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Active Surveillance with Delayed Intervention for Recurrent Low Risk Bladder Cancer

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Abstract

Introduction: Active surveillance with delayed intervention aims to minimize the discomfort, potential complications and costs associated with immediate treatment of recurrent low grade Ta tumors of the bladder. We reviewed the data supporting this management strategy for low risk bladder cancer.

Methods: A PubMed® query was performed to identify relevant literature on the topic of active surveillance for low risk bladder cancer. English language publications were reviewed and select data presented.

Results: Available data suggest that only 5% to 10% of patients diagnosed with a low grade appearing papillary bladder tumor will have progression in stage or grade. Coupled with the discomfort and potential for complications associated with transurethral resection, this supports the role of active surveillance for patients with small, recurrent, low risk bladder cancer. In addition, this management strategy stands to benefit the health care system by reducing the costs associated with caring for patients with bladder cancer.

Conclusions: Active surveillance with delayed intervention represents a safe and cost-effective strategy for patients with recurrent low risk bladder cancer.

Key Words: watchful waiting, urinary bladder neoplasms, risk assessment

Abbreviations and Acronyms

BCa = bladder cancer

TUR = transurethral resection

The American Cancer Society estimates that nearly 70,000 new cases of bladder cancer are diagnosed annually in the United States.[1] Worldwide this number approaches 390,000 cases, with the highest incidence rates in Europe and North America.[2] According to data from the Surveillance, Epidemiology, and End Results database approximately 50% of all patients with BCa will be diagnosed with a low risk tumor confined to the epithelium of the bladder (ie low grade Ta).[3] Although approximately half of these patients will experience a new tumor after initial treatment with transurethral resection, only a small minority will later have a high grade bladder tumor and even fewer will have a subsequent tumor which invades the basement membrane or

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muscle.[4–7] Given the favorable prognosis associated with low grade Ta tumors, some have advocated for expectant management (also called active surveillance with delayed intervention) as a strategy aimed at minimizing the discomfort, potential morbidity and costs associated with immediate re-treatment.[8–12] This approach is in contrast to the traditional view which has supported the complete eradication of all visible tumor immediately upon detection. We reviewed the overall approach, rationale and data supporting the use of active surveillance for low risk BCa.

Overall Approach

Active surveillance for recurrent low risk BCa involves monitoring patients with cystoscopy every 3 to 6 months. During this time 1 or several new bladder tumors may develop. However, treatment may be deferred as long as all tumors appear low grade and remain small. Indications for TUR or fulguration include a high grade cytology, a significant increase in tumor size, a change in appearance concerning for a high grade tumor or the development of symptoms (eg bleeding). The decision to delay treatment must be preceded by a conversation with the patient regarding the risks and benefits of active surveillance. In our experience once patients understand the low likelihood of an adverse consequence with this management strategy, they are pleased to avoid a return to the operating room for TUR.

Rationale for Active Surveillance

Natural History of Low Grade BCa

Urothelial tumors of the bladder are thought to develop along 2 divergent pathways.[13] The first of these pathways gives rise to low grade noninvasive lesions, which are believed to develop from areas of papillary hyperplasia. These tumors frequently harbor mutations in the HRAS and FGFR3 genes.[14–16] In contrast, the second pathway is characterized by high grade invasive tumors which are hypothesized to progress from areas of dysplasia or carcinoma in situ. Tumors along this pathway frequently harbor defective forms of the p53 and RB tumor suppressor genes, and only a small number of patients with low grade tumors will accumulate the genetic defects necessary to cross over to the more aggressive pathway.[14–16]

Although the molecular basis for these 2 distinct pathways was only recently elucidated, the concept of 2 distinct clinical trajectories has been apparent for many years. For example, in 1987 Jordan et al reported that only 4.4% of patients initially diagnosed with a low grade tumor had progression to invasive disease resulting in death.[4] A high grade tumor developed in an additional 3.3% of patients and was treated successfully. Similarly, in 1992 Prout et al reported that among a cohort of patients with low grade Ta tumors only 4.5% had progression to T1 or T2 disease.[5] Notably only a third of these patients received intravesical therapy and none received bacillus Calmette-Guérin. In a more recent report Holmäng et al found that among 116 patients with low risk BCa followed for at least 5 years only 4% had progression in stage.[6] Taken together, these data demonstrate that the majority of low grade Ta lesions behave in a benign or indolent fashion and, thus, support a role for deferred therapy.

Risks of Treatment

Although performed endoscopically in a minimally invasive fashion, TUR is associated with a moderate risk of complications. For example, in a large study of nearly 22,000 TUR procedures performed for BCa, Hollenbeck et al found that 4.3% of patients had a postoperative complication.[17] Most commonly these included urinary tract infections and gross hematuria. Similarly Nieder et al reported a complication rate of 5.8% after TUR.[18] Notably 60% of complications were attributed to bladder perforation requiring prolonged bladder drainage. In addition to complications related to TUR itself, this procedure places patients at risk for complications due to the need for general or spinal anesthesia. This is especially relevant for patients with BCa, many of whom are older and/or have smoking related comorbidities.

In contrast to TUR, simple fulguration (known as cystodiathermy) can be performed in the office setting with local anesthesia, thereby reducing the chance of complications. First described in the early 1990s[19,20] after the introduction of the flexible cystoscope,[21] office based fulguration is now commonly used in the field of urology. With office based fulguration complications are rare (less than 1%) and minor in nature.[19,20,22,23] A potential disadvantage of this approach is that the tumor tissue is ablated and, therefore, cannot be evaluated by a pathologist. However, this fact is not terribly relevant in the setting of low grade Ta tumors as the diagnosis is almost always readily apparent on visual inspection.

Herr investigated the accuracy of cystoscopy for predicting low vs high grade tumors.[24] After grade and stage were documented based on appearance alone, all patients underwent formal TUR. Overall 93% of low grade tumors were correctly classified based on cystoscopic appearance. Thus, the assessments of trained urologists are quite accurate in visually determining the grade and stage of papillary bladder tumors. Remarkably only 1 of 72 (1.4%) tumors was under staged or graded (in this case high grade T1 due to focal invasion) when a negative cytology was also considered.