Active surveillance for low-risk bladder cancer

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Abstract

Background: Most newly diagnosed bladder cancers present as non–muscle invasive bladder cancer (NMIBC). NMIBC is a heterogeneous disease with varying treatment options, follow-up schedules, and oncologic outcomes. We sought to review the role of active surveillance for low risk bladder cancer in the literature.

Methods: A PubMed search was performed using the following keywords: active surveillance, low risk, bladder, transurethral resection of bladder tumor, cost, and quality of life. Relevant articles were reviewed and utilized.

Results: Low-risk bladder cancer—defined as pTa low-grade papillary tumors—is the type of NMIBC with the most favorable oncologic outcome and which almost never progresses to muscle invasive disease or metastasizes. Bladder cancer has the highest per patient treatment costs of all cancers. One of the reasons is the high rate of recurrence. Patients with low-grade bladder tumors often experience a recurrence after primary transurethral resection. Many patients undergo multiple resections in the hospital.

Conclusions: Appropriately selected patients with recurrent low-risk bladder cancer could be managed with either office fulguration or cystoscopic surveillance. Active surveillance for patients with low-risk bladder cancer avoids or delays the surgical and anesthetic risks of a TURBT, thus optimizing quality of life without compromising the patient’s risk of cancer progression. Published by Elsevier Inc.

Keywords: Low risk; Bladder cancer; Active surveillance; Transurethral resection of bladder tumor; Cost; Quality of life

1. Introduction

Bladder cancer remains a significant health condition in the United States, with an estimated 73,510 new cases and 14,880 deaths from the disease expected in 2012 [1]. It is the sixth most prevalent malignancy in the United States, accounting for about 8% of the cancers in men and 2% in women. About 75% to 85% of newly diagnosed bladder cancers present as non–muscle-invasive bladder cancer (NMIBC), of which 70% are confined to the mucosa (Ta), 20% present as T1, and 10% as carcinoma in situ [2,3]. The vast majority of tumors are low grade. On the one hand, low-grade bladder tumors frequently recur, and patients with low-grade Ta tumors have minimal risk of progression in stage, metastasis, or death from urothelial cancer. On the other hand, high-grade bladder tumors frequently recur and have a significant risk of progression to muscle invasion or metastasis.

The initial management is transurethral resection (TUR) of all the visible tumors to reduce the risk of bleeding, eliminate further growth, and provide for optimal staging. A single dose of postoperative intravesical instillation of chemotherapy is also recommended [4]. NMIBC is a heterogeneous disease with varying treatment options, follow-up schedules, and oncologic outcomes. Considerations for appropriate treatment options in NMIBC must be made in conjunction with clearly defined goals to prevent disease recurrence and progression to muscle-invasive disease. The clinician must consider the side effects of each treatment. There is some risk associated with each surgery, which includes anesthesia, the trauma of repeated endoscopic resections, and uncommonly toxicity of intravesical therapy. One might also consider the expense of each intervention.

2. Natural history of low-risk bladder cancer

Clinical and molecular evidence suggests that urothelial carcinoma of the bladder arises by at least 2 different molecular pathways [5–8]. Most urothelial carcinomas belong to the low-grade pathway and are thought to develop from benign urothelium through a process of urothelial hyperplasia. On the contrary, the majority of invasive urothelial carcinomas are likely to originate from the
progression of dysplasia to carcinoma in situ and papillary high-grade noninvasive or invasive cancer. As our understanding of the molecular pathways in urothelial oncogenesis expands, it may allow the possibility of greater prediction of the risk of recurrence and progression of NMIBC and may play an important role in the timing and choice of treatment, as well as guide follow-up procedures [9].

Low-risk bladder cancer—defined as pTa low-grade papillary tumors—is the type of urothelial cancer with the most favorable outcome [10,11]. Patients have high risk of recurrence, but a very low risk of progression. The risk of recurrence is 15% to 61% and 31% to 78% after 1 year and 5 years, respectively, with a risk of progression of <1% after both 1 year and 5 years [10].

3. Active surveillance for low-risk bladder cancer

Active surveillance is not a new concept for urologists. This approach has been used in the management of patients with low-risk prostate cancer and small renal masses. The goal of active surveillance is to avoid or delay the morbidity associated with treatment, while still allowing for curative intervention if needed.

