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# Tumor Recurrence in the Remnant Urothelium of Females Undergoing Radical Cystectomy for Transitional Cell Carcinoma of the Bladder: Long-Term Results From a Single Center

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**Purpose:** We analyzed the risk factors and incidence of secondary TCC of the remnant urothelium in women following radical cystectomy for TCC of the bladder.

**Materials and Methods:** A total of 85 women with a mean age of 64.5 years with clinically localized TCC of the bladder underwent radical cystectomy between 1992 and 2004. Orthotopic bladder substitution was performed in 46 females, while 39 underwent nonorthotopic urinary diversion. Of the entire cohort 22 (26%) patients underwent cystectomy for multifocal or recurrent TCC. Followup examinations were performed at 6-month intervals.

**Results:** Mean followup in the entire cohort was 49.8 months (median 42). Intraoperative frozen sections obtained from the urethra and distal ureters were negative for TCC and CIS in all patients. Four women (4.7%) had TCC in the remnant urothelium at a mean of 56 months postoperatively. These patients had undergone cystectomy for multifocal or recurrent TCC (4 of 22 or 18%). No secondary TCC was seen in the 63 patients with solitary invasive or nonrecurrent bladder cancer ( $p < 0.05$ ). Urethral recurrence was found in 2 patients (4.3%) 65 and 36 months after orthotopic neobladder surgery, respectively. In the orthotopic group 1 patient (2.1%) had an upper urinary tract tumor 76 months after surgery, while in the nonorthotopic group 1 (2.5%) was found to have an upper urinary tract tumor 48 months postoperatively.

**Conclusions:** Recurrent or multifocal TCC may represent a risk factor for secondary TCC of the remnant urothelium after cystectomy. In our series all recurrent tumors were late recurrences (more than 36 months postoperatively). Because the rate of urethral recurrence in the current series corresponds to that reported in men (2% to 6%), urethra sparing cystectomy with orthotopic bladder replacement does not appear to compromise the oncological outcome in women.

*Key Words:* bladder; bladder neoplasms; cystectomy; urinary diversion; carcinoma, transitional cell

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Radical cystectomy is the standard treatment for nonmetastatic, high risk TCC of the bladder. In male patients orthotopic reconstruction of the bladder has been the preferred method of urinary diversion for several decades.<sup>1</sup> In women urethra sparing orthotopic substitution was long thought to be associated with an increased risk of local recurrence as well as voiding dysfunction. This is why orthotopic substitution in females has become more popular only in the last few years.<sup>2</sup> Because the number of patients is still small and followup is short, only few studies of tumor recurrence in the remnant urothelium, ie in the urethra and upper urinary tract, in female patients have been published to date. We report the long-term results of tumor recurrence in the remnant urothelium in women treated with different forms of urinary diversion following radical cystectomy at the department of urology at our institution.

## MATERIALS AND METHODS

Between 1992 and 2004, 85 women with a mean age of 64.5 years (range 34 to 82) with clinically localized TCC of the bladder who had undergone radical cystectomy were included in the study. Preoperative assessment included bimanual examination, laboratory tests and imaging with abdominal ultrasound, excretory urography, bone scintigraphy, and CT of the abdomen and chest. No patient had received neoadjuvant chemotherapy before cystectomy.

Patients were selected for orthotopic substitution according to general performance status, motivation and urethral competence. Impaired renal function, and tumor involvement of the bladder neck and/or urethra and vagina were considered contraindications to orthotopic bladder substitution.

The techniques of radical cystectomy, urethra sparing cystectomy and orthotopic neobladder surgery have previously been described in detail.<sup>3-6</sup> In all patients intraoperative frozen sections were obtained from the urethra and distal ureters.

Orthotopic bladder substitution was performed in 46 females, whereas in 39 nonorthotopic urinary diversion was done, including an ileal conduit in 30 and ureterosigmoidostomy in 9. The (table) lists clinical and histopathological data on all patients according to the type of urinary diver-

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<i>Clinical and histopathological data</i>		
	Diversion	
	Orthotopic	Nonorthotopic
No. pts	46	39
Median age at cystectomy (range)	64.2 (34–78)	66.4 (42–82)
No. recurrent &/or multifocal bladder Ca (%)	13 (28.2)	9 (23.0)
No. pathological stage:		
CIS	4	1
Ta	3	0
T1	16	8
T2	8	9
T3	14	13
T4	1	8
No. lymph node involvement (%)	5 (10.8)	9 (23.0)
Mean followup (range)	45.3	41.6

sion. Staging and grading were performed according to 1997 UICC guidelines and the 1974 WHO histopathological grading classification, respectively.

A total of 22 patients (26%) underwent cystectomy for recurrent and/or multifocal TCC, including 13 (28.2%) in the neobladder group and 9 (23.0%) in the nonorthotopic group. Of the patients 63 had single muscle invasive and nonrecurrent TCC of the bladder. Multifocality was defined as tumor at 2 or more sites in the histopathological specimen obtained by transurethral resection before cystectomy or in the final cystectomy specimen. Recurrence was defined as at least 2 recurrences of bladder TCC, including the last transurethral resection, before cystectomy.

