Management of the Prostate and Urethra in Patients Undergoing Radical Cystectomy

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ABSTRACT

For individuals with muscle invasive bladder cancer, radical cystectomy has remained the gold standard for treatment. Due to the common post operative complaints in patients undergoing radical cystectomy with orthotopic neobladder formation i.e. sexual dysfunction and urinary incontinence, members of the urologic community have sought ways to ameliorate these side effects with prostate and urethra sparing surgery. This review pre-sents that topic based on the contemporary literature regarding the management of the prostate and urethra in men and women undergoing radical cystectomy for muscle invasive bladder cancer.
Prostate sparing cystectomy remains controversial. Those in favor of it emphasize sub-stantial improvements in functional outcomes and the effect that it could have on patients' quality of life. Those opposed to it cite increased oncologic risk and violation of the oncologic principle of *en bloc* excision of at-risk organs. The most current information related to this ongoing debate is presented and discussed.

INTRODUCTION

Bladder cancer remains a significant public health problem throughout Europe and the rest of the world. While mortality from bladder cancer has trended downward over the last 2 decades in several western European nations, it has increased in some eastern European countries [1]. The worldwide prevalence of bladder cancer is believed to be over one million [2]. A majority of bladder cancers are non-invasive and respond well to local resection and adjuvant intravesical therapy if required. Unfortunately, recurrence rates for non-invasive disease are high (50-70%), with 10-15% of these tumors progressing to muscle-invasion.

As death rates from other genitourinary malignancies have decreased due to stage migration, less invasive means of treatment have been accepted into clinical practice [3, 4]. While one would expect a similar stage migration with individuals diagnosed with bladder cancer, recent reports suggest otherwise [5]. For individuals with muscle invasive bladder cancer, radical cystectomy has remained the gold standard for treatment with 5 year survival percentages ranging between 48-59% in contemporary series [6-9]. Survival has improved as a result of improved surgical technique, improved anesthesia, blood banking, antibiotic use, improved suturing materials, and the implementation of stapling devices [10]. While radical cystectomy outcomes have improved, especially in high volume centers, significant morbidity persists. Two of the most common post operative complaints in patients after undergoing radical cystectomy with orthotopic neobladder formation are sexual dysfunction and urinary incontinence. Because of this, members of the urologic community have sought ways to mediate these side effects with prostate and urethra sparing surgery. What follows is a brief review of the contemporary literature regarding the management of the prostate and urethra in men and women undergoing radical cystectomy for muscle invasive bladder cancer.

Contemporary Management of Prostate

Urothelial cell carcinoma (UCC) of the prostate has been reported in excess of 40% of men undergoing radical cystoprostatectomy for bladder cancer [11]. It is rarely encountered in the absence of bladder cancer and prostate sparing strategies have generated heated debate regarding how the prostate should be managed in individuals with bladder cancer [12].

Several theories have been presented to explain the pathogenesis of prostatic urothelial cell carcinoma. Since the prostatic urethra and large ducts are lined by transitional epithelium, it could develop in a synchronous manner at the time that a primary bladder lesion develops [13]. Alternatively, the prostate can be involved by direct extension of a bladder lesion posteriorly or directly through the bladder neck [14]. One could also argue that the same carcinogens that come in contact with the bladder transitional epithelium come into contact with the prostate or that cells shed from the upper tract take residence along the prostatic epithelium. Carcinoma *in situ* (CIS) could spread to involve the prostatic urethra and infiltrate the prostatic ducts. Reports suggesting that individuals with CIS or bladder neck involvement have higher rates of prostatic involvement support these hypotheses. Risk factors for prostatic involvement of UCC include multifocal urothelial cell carcinoma, carcinoma *in situ* and tumors involving the trigone [15, 16]. Involvement of the prostate is associated with urethral recurrence. If stromal invasion is present, the risk of recurrence is 64% compared to 25% in men with ductal or acinar involvement [17]. Stromal invasion upgrades the tumor stage to T4a and is associated with a 20% increase in nodal metastasis [18]. If the prostatic urethra is free of tumor, the risk of recurrence is approximately 5%. All patients undergoing radical cystectomy have their urethra inspected, but those with the above mentioned risk factors should undergo prostatic urethral biopsy.

