Long considered oncologically hazardous or functionally damaging, radical cystectomy with orthotopic urinary diversion is the accepted standard of care for invasive bladder cancer. A number of anatomical and clinical observations have come together to make orthotopic urinary diversion possible for female patients. Not only have these observations led to the development of an oncologically safe, low-pressure reservoir for urine, but also have improved the postoperative quality of life. Urethral sparing technique is safe for patients without bladder neck or trigonal tumors. Furthermore, improved understanding of the female urethral rhabdosphincter has decreased the likelihood of postoperative urinary incontinence. Finally, female sexual function may be preserved in patients who undergo preservation of the neurovascular tissue lateral to the vagina. These improvements have solidified orthotopic urinary diversion as the procedure of choice for selected female patients requiring radical cystectomy. Clin. Anat. 26:105–109, 2013.

**Key words:** radical cystectomy; women; orthotopic urinary diversion

**INTRODUCTION**

Urothelial carcinoma of the bladder is the fourth most common cancer in the United States that will affect up to 18,000 women in 2012 (Siegel et al., 2012). Anterior pelvic exenteration is the gold-standard treatment for those with muscle-invasive or recurrent high-grade tumors (Stein et al., 2001). For women this includes removal of the urethra, bladder, uterus, ovaries, fallopian tubes, as well as the anterior portion of the vagina (Marshal and Treiger, 1991; Granberg et al., 2008; Stein et al., 2009). This approach ensures an adequate soft tissue margin even for most locally advanced tumors that originate in the bladder. Yet, after the bladder has been removed, there is an obvious need for an oncologically safe and physiologically functional reservoir for urine. For nearly a century, the only continence alternative for women undergoing cystectomy was ureterosigmoidostomy, a form of urinary diversion fraught with significant oncologic, functional and metabolic concerns (Tollefson et al., 2010).

Over the last two decades, a greater understanding of the female continence mechanism, sexual function and a better appreciation of the patterns of urethral cancer recurrence in women with bladder cancer have facilitated the development and propagation of orthotopic urinary diversion for female patients. The purpose of this review is to outline the evolution of orthotopic urinary diversion in female patients and to highlight the anatomic principles that have made such diversion possible. This procedure was specifically selected for review as it was recently developed and modified directly following the discovery of critical anatomic relationships impacting urinary and sexual function.

**EVOLUTION OF CONTINENT URINARY DIVERSION IN FEMALE PATIENTS**

In 1852, Simon first described the diversion of urine into the sigmoid colon. Despite the fact that the patient did not survive, ureterosigmoidostomy...
became the primary mechanism for urinary diversion after cystectomy (Simon, 1852). Unfortunately, ureterosigmoidostomy was complicated by a high incidence of febrile urinary tract infections, metabolic acidosis, incontinence, and secondary malignancies. It was not until Bricker (1950) described the ileal conduit 100 years later that ureterosigmoidostomy was supplanted as the predominant form of urinary diversion.

Beginning in the 1990s efforts were made to advance lower tract urinary reconstruction with a goal to not only divert the urine and protect renal function, but also to provide patients with a continent means to store urine and allow for volitional voiding through the native urethra. It was hoped that such reconstruction would allow for a more normal lifestyle, improved quality of life and decreased dependence upon external appliances. The orthotopic ileal neobladder was developed to accomplish these objectives (Hautmann et al., 1988, 1993). Largely limited to male patients after radical cystectomy due to the extra margin of safety provided by a lengthy prostatic urethra, this mode of lower urinary tract reconstruction was felt to be inappropriate for female patients because of the presumed need for radical urethrectomy in women. Therefore, the development of orthotopic urinary diversion in women was limited to the very few patients undergoing cystectomy for benign disease (such as interstitial cystitis) and anecdotal experience in highly selected patients with urothelial carcinoma (Blute and Gburek, 1998).

IS IT SAFE? LET’S CHECK THE HISTOLOGY

The first question to be answered when urethral sparing radical cystectomy is planned is whether it is a sound oncologic procedure. Urothelial carcinoma is considered to be a pan-urothelial disease, with all components of the urothelium at risk for tumor implantation. Indeed, one of the reasons partial cystectomy has been relegated to highly selected patients with urothelial carcinoma is due to high rates (greater than 50%) of bladder recurrences (Lindahl et al., 1984; Sweeney et al., 1992) and successful transurethral resection for patients not healthy enough for radical exonerative surgery. Men also possess 3–6 cm of prostatic urethra that is only rarely involved by urothelial carcinoma. This lengthy urethra provides a significant margin of safety when resecting an aggressive malignancy. Females, on the other hand, have only 3–4 cm of urethra in total, of which approximately 80% is necessary for the preservation of urinary continence.