All patients were followed at 6-month intervals by physical examination, blood tests, urinary cytology and radiographic evaluation, alternately comprising contrast enhanced CT or ultrasound in combination with chest x-ray. When there was a history of CIS, additional excretory urography was performed annually. Cystoscopy, biopsy and retrograde pyelography were performed as indicated, ie in cases of hematuria, positive urinary cytology, suspicious radiological findings and irritative or obstructive voiding symptoms. Parameters recorded in all patients were followup, age, tumor stage, CIS, multifocality, orthotopic or nonorthotopic urinary diversion type and positive/negative lymph node status.

Data are expressed as the mean and range or absolute and relative frequency. Differences between the groups were analyzed using Fisher's exact test for qualitative variables and Student's t test for quantitative, normally distributed variables with  $p < 0.05$  considered statistically significant. SPSS 11.5. for Windows® (SPSS, Chicago, Illinois) was used for all statistical analyses.

## RESULTS

Mean followup in the entire cohort was 49.8 months (median 42, range 5 to 149). It was 45.3 months (median 42.4, range 2.4 to 138) in the neobladder group and 41.6 months (median 40.2, range 1 to 144) in the nonorthotopic group ( $p > 0.05$ ). Mean age in the 2 groups was 64.2 and 66.4 years, respectively ( $p > 0.05$ ).

In all patients intraoperative frozen sections from the urethra and distal ureters were negative for TCC. None of the patients had a positive urethral margin on permanent section analyses.

Four women (4.7%) had TCC in the remnant urothelium a mean of 56 months postoperatively (range 36 to 76). These

patients had a history of multifocal or recurrent disease (4 of 22 or 18%). None of the 62 patients undergoing cystectomy for solitary invasive bladder cancer had secondary TCC. This finding was statistically significant ( $p < 0.05$ ).

The presence/absence of CIS or positive lymph nodes did not result in a statistically significant difference concerning the urothelial recurrence rate ( $p > 0.05$ ). In patients with upper urinary tract recurrence there was no statistically significant difference in terms of the type of urinary diversion ( $p > 0.05$ ).

Urethral recurrence was found in 2 patients (4.3%) with an ileal neobladder at a mean followup of 50.5 months. In 1 patient multifocal muscle invasive bladder cancer (pT2) was found in the cystectomy specimen and she was diagnosed with urethral recurrence 65 months after cystectomy. In the other patient, who had recurrent CIS refractive to intravesical immunotherapy, urethral recurrence was seen 36 months after cystectomy. In 1 patient the recurrent tumor was detected when she presented with gross hematuria. The other patient was asymptomatic but was found to have positive cytology. In these 2 patients endoscopic examination revealed gross tumors, which were confirmed by biopsy. They underwent total urethrectomy and conversion to an ileal conduit. One patient had metastatic disease and died 4 months postoperatively, while the other died of ischemic heart disease 6 months after surgery.

UUTT was found in 1 patient (2.1%) in the orthotopic group 76 months after cystectomy and in 1 (2.5%) of the nonorthotopic group 48 months after cystectomy. The overall recurrence rate was 2.3%. The 2 patients had undergone cystectomy because of recurrent, high risk superficial bladder cancer (grade II pT1 and grade 22 pT1 with concomitant CIS in 1 patient, respectively). In these 2 patients gross hematuria prompted further evaluation. CT demonstrated a 1.2 cm tumor at the right ureteropelvic junction in the patient with a neobladder and a 4 cm tumor in the right renal pelvis in the patient with a conduit. In the patient treated with nonorthotopic diversion malignancy was confirmed by retrograde pyelography and endoscopic biopsy of the tumor. In the patient with a neobladder endoscopy could not be performed. Cytology was negative in the former case and not revealing in the latter. The patient with a neobladder received 3 cycles of neoadjuvant polychemotherapy. The 2 patients underwent nephroureterectomy. Histology revealed grade IV pT2Nx TCC in the patient with a neobladder and grade III pT3Nx TCC in the patient with a conduit. The patient with a neobladder died of nonHodgkin's lymphoma 41 months after nephroureterectomy, while the other is currently alive 30 months after nephroureterectomy.

## DISCUSSION

There are only sparse data concerning the risk factors and incidence of secondary TCC of the remnant urothelium in female patients following radical cystectomy for TCC of the bladder. In men the reported incidence and recurrence rate of secondary urethral tumors following radical cystectomy vary considerably with a recurrence rate of approximately 6% reported in long-term studies.<sup>7</sup> Risk factors that have previously been described are multifocality, recurrent tumors, bladder neck involvement and CIS.<sup>8</sup> Recently multivariate analysis including data on 768 male patients with a median followup of 13 years was reported by Stein et al.<sup>9</sup>

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