Treatment and Outcomes of Urethral Recurrence of Urinary Bladder Cancer in Women after Radical Cystectomy and Orthotopic Neobladder: A Series of 12 Cases

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Abstract

Introduction: The incidence, treatment, and outcome of urethral recurrence (UR) after radical cystectomy (RC) for muscle-invasive bladder cancer with orthotopic neobladder in women have rarely been addressed in the literature. Patients and Methods: A total of 12 patients (median age at recurrence: 60 years) who experienced UR after RC with an orthotopic neobladder were selected for this study from a cohort of 456 women from participating institutions. The primary clinical and pathological characteristics at RC, including the manifestation of the UR and its treatment and outcome, were reviewed. Results: The primary bladder tumors in the 12 patients were urothelial carcinoma in 8 patients, squamous cell carcinoma and adenocarcinoma in 1 patient each, and mixed histology in 2 patients. Three patients (25%) had lymph node-positive disease at RC. The median time from RC to the detection of UR was 8 months (range 4–55). Eight recurrences manifested with clinical symptoms and 4 were detected during follow-up or during a diagnostic work-up for clinical symptoms caused by distant metastases. Treatment modalities were surgery, chemotherapy, radiotherapy, and bacillus Calmette-Guérin urethral instillations. Nine patients died of cancer. The median survival after the diagnosis of UR was 6 months. Conclusions: UR after RC with an orthotopic neobladder in females is rare. Solitary, noninvasive recurrences have a favorable prognosis when detected early. Invasive recurrences are often associated with local and distant metastases and have a poor prognosis.

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Key Words
Bladder cancer · Cystectomy · Female · Relapse · Treatment outcome · Urethra

Introduction

In recent decades, radical cystectomy (RC) with extended pelvic lymph node dissection has become the mainstay of treatment for muscle-invasive bladder cancer. The treatment aims to provide long-term survival with an acceptable quality of life. Reconstruction of the lower urinary tract using orthotopic bladder substitution has increased the ac-
acceptance of radical surgical treatment by both physicians and patients [1], including older age groups [2, 3].

The initial reluctance to perform orthotopic bladder substitution in females was due to the short urethral length (hence, the proximity of the bladder neck and bladder tumor) and the fear of incontinence after removal of the proximal urethra adjacent to the bladder neck [4]. The added morbidity of urethrectomy, the longer surgical time, and the very high rate of negative pathology made physicians question the need for routine urethrectomy in females [5]. This paved the way for a wider use of orthotopic neobladders in women. According to recent anatomical dissection studies, the external female rhabdosphincter is located in the distal half of the urethra and is innervated by the pudendal nerve from below. Smooth muscle innervated by the autonomic nerve system via branches from the pelvic plexus running alongside the lateral vaginal walls is present throughout the length of the urethra. Hence, a careful technique of bladder neck and vaginal dissection will preserve the nerve supply and muscle structures necessary for continence [6].

Retrospective pathological studies have reported a 12% (range 6–46) rate of concomitant tumor (of any stage) in the bladder and the urethra in females. Bladder neck involvement is a strong risk factor for concomitant urethral malignancy, observed in 19–33% of urethral tumors. In contrast, urethral tumors have never been found in women with a tumor-free bladder neck. Some investigators found an association with tumor involvement of the anterior vaginal wall, but later studies failed to confirm this finding [4].

We describe the incidence, treatment, and outcomes in 12 cases of recurrence of urinary bladder cancer (UBC) in the female urethra after RC.

**Patients and Methods**

The 12 patients reported herein were selected from a multi-institutional collaborative cohort of 456 women who underwent RC for UBC in 1 of the 5 participating centers between 1994 and 2011. The median follow-up was 64 months (range 3–196). We retrospectively reviewed the clinical and pathological records of all 456 female patients for age, histology, tumor stage and grade, lymph node involvement, soft-tissue surgical margins, final urethral margin status, and survival [7].