While one must take into account the risk of urothelial cell cancer involvement of the prostate, there is also a risk of occult prostate cancer. Published rates of occult prostate cancer in men undergoing radical cystectomy range from 23 to 48%, perhaps explained by varying histopathological techniques of sampling [19-22].

The gold standard for high grade muscle invasive bladder cancer remains radical cystoprostatectomy. With the introduction of minimally invasive approaches for other genitourinary malignancies, urologists have sought to mitigate the morbidity associated with the treatment of muscle invasive bladder cancer. Some have suggested organ preservation, if possible, without compromising

cancer outcomes. Over the last decade, prostate sparing cystectomy has been performed in select candidates to improve clinical and functional outcomes associated with continence, potency and fertility. Several recent clinical series have described modifications to the classic radical cystectomy as a means of improving postoperative continence and potency rates [20, 23-27]. Several modified surgical approaches have been described including sparing of the prostate, seminal vesicles, and vas deferens. Before discussing 2 of the larger series of patients undergoing prostate sparing cystectomy, let's review a few reports detailing the pathologic findings of the prostate in men undergoing radical cystectomy.

Barbisan et al. recently reported their findings after examining whole-mount prostate sections of 248 consecutive men undergoing radical cystectomy over a 12 year period [28]. UCC involving the prostate was present in 94 (37.9%) patients with 78 (31.5%) individuals having UCC originating from the urethra or peri-urethral ducts. Stromal invasion was present in 36 specimens. Prostate cancer was present in 123 (49.6%) patients with the majority (78.1%) of tumors present in the peripheral zone. One hundred (81.3%) of the incidental prostate cancers discovered were deemed clinically insignificant.

Investigators from Vanderbilt reported their findings after examining whole-mount prostates from 121 consecutive radical cystoprostatectomy specimens [22]. The majority of prostates evaluated had no involvement of the apex by urothelial cell or prostate carcinoma, opening the door for apex sparing radical cystoprostatectomy. However, standardized guidelines for who would be an appropriate candidate for prostate sparing cystectomy need to be established.

Weizer et al evaluated the peripheral zone and capsule of the prostate in 35 patients who underwent radical cystoprostatectomy at the University of Michigan to help define the risk of occult malignancy with prostate capsule sparing cystectomy [29]. Specimens were evaluated for bladder and prostate cancer grade, stage, and the largest diameter of prostate cancer present. Twenty patients (57%) had evidence of cancer involving the prostate. Nine patients (26%) had UCC involving the prostate. Sixteen (47%) patients had prostate cancer, with a majority involving the peripheral zone or capsule. When performed, pre-operative transurethral prostate biopsy identified all patients with urothelial cancer involving the prostate. This study was one of the first evaluating the peripheral zone and capsule separately from the prostate adenoma and bladder to help determine the feasibility of prostate capsule sparing cystectomy. A significant percentage of individuals undergoing radical cystectomy will have cancer involving the prostate with no clinical variable accurately identifying these individuals pre-operatively. Pre-operative normal digital rectal exams and PSA levels within normal limits cannot rule out prostate cancer. Individuals who are candidates for capsule sparing radical cystectomy should have pre-operative prostate needle biopsies and urethral biopsies to assess risk.

Thorstenson et al recently reported their experience with prostate capsule and seminal sparing radical cystectomy with orthotopic neobladder formation [23]. They described the clinical outcome of 25 men with a mean follow up of 72 months. The men involved in their study had their seminal vesicles, posterior prostate and neurovascular bundles spared during surgery. During follow up, five patients developed metastases and died of bladder cancer. Four men were diagnosed with concomitant prostate cancer. Eighty-five percent (17/20) of the surviving patients had day-time continence while fifty percent (10/20) experienced complete nocturnal continence. Ninety-five percent were sexually active following prostate-sparing cystectomy.