Soloway et al. were the first to expectantly observe patients with papillary low-grade Ta bladder tumors [12]. Thirty-two patients with a history of low-grade Ta tumors and with a new tumor, which was endoscopically consistent with 1 or more small low-grade Ta tumors, were observed over a mean observation period of 38 months (range, 6–126 months). Only 3 (9%) progressed in stage or grade, and none progressed to stage T2 disease. There have been several subsequent studies following this first report. Gofrit et al. also demonstrated that expectant management may be an acceptable course in patients with low-risk disease [13]. They followed 28 patients and observed no grade or stage progression during an average 13.5-month follow-up. They also observed that initial tumor diameter was predictive of tumor growth during the observation period.

Pruthi et al. reported on 22 cases with low-risk papillary bladder tumors who were observed expectantly [14]. With a limited follow-up of 25 months, 8 tumors did not grow, 9 showed minimal growth, and 5 had moderate growth. Fifteen patients (68%) required no intervention and 7 (32%) needed repeat TUR or fulguration to control recurrent tumors. Two patients (9%) had high-grade tumor recurrence, but only 1 (4%) had an invasive tumor (not involving muscle). Two patients (9%) had grade progression, with 1 (4.5%) having stage progression as well. However, neither of these tumors progressed to muscle invasion.

Similarly, Hernandez et al. followed 64 patients with recurrent, small (<1 cm) NMIBC. The median follow-up was 38.6 months. The tumor histologic features before observation were stage pTa in 77.1%, stage pT1a in 22.9%, grade 1 in 67.1%, and grade 2 in 23%. After 10.3 months, 93.5% of the patients had not progressed in stage and 83.8% had not progressed in grade. None of the patients progressed to muscle-invasive disease [15]. However, it is important to emphasize that these authors included one-quarter of the patients with minimally invasive pT1 tumor. The safety of observing patients with a history of invasive tumors is unknown. Nevertheless, not a single patient from the 4 aforementioned studies had a life-threatening, muscle-invasive tumor developed during or after the observation periods.

Patients with small, recurrent papillary tumors may not require prompt resection. Flexible cystoscopy is a diagnostic procedure usually performed under local anesthesia and has been used as an alternative to rigid instrumentation in the outpatient setting since the mid-1980s [16,17]. It has been reported that in patients with negative cytologic findings, the correlation between the cystoscopic findings and the histologic features of the tumor is high, with an accuracy of 98% [18]. Experienced urologists can accurately identify low-risk bladder tumors by their endoscopic appearance, in which office fulguration via a flexible scope can be a safe and efficacious alternative to TUR [19,20]. However, no guidelines have been established for the ideal frequency of surveillance in patients with tumor under expectant management.

At our institution, the decision to observe a patient is based on his/her bladder tumor history (low-grade Ta bladder tumor on initial transurethral resection of bladder tumor [TURBT]) and the clinical characteristics of tumor (cystoscopic appearance of a low-grade tumor, tumor size, number of tumors, and the absence of hematuria). Patients are carefully counseled regarding the low malignant potential of the tumor, risks, and benefits, and they agreed to defer immediate treatment. Subsequent office cystoscopy is usually at intervals of 3 to 6 months. When in doubt, biopsy or resection should be performed.

Another potential advantage of active surveillance is prevention of tumor recurrences. There is extensive evidence that endoscopic resection of bladder tumors can disseminate cancer cells throughout the bladder, which can implant in the raw area that was just resected [21–23]. Hence, adopting this monitoring approach in patients with low-risk bladder tumors may reduce the recurrence rate.

4. Complications/risks of TURBT

Treatment for bladder cancer is not without risk. TUR of a bladder tumor has several risks associated with this procedure. The patient has either general or regional anesthesia. Complications related to the surgery have been reported. Collado et al. reported a series of 2,821 patients, of which there were complications in 145 patients (5.1%) [24]. These complications included bleeding (2.8%), perforation (1.3%), and medical complications (0.14%) such as lower limb thrombosis, pulmonary embolism, acute myocardial infarction, and cardiac arrhythmia. Nieder et al. reported on a series of 173 patients, of which there were complications in 10 patients (5.8%) [25]. These complications included bladder perforation (3.5%) and blood transfusion (2.3%).

