REVIEW ARTICLE

Diagnosis and treatment of urethral recurrence after radical cystectomy in the male

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KEYWORDS
Cystectomy; Urethra; Recurrence; Urothelial carcinoma; Diagnosis; Treatment

Abstract
Context: From 4 to 6% of males subjected to radical cystectomy due to urothelial carcinoma will have urethral recurrence (UR) during the follow-up.
Objective: To analyze the diagnosis, treatment and course of the patients with UR following a cystectomy.
Acquiring of evidence: Analysis of original articles and reviews related with the diagnosis, treatment, and course of patients subjected to radical cystectomy and who develop UR. The articles were obtained from a search in PubMed.
Synthesis of evidence: Most of the UR appear during the first 3 years of the cystectomy. Approximately 50% of the URs of contemporary series were diagnosed through urethral cytology, the patient being asymptomatic. The urethrectomy is the treatment of choice in patients with UR and cutaneous diversion. In patients with orthotopic bladder replacement (OBR): (1) the treatment of the intraurethral BCG can be useful in patients with carcinoma in situ (CIS), (2) papillary type conservative treatment in UR has contradictory results, and (3) when the urethrectomy is necessary, the ileal duct or conversion of the OBR in a continent urinary derivation can be used.
Conclusions: Urethral cytology is a test having high sensitivity and can contribute to the diagnosis of UR in the earliest stages. In patients with OBR, the diagnosis of a UR is a therapeutic challenge. The bladder tumor, urethral recurrence, and presence of an upper urinary tract tumor in 25% of the cases may be a cause of death in these patients.
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PALABRAS CLAVE
Cistectomía; Uretra; Recidiva; Carcinoma urotelial; Diagnóstico; Tratamiento

Diagnóstico y tratamiento de la recidiva uretral después de cistectomía radical en el varón

Resumen
Contexto: Entre un 4-6% de los varones sometidos a cistectomía radical por carcinoma urotelial presentarán recidiva uretral (RU) durante el seguimiento.
Objetivo: Analizar el diagnóstico, tratamiento y evolución de los pacientes con RU después de cistectomía.

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Introduction

Radical cystectomy with lymphadenectomy is the treatment of choice for muscle-invasive urethelial carcinomas and in non-muscle invasive bladder tumors (NMIBT) at risk of progression. Contemporary series show that between 4 and 6% of patients undergoing cystectomy will have urethral recurrence (UR) during the follow-up. The involvement by urethelial prostate tumor, and the presence of factors related to multifocality, such as previous history of NMIBT, presence of NMIBT in cystectomy piece, diffuse CIS, multiple tumor, and tumor of the upper urinary tract, have been associated with the appearance of UR after cystectomy.

The UR can be diagnosed after the onset of symptoms or by urethral cytology. Despite its high sensitivity, some authors question the usefulness of urethral cytology in the follow-up after cystectomy. Urethrectomy is the treatment of choice in patients with UR and cutaneous urinary divert. In patients with orthotopic bladder replacement (OBR), the diagnosis of a UR is a therapeutic challenge for the urologist. There exists limited information in the literature on how to respond to a UR in a patient with OBR, and what the evolution of these patients is. In this context, we analyze how the diagnosis of UR is performed, which is the best treatment is and what this evolution is.

Diagnosis of urethral recurrence

About 40% of urethral recurrences appear in the year after the cystectomy. Overall, most of them are diagnosed during the first 3 years, although recurrences have been reported beyond 5–10 years. It can be diagnosed by the appearance of symptoms or during routine post-cystectomy follow-up if urethral cytology is used routinely. The most common symptoms associated with UR are: urethrorrhagia, purulent urethral discharge, appearance of a urethral mass, and changes in urinary habits in patients with OBR. The diagnosis after the onset of diagnosis has classically been associated with urethral tumors in more advanced stage.

The usefulness of urethral cytology in the follow-up after cystectomy is controversial. On the one hand, it is a simple, well tolerated, minimally invasive, with high sensitivity (78–94%) exploration. It is an exploration with proven usefulness in clinical practice because about 50% of the URs in contemporary series were diagnosed by urethral cytology, the patient being asymptomatic.

