Defining and Treating the Spectrum of Intermediate Risk Nonmuscle Invasive Bladder Cancer

Ashish M. Kamat,*,† J. Alfred Witjes,‡ Maurizio Brausi,§ Mark Soloway,|| Donald Lamm,§ Raj Persad,§ Roger Buckley,¶ Andreas Böhle,** Marc Colombel** and Joan Palou**

From the Department of Urology, MD Anderson Cancer Center, Houston, Texas (AMK), Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands (JAW), Department of Urology, AUSL Modena, Modena, Italy (MB), Department of Urology, University of Miami School of Medicine, Miami, Florida (MS), Department of Surgery, University of Arizona, and BCG Oncology, Phoenix, Arizona (DL), Department of Urology/Surgery, Bristol Royal Infirmary & Bristol Urological Institute, Bristol, United Kingdom (RP), Department of Urology, North York General Hospital, Toronto, Ontario, Canada (RB), Department of Urology, HELIOS Agnes Karll Hospital, Bad Schwartau, Germany (AB), Department of Urology, Claude Bernard University, Hôpital Edouard Herriot, Lyon, France (MC), and Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain (JP)

Purpose: Low, intermediate and high risk categories have been defined to help guide the treatment of patients with nonmuscle invasive bladder cancer (Ta, T1, CIS). However, while low and high risk disease has been well classified, the intermediate risk category has traditionally comprised a heterogeneous group that does not fit into either of these categories. As a result, many urologists remain uncertain about the categorization of patients as intermediate risk as well as the selection of the most appropriate therapeutic option for this patient population. We review the current literature and clinical practice guidelines on intermediate risk nonmuscle invasive bladder cancer and, based on our findings, provide urologists with a better understanding of this heterogeneous risk group as well as practical recommendations for the treatment of intermediate risk patients.

Materials and Methods: The IBCG analyzed published clinical trials, meta-analyses and current clinical practice guidelines on intermediate risk nonmuscle invasive bladder cancer available as of September 2013. The definitions of intermediate risk, patient outcomes and guideline recommendations were considered, as were the limitations of the available literature and additional parameters that may be useful in guiding treatment decisions in intermediate risk patients.

Results: Current definitions and management recommendations for intermediate risk nonmuscle invasive bladder cancer vary. The most simple and practical

Abbreviations and Acronyms

AUA = American Urological Association

BCG = bacillus Calmette-Guérin

CIS = carcinoma in situ

CUETO = Club Urologico Espanol de Tratamiento Oncologico

EAU = European Association of Urology

EORTC = European Organisation for Research and Treatment of Cancer

IBCG = International Bladder Cancer Group

ICUD = International Consultation on Urological Diseases

IR = intermediate risk

MMC = mitomycin C

NBI = narrow band imaging

NCCN® = National Comprehensive Cancer Network

NMIBC = nonmuscle invasive bladder cancer

PDD = photodynamic diagnosis

SWOG = Southwest Oncology Group

TURBT = transurethral resection of bladder tumor

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* Correspondence: University of Texas MD Anderson Cancer Center, 1515 Pressler, Unit 1373, Houston, Texas 77030 (telephone: 713-792-3250; FAX: 713-794-482; e-mail: akamat@mdanderson.org).

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definition is that proposed by the IBCG and the AUA of multiple and/or recurrent low grade Ta tumors. The IBCG suggests that several factors should be considered in clinical decisions in intermediate risk disease, including number (greater than 1) and size (greater than 3 cm) of tumors, timing (recurrence within 1 year) and frequency (more than 1 per year) of recurrence, and previous treatment. In patients without these risk factors a single, immediate instillation of chemotherapy is advised. In those with 1 to 2 risk factors adjuvant intravesical therapy (intravesical chemotherapy or maintenance bacillus Calmette-Guérin) is recommended, and previous intravesical therapy should be considered when choosing between these adjuvant therapies. For those patients with 3 to 4 risk factors, maintenance bacillus Calmette-Guérin is recommended. It is also important that all intermediate risk patients are accurately risk stratified at initial diagnosis and during subsequent followup. This requires appropriate transurethral resection of the bladder tumor, vigilance to rule out carcinoma in situ or other potential high risk tumors, and review of histological material directly with the pathologist.

Conclusions: Intermediate risk disease is a heterogeneous category, and there is a paucity of independent studies comparing therapies and outcomes in subgroups of intermediate risk patients. The IBCG has proposed a management algorithm that considers tumor characteristics, timing and frequency of recurrence, and previous treatment. Subgroup analyses of intermediate risk subjects in pivotal EORTC trials and meta-analyses will be important to validate the proposed algorithm and support clear evidence-based recommendations for subgroups of intermediate risk patients.

Key Words: urinary bladder neoplasms; mycobacterium bovis; administration, intravesical; chemotherapy, adjuvant; risk

NONMUSCLE invasive bladder cancer includes Ta, T1 tumors and CIS and, therefore, by definition, is a heterogeneous disease with varying oncologic outcomes. Recently low, intermediate and high risk categories were defined to help predict prognosis and guide the treatment of patients with NMIBC. While low risk (ie solitary, primary low grade [G1] Ta) and high risk (ie any T1, high grade [G3] or CIS) disease has been well-defined using the TMN staging system as well as the 1973 and 2004 WHO grading classifications, the intermediate risk category has traditionally comprised all patients not included in either of these categories. Thus, IR disease consists of a heterogeneous group of patients ranging from those with a solitary but recurrent low grade Ta tumor, to those with multiple, frequently recurrent, intravesical treatment refractory low grade Ta tumors. Therefore, the IBCG has suggested that the IR category be subdivided into those with low-intermediate risk disease and those with high-intermediate risk disease.[1,2]

Given the heterogeneity of IR NMIBC, urologists are often uncertain about which patients fall into this risk category as well as the most appropriate intravesical treatment option for these patients (ie BCG or chemotherapy). A recent online chart review involving 102 urologists and 971 patients with NMIBC from Europe and North America demonstrated that the treatment of IR NMIBC (197 defined as multiple or recurrent low grade tumors) varied substantially, with 24% of subjects treated with TURBT alone, 42% with an immediate postoperative chemotherapeutic instillation, 29% with intravesical chemotherapy, 7% with BCG induction only, 11% with BCG induction plus maintenance and 7% with other therapies (eg surveillance, intravesical electromotive drug administration with MMC, outpatient laser fulguration etc).[3]

Even current clinical practice guidelines vary with respect to recommended therapeutic options for IR patients, with some advising active surveillance and office fulguration[4] and others recommending intravesical chemotherapy or maintenance BCG.[5,6] In this review we provide a better understanding of this heterogeneous risk group as well as practical recommendations for the management of IR disease based on the available literature.

MATERIALS AND METHODS

A comprehensive MEDLINE® search was conducted to identify published clinical trials, systematic reviews, clinical practice guidelines and meta-analyses that examined IR NMIBC between 1980 and 2013. Keywords included bladder cancer, non-muscle invasive, intermediate-risk, low-grade Ta, G1-2, recurrent tumors, multiple tumors, BCG, intravesical chemotherapy and TURBT. Reference lists of guidelines, meta-analyses and original papers were also reviewed to identify additional applicable literature.

The members of the IBCG (the authors) met on 3 occasions throughout 2012 and 2013 to critically review the identified literature and form a consensus on practical recommendations for the management of IR NMIBC. Data were stratified based on the expert opinion of group members and articles were included in the study if they focused primarily on IR disease (ie multiple or recurrent low grade [G1-2] Ta tumors). Articles focusing