tumor spreading and metastasis, if this is identified at an early stage of the disease; low risk patients on the other hand, might be spared aggressive treatment and followed-up at longer intervals. Furthermore, new prognostic parameters could provide additional arguments for therapeutic decisions in those cases where conventional prognostic parameters point to divergent prognostic outcomes.

These ongoing clinical implications must be considered experimental and need the proof of time. Nevertheless, it is a new approach along with that of morphology and biometric. But a reliable risk stratification is as yet unattainable and remains a chimera.

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1. Introduction

Transitional cell carcinoma (TCC) of the urinary bladder is a significant cause of morbidity and mortality worldwide. In Europe it is the second most common malignancy in urology with 120,000 new cases per year and 35,000 deaths in 2004 [1]. It is the third most prevalent malignant tumor in men [2]. In the United States, TCC is the fourth most common cancer and the sixth most common cause of cancer related deaths. In 2002, an estimated 56,500 new TCC cases and 12,600 TCC deaths were recorded [3]. At initial presentation, approximately 70% of patients have bladder malignancies confined to the epithelium or sub-epithelial connective tissue (stages Ta, T1, or carcinoma in situ [CIS]) and may be managed with transurethral resection (TURBT) with or without intravesical therapy. Despite treatment, the recurrence rate for these tumors can be as high as 50-70% [4,5]. Moreover, despite seemingly successful TURBT with or without intravesical therapy, as many as 10–35% of patients experience disease progression to muscle invasion [6–8]. Timely diagnosis and treatment of disease recurrence and progression may improve cancer control and quality of life outcome. While the number of new cases of bladder cancer diagnosed in Europe each year is equal to about one third of newly diagnosed prostate cancer cases [1], the bladder cancer health care costs are almost twice that of prostate cancer costs. The high incidence rate and protracted natural history of less aggressive components of Ta, T1, or CIS bladder cancer result in a high overall prevalence of these diseases, and inflate the cost of bladder cancer management. Currently, cystoscopy and urinary cytology represent the ''gold standards'' for surveillance of TCC recurrences.

Cystoscopy is the most efficient method presently available to detect primary or recurrent TCC of the bladder, but it is both costly and invasive and causes discomfort to the patient. Furthermore, flat tumors or carcinoma in situ may be difficult to detect [9]. An improvement on cystoscopy is the fluorescent cystoscopy: 5-aminolaevulinic acid (ALA) or its hexyl-derivative ester (HAL), precursors of the photosensitizer protoporphyrin IX are accumulated in cancer cells. Activated by blue light, cancerogenic degenerated cells emit a red fluorescence. Using this technique an increase in the detection rate, especially in flat lesions, was achieved [10].

Urine cytology complements cystoscopy by offering high sensitivity for the detection of high-grade TCC. However, urine cytology lacks the sensitivity to detect low-grade tumors and its quality is dependent on the availability of a highly skilled cytopathologist [11–13].

For many years there has been an ongoing research regarding prognostic factors in superficial TCC. First the tumor should be characterized better and secondly a prognosis should be given. But the prognostic value of various factors is not always the same and varies widely from author to author. These tables often are of scientific importance but in practice are not applicable. The idea in all of this is to create a valid risk stratification in the form of nomograms useable in daily practice to predict the subsequent evolution of the tumor accurately. The most recent and surely best tables are the EORTC risk tables published by Sylvester et al in March 2006 in European Urology [14].

2. Structure of risk tables

Different factors related to a patient's prognosis are identified. Each factor is subdivided into different levels and each level has a different prognostic importance which is represented by a score. The scores for the appropriate level of each factor are added together resulting in a total score. As the total score increases, the risk of recurrence or progression also increases.

The EORTC risk tables are composed of 6 factors: number of tumors, tumor diameter, prior recurrence rate, T-category, concomitant CIS and grade. All these data are morphological or biometric data and apparently reliable but deeper analysis shows that this could be a fallacy.

3. Analysis of the factors

3.1. *Number of tumors*

The standard treatment of superficial TCC is the complete resection of all visible lesions. First is to harvest tissue for the histopathological evaluation and second to remove the tumor burden totally. Unfortunately the TURB is not a standardized procedure and differs widely from institution to institution. Brausi et al. showed that there was a recurrence in 15.4% at first cystoscopy within 90 days after complete TURB of a single superficial TCC. Sixty-three European institutions participated in this study and the recurrence rate varied widely from 0–43%. The authors draw the conclusion that the quality of TURB differs widely between institutions but has a great impact on the recurrence rate of TCC [15]. Koloszy found residual tumors in 12.7% of pTa and in