

Original article

## Urethral recurrence in women with orthotopic bladder substitutes: A multi-institutional study

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### Abstract

**Objectives:** To evaluate risk factors for urethral recurrence (UR) in women with neobladder.

**Material and methods:** From 1994 to 2011, 297 women (median age = 54 y; interquartile range: 47–57) underwent radical cystectomy with ileal neobladder for bladder cancer in 4 centers. None of the patients had bladder neck involvement at preoperative assessment. Univariable and multivariable analyses were used to estimate recurrence-free survival and overall survival. The median follow-up was 64 months (interquartile range: 25–116).

**Results:** Of the 297 patients, 81 developed recurrence (27%). The 10- and 15-year recurrence-free survival rates were 66% and 66%, respectively. The 10- and 15-year overall survival rates were 57% and 55%, respectively. UR occurred in 2 patients (0.6%) with solitary urethral, 4 (1.2%) with concomitant urethral and distant recurrence, and 1 with concomitant urethral and local recurrence (0.3%). Bladder tumors were located at the trigone in 27 patients (9.1%). None of these patients developed UR. Lymph node tumor involvement was present in 60 patients (20.2%). On univariable and multivariable analyses, pathologic tumor and nodal stage were independent predictors for the overall risk of recurrence. UR was associated with a positive final urethral margin status ( $P < 0.001$ ) whereas no significant associations were found for carcinoma in situ, pathologic tumor and nodal stage, and bladder trigone involvement.

**Conclusions:** In this series, only 0.6% of women developed solitary UR. A positive final urethral margin was associated with an increased risk of UR. Women with involvement of the bladder trigone were not at higher risk of UR. © 2015 Elsevier Inc. All rights reserved.

**Keywords:** Female; Neobladder; Radical cystectomy; Recurrence; Urethral

### 1. Introduction

Radical cystectomy (RC) is the mainstay of treatment for women with muscle-invasive bladder cancer (BC) [1]. Orthotopic bladder substitutes (OBSs) have been shown to provide an oncologically safe option in women with invasive BC. According to single-center series, the rates of urethral recurrence (UR) in women with ileal neobladder range between 0%

and 1% [2–4]. Various risk factors for UR have been reported in these studies. These include a positive urethral margin at RC, primary tumor involvement of the bladder neck and lymph node-positive disease [5]. In addition, it has been questioned whether women with a primary tumor at the bladder trigone should be considered for an OBS [6].

Owing to the low incidence of UR in women with neobladder and the low number of included patients in prior series [2–4], none of these risk factors have been evaluated in depth thus far. Indeed, there is still uncertainty as to the clinical decision making for an OBS in women [7]. This is related to the issue of (i) whether it is necessary to perform

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an intraoperative frozen-section analysis (FSA) of the distal urethral margin when preoperative cystoscopic assessment excludes the presence of a tumor at the bladder neck [8], (ii) whether an orthotopic approach should be avoided in women with lymph node–positive disease at RC [7], and (iii) whether a primary tumor location at the bladder trigone is also associated with an increased risk of UR [6].

In a recent study we already reported on treatment and outcomes of urethral recurrence in our collective [9]. To adequately address these pertinent issues, we analyzed the outcomes of women who underwent RC with orthotopic bladder substitution in a multicenter setting.

## 2. Material and methods

### 2.1. Patient selection

This is a retrospective observational analysis of data from 4 international academic centers. Before initiation of data analysis, institutional review board approval and data sharing agreements were obtained at each study site. A computerized database was then generated to combine all data sets. Reports were generated to identify data inconsistencies, and through regular communication with all sites, all identified anomalies were resolved before analysis.

Of our database containing 456 patients we collected complete data on the 297 cases who underwent RC with ileal neobladder reconstruction for BC between 1994 and 2011. All patients were staged cM0 preoperatively. Patient medical records and physician records were reviewed to investigate the following clinical and pathologic parameters: age at RC, pathologic tumor stage at RC, lymph node tumor involvement at RC, underlying histology, number of retrieved lymph nodes, carcinoma in situ (CIS), primary tumor location, and final urethral margin status. Any patient lacking any of these parameters was excluded from analysis.

A prerequisite of this study was that all participating centers followed the same oncologic criteria. In all centers, the oncologic exclusion criteria for OBS were tumors staged cT4b at preoperative imaging, bladder neck involvement, bulky lymph node metastatic disease (cN3, not cN1–2), and a positive urethral margin at intraoperative FSA. By contrast, women with tumors located at the bladder trigone, but not at the bladder neck, were considered eligible for an OBS. Diffuse or multifocal CIS and multifocal tumors were considered contraindications for ileal neobladder. Evaluations for tumor staging and grading included abdominal ultrasound; excretory urography (intravenous pyelogram); chest x-ray; computerized tomography of the abdomen, pelvis, and chest; bone scintigraphy; bimanual examination with anesthesia; and multiple cold cup biopsies from the tumor, the trigone, and bladder neck if there was a suspicious finding on imaging or cystoscopy. In case of positive intraoperative frozen section of the urethral margin or positive preoperative biopsy of the bladder neck, women were excluded from orthotopic diversion.

The functional exclusion criteria included a preoperative glomerular filtration rate less than 60 ml/min, severe hepatic insufficiency, and stress urinary incontinence. Women with severe physical or mental disorders that would preclude them from the ability to perform clean intermittent catheterization in case of urinary retention were also considered ineligible for an OBS.

### 2.2. Operative technique

RC was performed open according to standardized techniques, including the removal of the tumor-bearing bladder, uterus, adnexes, and anterior vaginal wall [1]. Bilateral pelvic lymphadenectomy was performed in all centers. Nerve-sparing techniques for preservation of the lateral vaginal walls were performed whenever it was deemed oncologically feasible [1]. Different center-specific types of OBSs were constructed, as has been outlined in prior studies [11–13].

Intraoperative FSA of the distal urethral margin was routinely performed except for one center. In this center, a biopsy of the bladder neck was preoperatively performed to assess a patient's eligibility for an OBS; nonetheless, the presence of malignancy at the distal margin was routinely assessed at final histopathologic analysis.

### 2.3. Histologic assessment

All cystectomy specimens were processed according to standardized pathologic procedures at each institution. Dedicated genitourinary pathologists confirmed histology. All specimens were finally processed on formalin-fixed, paraffin-embedded sections. The histopathologic evaluation was based on the TNM classification of 2002 approved by the American Joint Committee on Cancer [14]. Tumors were graded according to the World Health Organisation 1973 classification [15]. Malignancy at the distal urethral margin was defined as either CIS or high-grade noninvasive or invasive carcinoma [15].

### 2.4. Follow-up

Patient medical records and physician records were also reviewed to determine clinical outcome. Patients generally were seen postoperatively at least every 3 to 4 months for the first year, semiannually for the second and third years, and annually thereafter. Follow-up examinations included radiologic imaging with cross-sectional imaging. In addition to physical examination with laboratory testing, intravenous pyelography, urethro-pouchoscopy, urine cytology, urethral washings, and bone scintigraphy were carried out at each institution.

Disease recurrence was defined as local when located in the surgical bed and as distant when located at distant organs. Urethral or upper tract recurrence was defined as an endoscopically confirmed tumor in the urethra or upper urinary tract, respectively. Clinical outcomes were measured from the date of cystectomy to the date of first documented recurrence, the date of death, or the date of

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