ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 34 (2016) 460–468

UROLOGIC ONCOLOGY

Seminar article

Follow-up in non–muscle-invasive bladder cancer—International Bladder Cancer Network recommendations

Wassim Kassouf, M.D.[a,*], Samer L. Traboulsi, M.D.[a], Bernd Schmitz-Dräger, M.D.[b], Joan Palou, M.D.[c], Johannes Alfred Witjes, M.D., Ph.D.[d], Bas W.G. van Rhijn, M.D., Ph.D.[e], Herbert Barton Grossman, M.D.[f], Lambertus A. Kiemeney, Ph.D.[d], Peter J. Goebell, M.D. Ph.D.[g], Ashish M. Kamat, M.D.[f,*]

[a] *Department of Urology, McGill University Health Centre, Montreal, Canada*
[b] *Urologie, Schön Klinik Nürnberg Fürth/Urologie, Fürth, Germany*
[c] *Servicio de Urología, Fundación Puigvert, Barcelona, Spain*
[d] *Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands*
[e] *Department of Surgical Oncology (Urology), Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*
[f] *Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX*
[g] *Department of Urology, University Clinic Erlangen, Erlangen, Germany*

Received 1 March 2016; received in revised form 26 May 2016; accepted 26 May 2016

Abstract

Objective: Non–muscle-invasive bladder cancer (NMIBC) comprises a wide spectrum of tumors with different behaviors and prognoses. It follows that the surveillance for these tumors should be adapted according to the risks of recurrence and progression and should be dynamic in design.

Methods and materials: Medline search was conducted from 1980 to 2016 using a combination of MeSH and keyword terms. The highest available evidence was reviewed to define different risk groups in NMIBC. The performance of different follow-up tools such as urine cytology, cystoscopy, and upper tract imaging in detecting bladder carcinoma was assessed. Different commercially available urinary markers were investigated to determine whether such markers would contribute to the surveillance of patients with NMIBC. A follow-up scheme based on the early evidence is proposed.

Results: A risk-based approach is paramount. Cystoscopy and cytology are recommended to be done at 3 months following transurethral resection of bladder tumor. For low-risk tumors, annual cystoscopy alone is sufficient; no upper tract evaluations or cytology is needed except at diagnosis. High-risk tumors should be followed up with a more intense schedule: cystoscopy every 3 months for 2 years, 6 months for 2 years, and then annually, with cytology at frequent intervals, and imaging for upper tract evaluation at 1 year and then every 2 years. Intermediate-risk tumors should be subclassified as per the International Bladder Cancer Group recommendations and when associated with 3 or more of the following findings (multiple tumors, size ≥ 3 cm, early recurrence < 1 year, frequent recurrences > 1 per year) then a surveillance strategy similar to that of high risk should be followed. Several urine markers were more sensitive than cytology in the detection of NMIBC; however, these tests are still costly, require specialized laboratories, and do not replace cystoscopy. Until better and cheaper markers are available, their routine use has not been integrated in the follow-up recommendation of current guidelines.

Conclusions: Surveillance of NMIBC should follow a risk-adapted approach, with a combination of cystoscopy, cytology, and upper tract imaging. The aim of this approach is to minimize the therapeutic burden of a disease with high recurrence rates without missing progressing tumors.

When designing a diagnostic pathway, first-line diagnostic imaging tests should have high sensitivity to ensure disease positives are included in the test population for further investigation. Second-line investigations should be highly specific, to ensure false-positives are minimized.

Keywords: Urine markers; Prediction; Recurrence; Risk; Surveillance; Follow-up

Introduction

Non–muscle-invasive bladder cancer (NMIBC) is the most common type of bladder cancer. This disease is characterized

* Corresponding authors.
E-mail addresses: wassim.kassouf@muhc.mcgill.ca (W. Kassouf), bernd_sd@yahoo.de (B. Schmitz-Drager), akamat@mdanderson.org (A.M. Kamat).