It has been recognized only recently that the female urethra is histologically and functionally distinct from the proximal male urethra. Some of these differences appear to be advantageous when designing orthotopic urinary diversion. For example, female patients possess both squamous and urothelial epithelium within the urethra. The distal portion of the urethra is typically covered with squamous epithelium while the more proximal portions of the urethra may be covered with urothelial epithelium. The extent of squamous epithelium and the level at which it transitions to urothelial epithelium varies considerably (likely in response to the influence of estrogen). Indeed, in some older patients, the level at which squamous epithelium transitions to urothelial epithelium may encompass the whole urethra, bladder neck and significant portions of the urinary trigone (Packham, 1971; Wiener et al., 1979; Stenzl and Holtl, 2003). Accordingly, it is not uncommon to observe squamous metaplasia encompassing a large portion of the bladder neck and urethra in postmenopausal women. Given that most female patients with invasive urothelial carcinoma are postmenopausal with a median age at diagnosis is 74 years old (Siegel et al., 2011, 2012), the amount of urothelium in the urethra and bladder neck exposed to malignancy may be less than previously appreciated. Clinical experience suggests that it is extremely rare for a urothelial tumor to implant within squamous epithelium if the primary tumor and the entire urothelium of the bladder has been removed.

This hypothesis may in part explain the low-rate of urethral tumor in female patients with high-grade bladder cancer. Defining the likelihood of urethral tumor has been the subject of a number of studies, the objective of which has been to map patterns of urothelial tumors and identify risk factors for urethral involvement. These studies have step-sectioned cystourethrectomy specimens in female patients and identified a risk of urethral involvement that ranges from 4–11% (Coloby et al., 1994; Stein et al., 1995). Importantly, however, these studies demonstrated that patients with urethral tumors almost exclusively possessed malignancy at the bladder neck and/or trigone (Stenzl and Holtl, 2003). No patients examined had a skip lesion from other locations in the bladder to the urethra. To further define the risk of urethral tumor in patients with urothelial carcinoma, a number of studies focused upon patients with noninvasive urothelial tumors of the bladder and evaluated for urethral recurrence. These studies have demonstrated that the risk of urethral recurrence is between 1.4 and 2% of patients (Ashallworth, 1956; Stenzl et al., 1995a,b). In fact, the likelihood of urethral recurrence was lower for female patients than male patients (Erckert et al., 1996). Furthermore, the only consistent risk factor for urethral tumor in female patients was contiguous extension of a tumor in the trigone or bladder neck.

To assess the primary risk factor for urethral involvement, contiguous extension of trigonal or bladder neck tumors, frozen section analysis of the distal margin of the urethral margin is now commonplace. This technique has been demonstrated to be a safe, efficient, and accurate measure of local extent (Stenzl et al., 2001). With these caveats in mind, the subject of urethral tumor recurrence has been the study of a number of clinical studies that now include greater than 500 female patients after radical cystectomy with orthotopic diversion (Table 1). With a median follow-up of greater than 30 months, solitary urethral recurrence has been documented in 4 patients (<1%) (Stenzl et al., 2001; Stein et al., 2002; Ali-el-Dein, et al., 2004; Lee et al., 2004; Hassan et al., 2004; Granberg et al., 2008).
FUNCTIONAL BASIS FOR DIVERSION: URINARY INCONTINENCE

Once orthotopic diversion was demonstrated to be oncologically safe, the next question was whether female patients would retain bladder control after resection of the bladder neck and proximal urethra (Table 2). Answering this question required a deeper understanding of how women maintain urinary continence before cystectomy as well as how this anatomy changes after anterior pelvic exenteration.

It has long been known that women undergoing distal urethrectomy for diverticula and/or primary urethral tumors may retain continence as long as the middle and proximal thirds of the urethra are preserved (Spence and Duckett, 1970). Continence was therefore presumed to be dependent upon bladder neck function. Radical cystectomy, however, resects that bladder neck as well as a portion of the proximal urethra. Continence would be dependent solely upon the urethral sphincter, a muscular complex poorly understood.