The intensity of the follow-up depended on each institution’s protocol. Recurrence in the surgical bed was defined as local, recurrence at distant organs was defined as distant, and recurrence in the urethra was defined as urethral. Clinical outcomes were measured from the date of cystectomy to the date of the first documented recurrence, the date of death, or the date of the last follow-up if the patient had not experienced disease recurrence. A positive urethral margin was a significant risk factor for urethral recurrence (UR) [7].

The present report describes the 12 recurrent patients identified within the defined cohort, including 1 who relapsed after the end of the original study (table 1).

**Results**

A total of 12 patients (median age at RC: 58 years; range 41–71) were studied. The bladder tumors were urothelial carcinoma in 8 patients (67%), squamous cell and adenocarcinoma in 1 patient (8%) each, and mixed urothelial carcinoma in 2 patients (17%). Three patients had lymph node-positive disease (2 with pN1 and 1 with pN2) at RC, and none had evidence of distant metastasis at RC (cM0). Urinary diversion was performed according to Studer or Hautmann (6 cases each). Two patients (G and L) received adjuvant cisplatin-based chemotherapy after RC.

The median time from RC to the detection of recurrence in the urethra was 8 months (range 4–55). Eight recurrences (67%) manifested with clinical symptoms which were pain-related in 4 patients, bleeding in 3, gross hematuria in 2, and urinary retention in 2. One recurrence was seen protruding from the urethra. The remainder were detected during follow-up or during a diagnostic work-up for clinical symptoms caused either by synchronous distant metastases or by pelvic recurrence.

Treatment with curative intent was given to 6 patients, and treatment with a palliative intent to was given to 3. Three women were unfit for or refused treatment. Open surgery was performed in 5 patients (including urinary undiversion in 3), radiotherapy was performed in 2 patients, chemotherapy was performed in 3 patients, and bacillus Calmette-Guérin (BCG) urethral instillations were used in 2 patients. Nine women (75%) died of cancer and 3 were still alive at the time of reporting. The median survival after detection of UR was 6 months (range 2–15). The most frequent sites of distant metastases were lymph nodes and bones.

**Discussion**

In our study, we gathered 12 cases of UR after RC with a neobladder substitution in women. This number is too low for statistically meaningful conclusions, but several observations can be made.

The advantage of maintaining a natural voiding pattern after RC must be weighed against the risk of a subsequent tumor recurrence in the remnant urethra. An 8.1% incidence of UR after cystoprostatectomy was reported in...
Table 1. Clinical and pathological characteristics of 12 female patients who experienced UR after RC and orthotopic neobladder