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5. Cost of TUR of bladder tumor/bladder cancer

The benefits achieved with active surveillance are not only a reduction in complications related to the treatment (e.g., anesthesia, bleeding, bladder perforation, bladder scarring), this practice also involves an added economic benefit by sparing the patients the expense of a surgical intervention. Among all the cancers, bladder cancer has the highest per patient treatment costs and the fifth highest overall cost [26,27]. Treatment of NMIBC in the United States costs over $150 million for a 5-year treatment course [28]. The high recurrence rate of bladder cancer necessitates long-term surveillance. The costs for bladder cancer treatment vary by country but range from $89,000 to $202,000 per patient [26]. Overall treatment costs are estimated at $3.4 billion annually, of which $2.9 billion are direct treatment-related costs. In the United Kingdom, the largest bladder cancer expenditure is for TURBT, an estimated 71% of the total costs [29].

Cooksley et al. created a clinical model to estimate the lifetime costs related to bladder cancer treatment and complications, utilizing the Surveillance, Epidemiology, and End Results-Medicare database [30]. They identified 4,863 patients who were diagnosed with bladder cancer, of which 74% had NMIBC. Within this group, 921 patients (25%) later progressed to muscle-invasive disease. Most of the costs were after the initial diagnosis, and the mean annual postdiagnosis continuing care costs per patient were $4,975, $7,100, and $17,437 for Tis-Ta, T1, and T2+, respectively. A large portion of costs were related to complications, with complication-related reimbursement totals of 27% and 37% of total costs in patients with muscle-invasive bladder cancer and in patients with NMIBC, respectively. The patients with muscle invasion have a lower complication cost proportion due to a higher overall cost for treatment.

Another group utilized a model to simulate treatment of NMIBC with and without intravesical chemotherapy in conjunction with fulguration vs. TURBT [31]. They showed that at a 5-year follow-up the most cost-effective strategy was office fulguration without the use of intravesical chemotherapy ($654.8/quality-adjusted life year). This was followed by office fulguration with the use of intravesical chemotherapy ($687.84/quality-adjusted life year). The increased cost of the chemotherapy outweighed the increased effectiveness benefit in reducing recurrences. The cost of TURBT was the most significant driver of cost in their model. Therefore, office-based management can lower the cost burden of treating low-risk NMIBC.

6. Quality of life

Most published studies on assessment of health-related quality of life were related to patients who had radical cystectomy for muscle-invasive bladder cancer. Few reports have attempted to address the health-related quality of life of patients with NMIBC. Low-grade bladder tumors are rarely lethal, although there is a high recurrence rate after primary TUR. Many patients undergo multiple TURs as these tumors recur. It is not surprising that this condition is frustrating to patients. Yoshimura et al reported that the general health perceptions (as measured by the short form-36) in patients with NMIBC were severely impaired compared to population norms [32]. Following the first few TURBTs, physical functioning, social functioning, and emotional domains have been shown to demonstrate impairment [32]. Furthermore, it has also shown that intravesical treatment for prevention of recurrence increased the score of bodily pain [32]. In the first population-based study on the effect of cancer on health-related quality of life of older Americans, Reeve et al. demonstrated that patients with bladder cancer had a statistically significant decline in physical health compared with control subjects and greater mean reductions in general well-being as measured by the short form-36 than patients with prostate and breast cancer [33].

7. Conclusion

 Appropriately selected patients with recurrent low-risk bladder cancer could be managed conservatively with either cystoscopic surveillance or office fulguration of the tumor. Active surveillance for patients with low-risk bladder cancer avoids or delays surgical and anesthetic risks of a TURBT and additionally, optimizes quality of life without compromising the patient’s risk of cancer progression. This may result in substantial cost savings to an ever-increasing healthcare system. Larger studies and randomized controlled trials are needed to validate the safety and efficacy of expectant low-risk bladder tumor management. In the future, molecular biomarkers may play an important role in the timing and the choice of treatment, as well as guiding follow-up strategies.

References