The urethral sphincter is an omega-shaped muscular complex that consists of multiple layers of both smooth and striated muscle. Numerous authors have characterized the transition from smooth muscle to striated muscle in the mid-urethra to the distal third of the urethra (Borirakchanyavat, 1997; Colleselli et al., 1998). The smooth muscles are primarily innervated by autonomic fibers that originate in the pelvic plexus. Branches of the pudendal nerve primarily innervate the striated muscles. The hypogastric nerves traverse the pelvis along the sides of the lumbar spine. Initially these nerves course medially and then posteriorly to the ureter (Yamaguchi et al., 2011). The somatic nerves originate from S2 to S4 and course laterally to the vertebrate and ultimately along the levator ani muscle underneath the endopelvic fascia. They lie immediately adjacent to the bladder’s inferior vascular pedicle and continue along the anterior wall of the vagina to innervate the urethra. Because of location of the location of the somatic pathway, it is susceptible to injury during the dissection of the bladder pedicle and during identification and transection of the inferior vascular pedicle. Indeed, it has long been known that bladder dysfunction, particularly urinary incontinence, is a common long-term complication of radical hysterectomy. It is presumed that this urinary dysfunction is due to interruption of the neurons innervating the bladder, urethra and pelvic floor muscles.

These observations, in concert with the development and popularization of nerve-sparing radical prostatectomy (Walsh and Mostwin, 1984), have led to the development of nerve-sparing radical cystectomy in female patients. Performing an anterior exenteration with complete resection of the vagina with the caudal margin below the bladder neck would result in the dissection of the majority of these autonomic nerves to the female urethra. On the contrary, a careful dissection of the lateral vaginal walls, bladder neck and proximal urethra leaves the plexus fibres to the urethra intact and preserves the sphincter mechanism. Wide dissection in the region of the upper hypogastric nerves crossing the common iliac artery may compromise the results of nerve-sparing dissection at the level of the vaginal wall.

Similarly, the suspensory fascial attachments of the remnant urethra to the pelvis are critical to the maintenance of continence after surgery. Division of these fascial attachments may result in urethral hypermobility, angulation, and poor functional outcome. Preservation of the endopelvic fascia and the pubourethral ligaments anterior to the bladder neck is important in maintaining the appropriate anatomic relationships as the urethra courses through the pelvic floor. This support system is augmented by the infrapelvic fascia (levator ani and pubococcyegeus muscles) and by the connective supporting tissues of the anterior vaginal wall surrounding the urethra. Dissection of the cystectomy specimen off of the anterior vaginal wall may assist in maximizing preservation of support structures and innervation to the anterior urethra, factors that may be important in maintaining passive and voluntary urinary control (Chang et al., 2002; Cole and Smith, 2011).

Finally, chronic urinary retention after cystectomy and orthotopic urinary diversion remains a significant issue for female patients. Although some have suggested this chronic retention is secondary to hypeontractility of the neobladder wall, there is now strong evidence that urinary retention is caused by anatomic, rather than functional or neurogenic reasons (Ali-El-Dein et al., 2002). Videourodynamics has demonstrated a falling back of the pouch into the pelvic cavity which results in an acute angulation of the neobladder-urethral junction. Reconstruction to the pelvic floor after cystectomy increases the back support of the pouch which may result in a significant decrease in urinary retention.

FUNCTIONAL BASIS FOR DIVERSION: SEXUAL DYSFUNCTION

In addition to cancer survival and urinary control, identification of other chronic treatment-associated conditions is important. Although poorly recognized, the primary source of self-assessed distress among patients undergoing radical cystectomy is impaired sexual function (Henningson et al., 2002, 2003). In fact, three of the five most important specific symptoms causing long-term postoperative distress in 78 women with cystectomy were disrupted vaginal anatomy, vaginal problems during sexual activity, and pain at intercourse (Henningson et al., 2003). Sexual function may be affected in women during cystectomy due to locally advanced disease or damage to adjacent tissue during the procedure. Bjerre et al. (1997) evaluated the sexual profile after urinary diversion in 37 women who underwent cystectomy coital frequency was low, 30% recommended sexual counseling and almost one-third gave physical problems or decreased desire as the reason. Furthermore, Zippe et al. (2004) reported objective outcome data about 34 sexually active females undergoing cystectomy for bladder cancer. At a median follow-up of 24 months, they showed a significant decreased total score of the Female Sexual Function Index. The most frequently reported
complaints were that reaching orgasm was either difficult or impossible (45%), vaginal lubrication decreased (41%), sexual desire decreased (37%), and dyspareunia occurred (22%). Only 48% of the patients were able to have successful vaginal intercourse after surgery, 52% complained of a significant decrease in sexual satisfaction.