<table>
<thead>
<tr>
<th>Patient</th>
<th>RC date</th>
<th>Age at RC, years</th>
<th>Pathological stage and grade at RC</th>
<th>Histology at RC</th>
<th>Neobladder type</th>
<th>Time to recurrence, months</th>
<th>Recurrence detected</th>
<th>Recurrence stage</th>
<th>P or M at diagnosis/ later in the follow-up</th>
<th>Time to death, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29/05/1996</td>
<td>66</td>
<td>pT3a pN0 G3</td>
<td>urothelial</td>
<td>H</td>
<td>8</td>
<td>C</td>
<td>cT3</td>
<td>M</td>
<td>3</td>
</tr>
<tr>
<td>B</td>
<td>26/02/1998</td>
<td>55</td>
<td>pT2b pN0 G3</td>
<td>urothelial</td>
<td>H</td>
<td>4</td>
<td>C</td>
<td>cT3 N3</td>
<td>M</td>
<td>3</td>
</tr>
<tr>
<td>C</td>
<td>27/02/1996</td>
<td>56</td>
<td>pTa pN0 G1</td>
<td>urothelial</td>
<td>S</td>
<td>NR</td>
<td>C</td>
<td>pT3 G3</td>
<td>–/–</td>
<td>–</td>
</tr>
<tr>
<td>D</td>
<td>23/06/2008</td>
<td>66</td>
<td>pT2a pN0 G3</td>
<td>urothelial</td>
<td>S</td>
<td>7</td>
<td>C</td>
<td>pT4 G3</td>
<td>P/M</td>
<td>5</td>
</tr>
<tr>
<td>E</td>
<td>11/09/2007</td>
<td>71</td>
<td>pTis pN0</td>
<td>urothelial</td>
<td>S</td>
<td>21</td>
<td>F</td>
<td>CIS</td>
<td>–/–</td>
<td>–</td>
</tr>
<tr>
<td>F</td>
<td>30/03/2009</td>
<td>64</td>
<td>pTis + pT3b pN0 G3</td>
<td>urothelial + squamous</td>
<td>S</td>
<td>7</td>
<td>F</td>
<td>CIS</td>
<td>–/–</td>
<td>–</td>
</tr>
<tr>
<td>G</td>
<td>12/10/2008</td>
<td>66</td>
<td>pTis + pT2b pN0 G2</td>
<td>urothelial</td>
<td>S</td>
<td>55</td>
<td>W</td>
<td>NR</td>
<td>M</td>
<td>7</td>
</tr>
<tr>
<td>H</td>
<td>22/04/2005</td>
<td>63</td>
<td>pT2a pN0 G2–3</td>
<td>urothelial + adenocarcinoma</td>
<td>S</td>
<td>52</td>
<td>W</td>
<td>NR</td>
<td>M</td>
<td>15</td>
</tr>
<tr>
<td>I</td>
<td>23/04/1997</td>
<td>51</td>
<td>pT3a pN0 G3</td>
<td>adenocarcinoma</td>
<td>H</td>
<td>12</td>
<td>C</td>
<td>pT1 G3</td>
<td>P</td>
<td>7</td>
</tr>
<tr>
<td>J</td>
<td>22/04/1995</td>
<td>47</td>
<td>pT3a pN1 G2</td>
<td>squamous</td>
<td>H</td>
<td>8</td>
<td>C</td>
<td>pT1 G3</td>
<td>P/M</td>
<td>7</td>
</tr>
<tr>
<td>K</td>
<td>25/02/2002</td>
<td>51</td>
<td>pTis + pT3b pN0 G3</td>
<td>urothelial</td>
<td>H</td>
<td>13</td>
<td>F</td>
<td>pT3 G3</td>
<td>P</td>
<td>NR</td>
</tr>
<tr>
<td>L</td>
<td>13/07/2008</td>
<td>41</td>
<td>pT3a pN1 G3</td>
<td>urothelial</td>
<td>H</td>
<td>10</td>
<td>C</td>
<td>pT3 G3</td>
<td>P</td>
<td>2</td>
</tr>
</tbody>
</table>

Patient A presented with bleeding, pain and acute urinary retention. At that time, she had already been receiving paclitaxel and radiotherapy for public bone metastases diagnosed previously. After the detection of UR, only optimal supportive care was administered. Patient B had recurrence in the urethra, which caused pain and was palpable on physical examination. During an attempted surgical removal, advanced disease with metastatic deposits was found. The urinary diversion was transformed into a Mainz pouch II. Soon thereafter, she developed a colocutaneous fistula and nephrostomy tubes had to be inserted. Patient C was diagnosed with UR originating in the distal urethra as detected by both ultrasonography and physical examination. After surgical removal of the recurrence, she was free of disease for the entire follow-up. Patient D had recurrence manifesting as a painful mass protruding from the urethra and causing urinary retention. Surgical treatment included removal of the vagina and neobladder infiltrated by the tumor and conversion of the urinary diversion into an ileal conduit. The recurrence histology was pT4 G3 urothelial carcinoma with myxoid features. Patient E had UR diagnosed by urethral wash-out cytology and confirmed by a biopsy. She was treated with 6 urethral BCG instillations repeated every 3–6 months. She was the only one of this series to have a positive urethral margin at the final histopathology, yet she counts among survivors, being free of disease for 45 months after the operation. Patient F had her recurrence diagnosed by urethral cytology. The disease was eradicated via BCG instillations, but recurred again as CIS 3 years later. Conservative management with BCG was on-going at the time of reporting. Patient G received adjuvant gemcitabine + cisplatin after RC. She presented with a subileus caused by UR originating from the proximal urethra and bladder neck, infiltrating the neobladder, vagina, and rectum. Surgical treatment was attempted with partial vaginal, ileal, and total rectal resection. Multiple pelvic and peritoneal metastases were discovered. The patient received palliative chemotherapy. Patient H had UR detected during a work-up for an epileptic seizure caused by a synchronous brain metastasis. Radiotherapy failed to control the disease and she died with brain and pulmonary metastases. Patient I was unfit for the treatment of her urethral recurrence. Patient J presented with bleeding and gross hematuria as symptoms of squamous cell carcinoma UR. Urethrectomy was performed with conversion of the neobladder to a catheterizable continence reservoir. Nevertheless, she died of disease progression with lymph node and osseous metastases. Patient K was diagnosed with UR on follow-up imaging along with a concomitant pelvic mass. She was unfit for curative treatment. Patient L received adjuvant cisplatin-based chemotherapy after RC. UR manifested with pain and was evident on physical examination. Palliative gemcitabine and radiotherapy administration followed. H = Hautmann neobladder; S = Studer neobladder; C = by clinical symptoms; F = during follow-up; W = during a work-up for unrelated clinical symptoms; P = pelvic recurrence; M = distant metastasis; NR = not reported.