http://dx.doi.org/10.1016/j.urolonc.2016.05.028
1078-1439/

by a high-recurrence probability ranging between 31% and 78% and progression rates of 0.8% to 45% at 5 years without the use of bacillus Calmette-Guerin (BCG) [1]. With BCG becoming standard in the treatment of NMIBC, the late recurrence probability dropped to 25.9% to 55.4% and progression rates between 2.4% and 18.9% at 5 years [2]. This entails that NMIBC requires frequent follow-up, often lifelong. Significant differences in disease behavior, aggressiveness, and prognosis exist between low-grade Ta and high-grade T1 urothelial carcinoma (UC). These differences influence the follow-up strategy and treatment methods. Low-risk NMIBC is characterized by a relatively benign behavior, intermediate-risk UC is characterized by a higher rate of recurrence and a low progression rate, whereas high-risk UC is characterized by a high recurrence and progression rate. The concept of risk-adapted surveillance is important, as the major concern in low-risk tumors is to reduce the use of invasive procedures altogether. On the contrary, the main concern for high-risk tumors is to increase the detection of all aggressive tumors or predict their recurrence. In this review we assess the usefulness of urine cytology (and other urinary markers), cystoscopic techniques, and upper tract imaging in the follow-up of patients with NMIBC. We also propose a follow-up strategy for NMIBC according to the different tumor risk groups.

Methods and materials

A Medline search was performed using the following Mesh and keyword terms: urine markers, prediction, recurrence, risk, surveillance, follow-up, and urinary bladder neoplasms. The search was limited to articles in the English language from January 1980 to January 2016. Articles were selected based on relevance, and level of evidence. Prognostic factors for recurrence, progression, and survival in NMIBC were reviewed. Relevant research pertaining to risk classification of UC was studied. The use of cystoscopy, cytology, and upper tract imaging was reviewed in the context of follow-up in NMIBC. The usefulness and limitations of the commercially available urinary markers was investigated in the context of follow-up as well. A set of recommendations based on the evidence found was proposed for follow-up of NMIBC.

Results

Risk group stratification of patients with NMIBC

Risk stratification of patients allows classification of disease according to the risk of recurrence and progression. It allows physicians to devise a treatment and follow-up scheme appropriate for each category. Predictors of disease recurrence and progression were already identified. The EORTC-GUCG developed risk tables based on 7 randomized trials that included 2,596 patients with NMIBC who did not receive BCG treatment. The prognostic factors that conferred risk for recurrence and progression included: number and size of tumors, prior recurrence rate, T category, grade, and presence of concurrent carcinoma in situ (CIS) [1]. The same group evaluated prognostic factors for recurrence, progression, and survival for patients treated with BCG induction with 1 to 3 years of maintenance [2]. Factors associated with recurrence were grade, prior recurrence rate, and number of tumors. Stage and grade were prognostic factors for progression and disease-specific survival.

Other prognostic factors have been shown to influence recurrence and progression. In general, the findings of cystoscopy performed 3 months after tumor resection is an important prognosticator of recurrence and progression [3]. Depth of lamina propria invasion was noted to be a significant risk factor that tripled the risk of progression [4]. Although lymphovascular invasion (LVI) has been shown to be an independent factor for progression in patients with NMIBC [5], the actual effect on prognosis in high-grade T1 has been questioned by a recent meta-analysis on 15,215 patients. For patients with high-grade T1, the effects of LVI have been noted to be correlated with depth of invasion into lamina propria; it is, therefore, unclear whether LVI independently predicts outcome or if the detrimental effect was already captured by pathologic information on T1 substaging [4].

Female sex is a significant risk factor for progression in patients with high-grade T1 [4,6]. The prevalence of prostatic urethra CIS was reported to be as high as 11.7% in men with T1 high-grade disease and was strongly associated with recurrence and progression [6]. The presence of variant histology in transurethral resection (TUR) of bladder tumor (TURBT) is associated with locally aggressive disease [7]. Divergent histology is still underreported in pathology specimens and is associated with early progression to muscle-invasive disease [8]. Micropapillary variant is of special importance because of its poor response to BCG.

We recognize a category of patients deemed at very high-risk for progression. Those include all T1HG with one or more of the following adverse prognostic factors: multiple or large tumors, presence of variant histology, concomitant CIS in the bladder or prostatic urethra, and LVI.

Upper urinary tract recurrences in NMIBC

Upper urinary tract tumors (UTUC) are associated with NMIBC. The prevalence of synchronous upper tract UC with NMIBC is low. A retrospective analysis of 1,529 patients with NMIBC showed a prevalence of 1.8%. The location of tumor at the trigone was associated with a 6-fold risk of having synchronous UTUC [9]. The presence of CIS in the bladder is a risk factor for extravesical involvement. Solsona et al. followed up 138 patients with bladder CIS, 786 patients with NMIBC, and 179 patients with invasive bladder cancer treated with cystectomy for a period of 8 years. Overall, 24.6% of patients with CIS developed upper