Rozet et al have reported outcomes of the largest group of men treated at a single institution with prostate sparing cystectomy for muscle invasive disease [25]. Over a 12 year period, 117 patients were treated with prostate sparing cystectomy without neoadjuvant chemotherapy for bladder cancer at the Institut Mutualiste Montsouris in Paris, France. Nine individuals had perioperative frozen sections demonstrating prostatic urothelial carcinoma and underwent radical cystoprostatectomy. Long-term oncologic results were available for the remaining patients. The rate of local and distant recurrence was 4.7% and 34%, respectively, at 20 months. The overall 5 year survival rate was 67% with 77% of those with pT2N0 or less surviving, compared to 44% for pT3N0 and 22% for those with node positive disease. This study represents the largest prospective cohort of patients treated by prostate sparing cystectomy to date. Their outcomes are comparable with the largest published series of cystoprostatectomy, but there were a few limitations making comparison with other reports difficult.

Prostate sparing cystectomy is one of the most controversial topics in urologic oncology. Those in favor of it emphasize substantial improvements in functional outcomes and the effect that it could have on patients' quality of life. Those opposed to it are sceptical of the perceived increased oncologic risk and violation the oncologic principle of *en bloc* excision of at-risk organs [30]. Little data regarding the long-term oncologic outcomes with prostate-sparing cystectomy is available and critical questions remain unanswered regarding the overall efficacy of this procedure.

Contemporary Management of Urethra

Whether or not the urethra should be removed at the time of radical cystectomy was once a controversial issue within the field of urologic oncology. Original proponents of urethrectomy at the time of cystectomy advocated it because of the usually advanced disease present at the time of diagnosis of urethral recurrences, technical difficulty of urethrectomy because of postoperative fibrotic changes at the urethral stump, and questionable utility of leaving the urethra behind in those with cutaneous urinary diversions [31, 32]. Most advocated routine removal until Raz and Skinner reported their experience with 174 men who underwent radical cystectomy for bladder cancer [33]. They concluded that routine urethrectomy is not indicated unless overt urethral cancer was present pre-operatively or positive margins were present at the time of cystectomy. Since then, the indications and optimal timing of urethrectomy have been debated in the literature.

The reported incidence of urethral recurrence after radical cystoprostatectomy for bladder cancer has ranged from 4 to 17% with a large review suggesting a 10.1% recurrence rate [34-36]. Urethrectomy at the time of cystectomy is advocated for those with an increased risk of urethral recurrence. UCC invading the prostatic stroma is an indication for urethrectomy at the time of cystectomy as these individuals have a higher risk of recurrence [37]. Other features that confer an additive risk of urethral recurrence include carcinoma *in situ*, cancer at the bladder neck, and tumor multiplicity [38]. Urethral recurrences of UCC are troublesome as they are often indicators of metastatic disease. Investigators from the University of Southern California retrospectively reviewed their database of 1,054 patients who underwent radical cystectomy and urinary diversion for UCC over a 26 year period in 2004 [39]. Urethral recurrence was documented in 47 patients after a median follow up of 18.5 months, with 42% being diagnosed within the first year. Thirty-six died at a median follow-up of 26 months, 25 of whom had metastatic disease. Poor outcomes associated with urethral recurrences may be secondary to the *lamina propria* being the only barrier between the urethral mucosa and *corpora cavernosa* with its rich blood supply and access to the systemic circulation [40]. Complete urethrectomy has been proven superior to local resection in the management of individuals who develop UCC recurrences in the urethra.

