High-Risk Nonmuscle Invasive Bladder Cancer

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KEYWORDS

• Nonmuscle invasive bladder cancer • High-risk bladder cancer • High-grade T1 • HGT1 • Carcinoma in situ • CIS • TUR • reTUR

KEY POINTS

- Advanced age (≥70 years), female sex, larger tumor size, and multiple tumors are associated with increased progression and, for some of these factors, also decreased cancer-specific survival. Bacillus Calmette-Guérin has also been shown to impact progression and also recently on cancer-specific survival.
- Updated information on large series and a meta-analysis has helped set the risk of progression in 20% of high-grade T1 cases.
- Deep lamina propria invasion combined with age, tumor size, associated carcinoma in situ and other risk factors described should be used for patient stratification in future clinical trials. Future research should attempt to combine these prognostic factors into a risk-prediction nomogram in which validation in a prospective cohort would also be of value.
- Identifying that 20% of patients with risk of progression would allow to indicate selectively both repeat transurethral resection and early cystectomy, preserving bladders in less-risk cases.

INTRODUCTION

Approximately 75% of the 386,000 new cases of bladder cancer diagnosed worldwide annually are nonmuscle invasive bladder cancer (NMIBC). In the United States, there are currently 500,000 survivors of bladder cancer, mainly of this NMIBC subtype.[1] It is still unclear what clicks the progression and makes 20% of high-risk NMIBC[2] progress to an invasive and extremely aggressive tumor. Expert recommendations on the optimal treatment strategy for patients within this category range from conservative therapy to early radical cystectomy.[3,4] There is a strong claim to reexamine the

The authors have nothing to disclose.

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Hematol Oncol Clin N Am 29 (2015) 227–236
http://dx.doi.org/10.1016/j.hoc.2014.10.009 **hemonc.theclinics.com**
0889-8588/15/$ – see front matter

treatment algorithm for these patients, to improve risk stratification, and to find the tools to identify this 20% with the potential of invasiveness.

The first issue to overcome when addressing high-risk bladder cancer is the mere definition of this category. There is no consensus among guidelines as to the risk-level definitions. As a consequence, an international committee of experts on bladder cancer management, the International Bladder Cancer Group (IBCG), reviewed all of these guidelines and published in 2008[5] and updated in 2011[6] their take on these variations. Their recommendation was to include as high-risk NMIBC any T1, G3, and/or carcinoma in situ (CIS). Originally, the European Association of Urology's (EAU) guidelines (2001) included as high-risk NMIBC all T1, G3 (multifocal or highly recurrent), and CIS.[7] With the introduction of the European Organization for Research and Treatment of Cancer's (EORTC) risk tables, an attempt was made in the 2011 version of the guidelines to use the risk calculator.[8] Currently, the definition of high-risk NMIBC for this association has, in part, gone back to the original definition and considers any of the following to be a high-risk NMIBC: T1 tumor or G3 (high grade) tumor or CIS, together with any multiple, recurrent, and large (>3 cm) Ta G1G2 tumors, if all conditions are present. This definition is quite similar (though not exact) to the definition recommended by the IBCG and, as in that case, involves using the old World Health Organization's (WHO) grading system (G1, G2, G3) instead of the updated high and low grade.

Throughout the past 2 decades, the variability in the definition of risk levels, together with the changes in the WHO's grading system and the staging system, has introduced elements of bias. Besides, there are variations in definitions of outcomes or prognostic factors, which might also lead to heterogeneity.[9] Finally, there is a lack in the literature of randomized data and large studies for HGT1 bladder cancer since the advent of bacillus Calmette-Guérin (BCG) in the early 1990s. Most of these studies are retrospective observational studies, which, compared with randomized controlled trials, are subject to various selection biases, carrying a higher risk of uncontrolled confounding factors, with potential preferential reporting of positive findings.

Regardless of the definition used, the clinical care of high-risk NMIBC is directed at preventing progression to muscle invasion because this event marks a dramatic increase in the risk of metastasis and disease-specific mortality. This is as opposed to low- and intermediate-risk NMIBC, for which the focus is on cost and quality-of-life issues. In this update, to keep a focus on progression, prognostic factors, and treatment strategies, the authors use the more restricted definition of high-risk NMIBC contemplating only HG cases, mainly HGT1 and CIS, as well as the more rare case of HGTa.

PROGNOSTIC FACTORS

Classically, around 30% of these tumors have been considered to progress,[10] with this being part of the currently outdated rule of thirds for HGT1. A new lower cutoff of 21% has been established in a meta-analysis based on more than 12,000 HGT1 cases,[11] consistent with a previous review of high-risk NMIBC based on 3088 patients from 19 trials[2] and a recent multicenter study of 2451 HGT1 cases.[12] Compared with other HGT1 reports with higher progression estimates of up to 40%,[3,13,14] this lower rate may represent true improvements in HGT1 prognosis over time[11] and, in part, may also reflect a shift in the definition mentioned in the earlier section. Along the same line, the rates of mortality for this group of bladder cancer were reported to reach 34%[3]; but these recent reports show a 9% to 14% mortality,[2,11,12] with 79% of patients retaining their bladders.[12]