Urethral Recurrence after Radical Cystectomy with a Neobladder

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metastases at the time of UR diagnosis. Conversely, 3 females who were alive at the time of reporting had neither pelvic recurrence nor distant metastasis during follow-up. The primary bladder tumor stage was a predictor of survival. Of the 3 survivors among our patients, 2 had non-muscle-invasive bladder cancer at the time of RC (pTis and pTa). Nine out of 10 muscle-invasive primary UBC were followed by UR with a concomitant pelvic mass and/or distant metastasis. Ultimately, all died of cancer.

Surgical removal of the recurrence with a curative intent was attempted in 5 of our 12 patients, but the disease was truly eradicated in only 1 patient (patient C). The neobladder had to be changed to a Mainz pouch II, an ileal conduit, and a catheterizable continent reservoir in patients B, D, and J, respectively. Recurrences in the form of CIS have been successfully treated with BCG instillations of the urethra; this approach was described previously by Varol et al. [20]. When chemotherapy was administered, it was done with a palliative intent. The longest survival (15 months) was observed in patient H, who was treated with radiotherapy; the time to recurrence and the final grade 2–3 at RC suggest that her bladder cancer in general had a less aggressive character. Therefore, it seems that survival after UR treatment depends rather on the nature of the recurrence than on the treatment modality.

The oncological efficiency of follow-up in patients after RC is controversial [21, 22]. In our 12 patients, UR were detected based on symptoms in 1 of 3 patients who were still alive at the time of reporting and in 6 of 9 patients who died of the disease. Those who died of aggressive tumors might have – or might not have – been saved by earlier detection. However, we may assume that the 2 women with urethral CIS detected at follow-up would likely have progressed over time to muscle-invasive disease had they not been diagnosed and treated.

Given the easy anatomical accessibility of the female urethra, it can easily be checked during follow-up after RC. At a minimum, the patient can be asked about a history of gross hematuria and/or pain on micturition, and a digital vaginal examination can be performed [18]. A vaginal ultrasound gives excellent resolution of the urethral region. Introital ultrasonography might be a reasonable alternative but, to the best of our knowledge, no study has addressed this issue in a systematic manner. With regard to the CIS cases in our cohort and their long-term survival, urethral wash-out cytology [20] can be considered at least for patients at risk (i.e. those with CIS in the primary UBC at RC). Because of the broad time frame (6–55 months) in which the UR developed in our patients, it is difficult to draw conclusions regarding the optimal duration and frequency of follow-up in women with orthotopic neobladders.

### Conclusions

Recurrence of a bladder tumor in the female urethra after RC with an orthotopic neobladder is a rare event. Noninvasive recurrences (pTa-1 and CIS) are usually not accompanied by pelvic or distant metastasis and their prognosis is relatively favorable with adequate treatment. In contrast, if UR is associated with a local or distant disease relapse, the prognosis is dismal.
References


Urethral Recurrence after Radical Cystectomy with a Neobladder

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