In the series by the Fundación Puigvert, 10 out of 13 URs diagnosed by cytology were superficial (pTis, PTa), and 11 out of the 17 clinically diagnosed were infiltrating (pT1–pT4). Giannarini et al., in patients with OBR, diagnosed 21 out of 24 URs by urethral cytology. The survival of patients with this diagnosis was slightly higher than that of those clinically diagnosed. In fact, cytology allowed for the early detection of 12 cases with urethral CIS that were treated conservatively. Possibly, the high sensitivity of urethral cytology contributes to the diagnosis of UR in earlier stages. On the other hand, the Guidelines of the EAU 2011 question the performance of urethral cytology, due to the failure to objectify greater survival in patients with UR diagnosed by cytology, compared to those diagnosed by symptoms. In general, these studies have the disadvantage of the scarce number of patients to be able to make important recommendations, and admitted that they kept using the routine urethral cytology.

In the final survival of patients with UR, other factors such as bladder tumor itself are involved, and in about 20% of the cases, the appearance of an upper tract tumor. Therefore, it is very difficult to properly assess the impact of the use of cytology on survival.

The urethral cytology sample is obtained by inserting a poorly lubricated 14Fr Nelaton probe to the membranous urethra. In the event that the patient has an OBR, they are instructed to contract the sphincter and perineal muscles to subsequently carry out two 50 cm saline irrigations, as the probe is withdrawn. If there is palpable urethral mass or solid urethral injury, it is advisable to perform a urethral and abdominal and pelvic MRI for better local staging.
Table 1  Incidence and presentation of urethral recurrences after radical cystectomy.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of cystectomies</th>
<th>UR (%)</th>
<th>Diagnosis symptoms</th>
<th>Asymptomatic diagnosis</th>
<th>Median follow-up after UR (m)</th>
<th>Overall survival at 5a.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. (%)</td>
<td>Median T to Dx (m)</td>
<td>No. (%)</td>
<td>Median T to Dx (m)</td>
</tr>
<tr>
<td>Donat et al. (6) 2001</td>
<td>235</td>
<td>15 (6.4)</td>
<td>1 (7)</td>
<td>24</td>
<td>14 (93)</td>
<td>-</td>
</tr>
<tr>
<td>Clark et al. (7) 2004</td>
<td>1054</td>
<td>47 (4.4)</td>
<td>24 (57)</td>
<td>30.9</td>
<td>13 (31)</td>
<td>11.6</td>
</tr>
<tr>
<td>Nieder et al. (8) 2004</td>
<td>218</td>
<td>8 (3.7)</td>
<td>None</td>
<td>-</td>
<td>8 (100)</td>
<td>12.8</td>
</tr>
<tr>
<td>Huguet et al. (4) 2008</td>
<td>729</td>
<td>34 (4.6)</td>
<td>21 (61.7)</td>
<td>15</td>
<td>13 (38.2)</td>
<td>11</td>
</tr>
<tr>
<td>Giannarini et al. (9) 2010</td>
<td>479</td>
<td>24 (5)</td>
<td>3 (12.5)</td>
<td>-</td>
<td>21 (87.5)</td>
<td>-</td>
</tr>
</tbody>
</table>

Median T to Dx (m): median time to diagnosis (in months); No.: number; UR: urethral recurrence.
a 5 cases were urethral tumors diagnosed after prophylactic urethrectomy.
b Only orthotopic bladder replacements.
c Only 42 patients evaluable for symptoms. The remaining 5 were urethral tumors diagnosed after prophylactic urethrectomy.

Most authors advocate urethroscopy with biopsy to confirm the diagnosis of UR. In cases with positive cytology without macroscopic lesions, cytology or urethral biopsies are performed at random. In patients with OBR, urethroscopy with biopsy taking will be essential to assess a possible conservative treatment.1,12 In cases with cutaneous diversion and positive urethral cytology, the need for biopsy before urethrectomy would be debatable. In some patients with positive urethral cytologies, no tumor has been objectified in the urethrectomy pieces. Lin et al., in 17 asymptomatic patients and with positive urethral cytology, observed 9 cases with CIS, 1 pT1, and 7 pT0.11 This 37% of pT0 was attributed to the denudation of the mucosa by the barbotage of pathological study of these urethras, supported this possibility.11 Similarly, Varol et al., in 6 patients with OBR and positive urethral cytology, failed to objectify CIS in endoscopic biopsies, but managed to objectify denuded urethri.12

