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Contemporary Management of the Urethra in Patients After Radical Cystectomy for Bladder Cancer

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An estimated 60,240 new cases of bladder cancer were expected to be diagnosed in 2004. Of these, approximately 30% to 40% were expected to present with or ultimately develop muscle invasive disease [1]. In the United States, the most accepted management of patients with muscle invasive disease is radical cystectomy with bilateral pelvic lymph node dissection [2]. With removal of the bladder, management of the urethra becomes an important consideration. Several decades ago, the prognosis of patients with symptomatic recurrence of transitional cell carcinoma (TCC) in the urethra was poor [3,4]; therefore, some early investigators advocated routine en bloc removal of the urethra in men and women at the time of cystectomy [4]. This recommendation was based on the rationale that the retained "dry" urethra was of no significant value to the patient and served only as a source of potential morbidity and mortality, analogous to the distal ureter in patients with upper tract TCC. The major argument against routine en bloc urethral resection at the time of cystectomy was based primarily on reports demonstrating increased postoperative morbidity in these men [5–7]. Currently, owing to the pioneering work of Camey and the growing acceptance of orthotopic urinary diversion, management of the retained urethra after radical cystectomy has taken on new importance [8]. This review discusses urethral TCC after radical cystectomy, with particular emphasis on its incidence, risk factors for recurrence, diagnosis, screening tests, and the treatment and outcome among these patients.

Urethral involvement by TCC after radical cystectomy could arguably be due to synchronous or metachronous disease. The urethral involvement may occur owing to unrecognized TCC in the urethra at the time of cystectomy, growth of TCC from a positive margin, recurrence owing to tumor spillage or implantation, or de novo TCC that arises owing to the "field change" throughout the urothelium of patients with TCC. Although it is difficult to assign with certainty each episode of urethral "recurrence" after cystectomy to one of these categories, it is generally believed that most urethral TCC after cystectomy is caused by de novo metachronous development of urethral disease analogous to the development of upper tract TCC [9]. Nevertheless, because of the inherent uncertainty in determining whether urethral involvement by TCC after cystectomy is truly a recurrence, the terms *urethral TCC* and *urethral recurrence* are used interchangeably throughout the remainder of this article.

Rate of urethral transitional cell carcinoma in men

The reported incidence of urethral TCC after radical cystectomy has ranged from 0% to 18% across several series [3,8,10–30]. An early attempt to pool the data from series before 1994 estimated the overall incidence rate to be 10.1% [9]. More recently, a meta-analysis pooling the results from that study along with five additional series concluded that the overall incidence after cystectomy was 8.1% [31]. In one of the largest contemporary cystectomy series from the University of Southern California, the rate was 7.9% [26]. The overall rate of urethral TCC is approximately 8% to 10% across all patients.

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The median time to recurrence across series has ranged from 1.5 to 2.2 years, with most recurrences occurring before 5 years [10,11,19,26,32–34]. Some cases of urethral TCC are diagnosed up to 20 years after radical cystectomy [4,26,32]; therefore, it is critical that the retained urethra, whether "dry" or still functionally associated with an orthotopic diversion, be monitored for the remaining lifetime of the patient.

Risk factors in men

A variety of cancer characteristics have been associated with the incidence of urethral TCC after radical cystectomy in men. These factors include multifocal disease [10,11,13,18,20,22,25,35–38], the presence of carcinoma in situ (CIS) [10,20,37,39], upper tract TCC [4,11,20,23,37], involvement of the bladder neck with tumor [10,11,20,25], and involvement of the prostatic urethra [10–12,20,22,39,40]. Data for the majority of these risk factors are contradictory and have been discussed extensively in previous reviews [9,41,42]. As noted previously, the presence of CIS has been associated with urethral TCC in several series. Other series have refuted this claim and reported rates of urethral TCC for patients with pathologic CIS of the bladder ranging from 4.5% to 5% [11,12], comparable with the overall rate of 8% to 10% among unselected patients.

Across studies, the most consistent risk factor for urethral TCC after radical cystectomy in men is prostatic involvement [10–12,20,22,39,40]. Ashworth first reported this association when examining seven patients with urethral TCC, five of whom (71%) had a history of prostatic TCC [25]. This risk seems to be directly proportional to the degree to which the prostate is involved. A study by Hardeman and Soloway reviewed their experience with 30 patients who had TCC of the prostate; 11 (37%) urethral recurrences were reported overall [12]. There were no recurrences among the patients with TCC confined to the mucosa, 25% in patients with ductal involvement, and 67% in patients with stromal invasion. Similarly, a report by Levinson et al demonstrated a strong association between prostatic TCC and urethral recurrence after radical cystectomy [11]. Of the six urethral recurrences reviewed, 67% had a history of prostatic TCC. Again, this rate was directly proportional to the depth of involvement. There were no recurrences among patients with only mucosal involvement, whereas the rates for those with ductal involvement or stromal invasion were 10% and 30%, respectively. In another study of 436 radical cystectomy patients, the 5-year probability of urethral recurrence was 6% for patients without prostatic TCC involvement compared with 15% for patients with superficial involvement and 21% for those with stromal invasion of the prostate ($P = .0002$) [26]. Taken together, the literature demonstrates that the most important risk factor for urethral recurrence is prostatic stromal invasion.

The question has been raised whether men who are candidates for radical cystectomy should undergo routine biopsy of the prostatic urethra before surgery to determine their eligibility for orthotopic diversion. A prospective series of 118 patients by Lebret et al has examined the utility of preoperative prostatic biopsies versus intraoperative frozen section analysis of the prostatic urethral margin at the time of cystectomy in predicting urethral recurrence [27]. They found that intraoperative frozen section was more accurate than any preoperative parameter, including preoperative prostate biopsies, in predicting urethral recurrence. As a result, it is routine practice at the authors' center and many others to base a patient's eligibility for orthotopic diversion, at least with respect to the risk for urethral TCC, on intraoperative frozen section analysis at the time of radical cystectomy. It is imperative that a full discussion take place with the patient before surgery on the preferred option (ie, conduit versus continent cutaneous reservoir) should the frozen section be positive [26,27].

Risk factors in women

It is almost universally accepted that women who are not undergoing orthotopic diversion should undergo en bloc resection of the entire urethra at the time of cystectomy, because this step adds minimal time or morbidity to the operation [31]. The risk of urethral TCC in women has become an issue only since the introduction and popularization of orthotopic diversion among carefully selected women undergoing radical cystectomy in the early 1990s [43–48]. The estimated overall risk of urethral TCC in women at the time of cystectomy is not as well studied as in men. An early report by Ashworth found an incidence of 1.4% among 293 women [25]. In a large series of 356 women undergoing radical cystectomy, the incidence of