To address these concerns, surgeons and anatomiasts came together to identify the anatomic basis of female sexual dysfunction. Cadaveric dissections demonstrated that the neurovascular bundles course on the lateral walls of the vagina and may be easily damaged by removal of the bladder, urethra and anterior vaginal wall (Stenzl et al., 1995a,b, 1998; Schoenberg et al., 1999). Moreover, the clitoris may be significantly devascularized when the urethra is transected (Berman et al., 2003; Zippe et al., 2005). Awareness of these anatomic relationships has facilitated the development of nerve-sparing radical cystectomy for female patients. This approach has decreased the frequency of postoperative sexual dysfunction. Bhatt et al. (2006) assessed female sexuality in six patients who had undergone nerve-sparing cystectomy and seven patients who had undergone non-nerve-sparing cystectomy. In the nerve-sparing group, the baseline and 12-month postoperative scores showed a minimal decline in results, whereas a significant decline or difference was found in the non-nerve-sparing group. In the non-nerve-sparing group, six of seven women ultimately discontinued sexual intercourse. Using the validated Functional Assessment of Cancer Therapy-Vanderbilt Cystectomy Index, Large et al. (2010) reported that women undergoing orthotopic neobladder or Indiana Pouch reconstruction had no differences for physical, social, emotional, functional, and cystectomy-specific health-related quality of life (HRQOL) domains. Multivariate analysis considering patient age, diversion type and time from surgery revealed no significant interaction between HRQOL and age, stage or diversion type. Therefore, it is thought that the primary source of sexual dysfunction after cystectomy is secondary to the cystectomy itself, rather than the mechanism or location of the urinary diversion.

**SUMMARY**

Radical cystectomy remains the most commonly recommended treatment for healthy female patients with invasive bladder cancer. Orthotopic urinary diversion can provide excellent oncologic outcomes with a minimal risk of urethral recurrence. Furthermore, after the improved understanding of the female urethral sphincter, the procedure has been modified to provide improved urinary control after surgery. Finally, female sexual function can be safely preserved in patients undergoing neurovascular preservation.

**REFERENCES**


**TABLE 1. Tumor Recurrence Within the Retained Urethra After Radical Cystectomy and Orthotopic Urinary Diversion in Women**

<table>
<thead>
<tr>
<th>Series</th>
<th>Number of patients</th>
<th>Median follow-up (months)</th>
<th>Urethral recurrences (pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akkad et al.</td>
<td>46</td>
<td>45</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Ali-El-Dein et al.</td>
<td>145</td>
<td>17</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Granberg et al.</td>
<td>59</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Hassan et al.</td>
<td>29</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>53</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Stein et al.</td>
<td>88</td>
<td>30</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Stenzl et al.</td>
<td>102</td>
<td>26</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE 2. Criteria Used to Exclude Female Patients From Orthotopic Urinary Diversion After Radical Cystectomy**

<table>
<thead>
<tr>
<th>Patient-related criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic renal insufficiency (eGFR &lt; 30)</td>
</tr>
<tr>
<td>Inability or refusal of intermittent catheterization</td>
</tr>
<tr>
<td>Significant stress urinary incontinence</td>
</tr>
<tr>
<td>Prior radiation therapy to retained urethra or small intestines</td>
</tr>
<tr>
<td>Abnormal bowel function</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer-related criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor or significant dysplasia at urethral margin (frozen section)</td>
</tr>
<tr>
<td>Significant tumor involvement of the anterior vagina</td>
</tr>
<tr>
<td>Multiple positive lymph nodes</td>
</tr>
</tbody>
</table>


Simon J. 1852. Ectopia vesicae (absence of the anterior walls of the bladder and pubic abdominal parieties); operation for directing the orifices of the ureters into the rectum: Temporary success; subsequent death; autopsy. Lancet 60:568–570.


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