The systematic use of urethroscopy in the follow-up after cystectomy is not covered by the limited incidence of UR. However, some authors recommend it to patients with OBR and risk factors for recurrence.13 There are no established guidelines for follow-up of the post-cystectomy urethra either. A follow-up based on the presence or absence of risk factors for UR seems a reasonable option. Patients with tumor in the prostatic urethra and multifocal disease should be followed with half-yearly cytology for 3 years, and then annually. In the remaining patients, annual cytology would be enough.4

Treatment of urethral recurrences

Patients with cutaneous diversion

Urethrectomy is the treatment of choice in patients with UR and cutaneous diversion. The entire urethra must be excised because in subtotal urethrectomies without removing the navicular fossa, up to a 30% of recurrences have been described at that level.14 The urethrectomy is performed perineally, ensuring the removal of the proximal end, which is sometimes difficult. The possibility to perform preservation of erectors during urethrectomy is described. In patients with indication for cystectomy and urethrectomy in the same act due to simultaneous urethral and urothelial carcinomas, it is useful to have 2 surgical teams: one to perform cystectomy, and another one to access the urethra perineally. It is also possible to remove the urethra en bloc with the bladder, via the prepubis, without the need for a perineal access.15

Patients with orthotopic bladder replacement (OBR)

The UR is a rare but critical problem in patients with OBR5,7,9,12,16-18 (Table 2). In the urethra, the submucosa is the only barrier between the mucosa and the vascularized corpus spongiosum. Many authors attribute the poor prognosis of the UR to this anatomical peculiarity.19,20 Therefore, most authors consider the UR with pTis stages (carcinoma in situ) and pTa (papillary tumor that affects the mucosa) superficial, and the UR with ≥pT1 stages infiltrating, as the pT1 tumor invades the subepithelial connective tissue.4,7

In very selected cases, it is possible to preserve the urethra and maintain the quality of life provided by the OBR. If the UR corresponds to a CIS, BCG may be used. The Fundació Puigvert group was the first to report the use of uncomplicated intraurethral BCG in a patient with Studer OBR and CIS in the urethra. The patient remained free of disease after 120 months of treatment.16 Varol et al. performed treatment with intraurethral BCG in 2 patients with CIS and in 4 with denuded urethritis with repeated positive urethral cytologies. In 5 cases (83%), response to BCG was objectified. The instillations were performed through a two-way 14 FR urethral catheter with a ligature distal to the balloon, and with holes created by puncture, proximal to the balloon (at 0.5 cm thereof). After inserting the urethral catheter, the balloon was inflated and instillation of a dilution of 3 vials of BCG in 150 ml of saline was started.12

Therefore, although there is little evidence, the BCG can be given to patients with OBR and urethral CIS in an attempt to preserve the neobladder.
Table 2  Urethral recurrence in patients with orthotopic bladder replacement: incidence, pathologic features, treatment, and evolution.