Most now advocate frozen section analysis of the urethral stump during radical cystectomy to determine whether or not to perform a simultaneous urethrectomy. A review of more than 100 patients who had frozen section analysis of the urethral stump at the time of cystectomy did not reveal urethral recurrence in those with negative frozen sections after a 10-year minimum follow up [41].

Using the surveillance, epidemiology and end results (SEER) database, Nelles et al. investigated urethrectomy following radical cystectomy in men, with a focus on outcomes [42]. Of the 2,401 men who underwent radical cystoprostatectomy over an 11 year period, 195 (8.1%) men underwent urethrectomy, with stage being the only significant predictor. Fifty-three percent (103) were simultaneous or staged operations performed within 6 weeks of cystoprostatectomy, while the remaining 92 procedures were performed for observed urethral recurrence at a median of 9 months (range 2 to 79) after cystectomy. Their retrospective review revealed a higher survival in men who underwent simultaneous urethrectomy with radical cystoprostatectomy, but this was not statistically significant. Urethrectomy did not confer a significant independent survival benefit.

To address the question of whether or not orthotopic neobladder formation has led to the conservation of more urethras with a subsequent increase in urethral recurrence rates, Freeman et al. compared urethral recurrence rates amongst men who underwent neobladder formation and cutaneous diversion [43]. One hundred and seventy-four men with ileal neobladders were compared to 262 with cutaneous urinary diversions. The overall risk of urethral recurrence was 7.8% at 5 years. For those with an ileal neobladder, the risk of recurrence was 2.9% compared to 11.1% in those with a cutaneous diversion. This suggests that a functional urethra decreases the risk of recurrence. While the reasons for this remain unknown, some have postulated a number of intrinsic physiological, biochemical, genetic and immunological characteristics of the ileum.

Radical cystectomy in women requires a special understanding of the pelvic anatomy to preserve striated sphincter function in women who desire an orthotopic neobladder. Urethra sparing cystectomy was initially feared because of concerns regarding oncologic outcomes and a perceived increased risk of recurrence. Over the last 15-20 years, radical cystectomy with orthotopic neobladder formation has been proven as a viable option with good oncologic outcomes.

When orthotopic bladder substitution is planned in women, it is necessary to remove the bladder neck and the proximal portion of the urethra, leaving a major portion of the urethra with the rhabdosphincter distally [44]. To obtain satisfying micturitional results after orthotopic bladder substitution, it is important to resect the bladder neck together with an adjacent segment of the urethra, as a low-pressure intestinal reservoir lacks the pressure to overcome the passive resistance of the full length of the urethra [45]. Approximately 80% of the urethra should be preserved to perform continent orthotopic neobladder formation [45]. In the female urethra, the transition level between squamous and transitional epithelium varies [46]. As women age, this transitional zone moves cranially, most likely secondary to the lack of estrogen [47]. Because of this, the remaining urethra after cystectomy may be primarily composed of entirely squamous epithelium, with little transitional cell epithelium.

Investigators from the Medical University of Innsbruck in Austria analyzed the risk factors and incidence of recurrent UCC in women who underwent radical cystectomy with orthotopic bladder substitution (46) or non-orthotopic urinary diversion (39) at their institution [48]. Urethral recurrence was found in 2 patients (4.3%), 65 and 36 months after orthotopic neobladder surgery, respectively. Recurrent or multifocal UCC represented a risk factor for recurrence as none of the women with a solitary invasive lesion or primary lesion recurred after a mean follow up of 49 months. A meta-analysis in 2002 revealed a slightly lower incidence of urethral recurrence in the remnant female urethra after radical cystectomy [46]. This supports other published reports of good oncologic outcomes in properly selected women who undergo radical cystectomy with orthotopic neobladder formation.

CONCLUSIONS

While established guidelines are in place for clinical decision making regarding the management of the urethra in patients with muscle invasive bladder cancer, prostate sparing cystectomy remains controversial. With time, prostate sparing cystectomy with a standardized technique should emerge to preserve potency and improve continence in appropriate surgical candidates.

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