<table>
<thead>
<tr>
<th>No. of cystectomies + OBR</th>
<th>UR (%)</th>
<th>UR location</th>
<th>UR risk factor</th>
<th>UR pathological stage</th>
<th>Treatment</th>
<th>Median follow-up (months)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huguet et al. (16)</td>
<td>138</td>
<td>5 (3.6)</td>
<td>Anastomosis 2</td>
<td>G2T2, 2</td>
<td>TUR 2, BCG 1, Urethrectomy + Diversion A 2</td>
<td>50 m from UR</td>
<td>2 alive without disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bulbar-Penile 2 Multiple 1</td>
<td>G1T2, 1</td>
<td>CIS 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCG ± TUR 10 (02 Required Urethrectomy + Diversion A), Urethrectomy + Diversion A 1, QT 2, No treatment 2</td>
<td>61 m from UR</td>
<td>5 alive without disease</td>
</tr>
<tr>
<td>Varol et al. (12)</td>
<td>371</td>
<td>15 (4)</td>
<td></td>
<td>Multifocality 15</td>
<td>TUR + 5FU 3 (2 Required Urethrectomy + Diversion B), Distal urethrectomy + Perineal urethrostomy, Urethrectomy + Diversion B 3, QT 3 Unknown 2</td>
<td>18 m from cystectomy</td>
<td>4 alive without disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TUR 1, Urethrectomy + Diversion C 3, QT 1, Unknown 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clark et al./Stein et al. (2,7)</td>
<td>395</td>
<td>16 (4)</td>
<td></td>
<td></td>
<td>TUR 4 (3 Required Urethrectomy + Diversion A, C)</td>
<td>65 m from cystectomy</td>
<td>4 alive without disease</td>
</tr>
<tr>
<td>Taylor et al. (17)</td>
<td>260</td>
<td>6 (2.3)</td>
<td>Anastomosis 2</td>
<td>T3 4</td>
<td>TUR 1, Urethrectomy + Diversion A, C</td>
<td>18 m from cystectomy</td>
<td>4 alive without disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bulbar-Penile 4</td>
<td></td>
<td>T2 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshida et al. (18)</td>
<td>77</td>
<td>4 (5)</td>
<td>Bulbar-Penile 4</td>
<td></td>
<td>TUR + BCG 13 (2 Required Urethrectomy + Diversion A, C)</td>
<td>65 m from cystectomy</td>
<td>4 alive without disease</td>
</tr>
<tr>
<td>Giannarini et al. (9)</td>
<td>482</td>
<td>25 (5)</td>
<td></td>
<td></td>
<td></td>
<td>11 alive without disease</td>
<td></td>
</tr>
</tbody>
</table>

Diversion A: partial exeresis of the Studer neobladder and use of the isoperistaltic loop (chimney) as an ileal conduit; Diversion B: exeresis of the anastomosis + conversion to continent cutaneous diversion (no technique on continent mechanism is recorded); Diversion C: exeresis of the anastomosis + conversion to continent cutaneous diversion (Mitroffanof procedure or Monti’s technique); QT: quimiotherapy; TUR: transurethral resection; UR: urethral recurrence; OBR: orthotopic bladder replacement; PU+: presence of tumor in prostatic urethra.
When the UR corresponds to a papillary tumor, treatment by transurethral resection (TUR) with or without associated BCG is possible, but not always with satisfactory results. Miller and Benson successfully treated a multiple urethral recurrence (Ta G2-3) with TUR, the patient remaining free of disease 14 months after surgery.\(^1\) Leissner et al. also reported successful treatment with TUR of 2 patients with recurrence (TaG3 and T1G3). Both were free of disease at 59 months.\(^2\) But analyzing series with more cases and longer follow-up, conservative treatment with TUR with or without associated BCG was not always successful. Varol et al. considered that none of the 4 papillary recurrences (TaG2, TaG3, T2+CIS, TaG3+CIS) in their series treated with TUR and BCG responded to the treatment. Two required subsequent urethrectomy, and the other two died of metastasis.\(^3\)

Clark et al. treated 3 low-risk recurrences or CIS with TUR and intraurethral 5-fluorouracil. Two required urethrectomy at 10 and 12 months due to local recurrence. Both died of metastatic disease.\(^4\) Taylor et al. treated 4 patients with recurrence with TUR, all Ta; but it was only possible to preserve the urethra in one case. The remaining 3 required rescue urethrectomy due to new relapses. In 2 of these cases, the final pathological stage was higher than the initial endoscopical one.\(^5\) Given that all these patients were free of disease, the authors consider an initial attempt to preserve the urethra feasible, and they advise urethrectomy in the event of a new recurrence.\(^6\) In the series by the Fundació Puigvert, 2 patients with relapse (G2T2) were treated with TUR. One died not because of urological reasons after 77 months, and another one because of metastatic disease after 15 months.\(^7\)

Given the available experience, it is very difficult to draw conclusions about the possibility to perform conservative treatment in a UR of papillary aspect. It could be valued in low-grade Ta tumors, performing very strict subsequent follow-up, and ≥T1 high-grade tumors would be doubtful candidates for conservative treatment.

In case of being necessary to perform urethrectomy in a patient with OBR, treatment becomes a surgical challenge. In the URs distal to the sphincter area, partial urethrectomy with perineal urethrostomy could be an option in patients not candidate for more aggressive treatments. This treatment would mean assuming again the possibility of recurrence in the remnant urethra. Clark et al. performed partial urethrectomy with perineal urethrostomy to 5 out of 14 patients (36%) with OBR and half-penile or distal recurrence. In 2 cases, it was necessary to perform total urethrectomy and conversion to continent urinary reservoir because of the presence of positive margins in the pathological study of partial urethrectomy.\(^8\)

In patients with Studer OBR and need for urethrectomy, partial resection of the neobladder and use of the isoperistaltic ileal chimney for the development of a new ileal conduit is a good surgical option.\(^9\) It seems interesting to note that Yoshida et al., using this technique, needed to interpose a segment of 5 cm of ileum between the ileal chimney and the abdominal wall, because the ileal chimney was strongly adhered to the retroperitoneum and had scarce length.\(^9\)

In patients with OBR different from Studer's technique, urethrectomy with resection of the anastomotic area between the urethra and neobladder, closure of the defect, and creation of a continent urinary reservoir was the most used technique. Continent reservoirs are described using appendicocolic-vesicostomies (Mitrofanoff's technique) or ileo-vesicostomies (with Monti's technique or with ileal segments with distal invagination).\(^10\) These are surgeries of high technical difficulty and prolonged operative time.\(^11\)

**Evolution of patients with recurrence**

The median survival of patients with UR after cystectomy is between 28 and 53 months, and the 5-year survival of 35–43%.\(^12\) In the literature, there are conflicting data on which factor is most decisive in the survival of these patients: bladder tumor due to which cystectomy or recurrence itself were performed.

Lin et al. found that in 24 males who underwent urethrectomy after cystectomy due to UR, only the pathological stage of the cystectomy had an impact on survival.\(^13\) In 47 patients with UR, Clark et al. found that the most determining factor in survival in their series was the pathological stage of the uretra.\(^14\) These disparate results were attributed to the differences between the two study populations. In the study by Lin et al., 9 (37%) urethrectomy pieces were pT0, 12 (50%) pT1S, and 3 pT1 (12.5%)\(^15\). On the other hand, Clark et al. excluded the pT0 from their study, and 19 patients (40%) had infiltrating disease (≥pT1)\(^16\). That is, Clark's series clearly had patients with UR and more adverse histologies. Both studies considered T1-T4 tumors infiltrating.

Huguet et al. did not include T0 either, and they showed 14 cases (41%) of infiltrating recurrence. In this series, neither bladder pathological stage nor urethral stage was independent factors associated with survival. There were 3 reasons that could explain these results. First, there was some association between bladder and urethral histologies of good prognosis (12 out of 17 superficial URs appeared in cystectomies due to organ-confined tumor). Therefore, in few cases were bladder stages of adverse prognosis associated with good-prognosis UR and vice versa, being, then, difficult to statistically determine a greater impact on the survival of a tumor compared to the other. Secondly, when we analyzed the possible cause of death in 17 cases with UR, in 7, it was not possible to determine if the cause had been the bladder tumor or the recurrence itself. Thirdly, 26% of the patients with UR had a history of upper urinary tract tumor, another factor that could influence the survival.\(^17\) This last point is important, because the tract tumors after cystectomy are usually high grade and stage.\(^18\)

**Conclusions**

Although recurrences have been reported beyond the 5–10 years, most of the times, the UR appears during the first 2–3 years after the cystectomy, a period which also developed the majority of tumor recurrences (local or systemic) in these patients. For this reason, it may be difficult to establish if the recurrence of the disease, if any, is due to the bladder or urethral tumor.

The symptoms most often associated with UR are urethrorrhagia, urethral discharge, urethral mass, and changes in urinary habits in patients with OBR. The urethral cytology is a test with high sensitivity and it may contribute to
the diagnosis at earlier stages. There are no established guidelines for follow-up of the post-cystectomy urethra. A follow-up with urethral cytology based on the presence or absence of risk factors for UR would be a reasonable option.

Urethrectomy is the treatment of choice in patients with UR and cutaneous diversion. In patients with OBR and CIS in the urethra, treatment with BCG can be offered. In selected cases of papillary and low-grade recurrences, the urethra could be preserved. In the event of requiring urethrectomy in patients with OBR, you can opt for the exeresis of the neobladder, and the creation of an ileal conduit, or the neobladder conversion to a continent reservoir.

Conflict of interest

The authors declare that they have no conflict of interest.

References