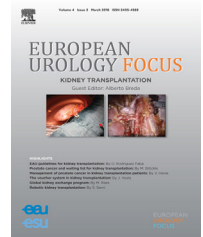


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Review – Bladder Cancer

Follow-up of the Urethra and Management of Urethral Recurrence After Radical Cystectomy: A Systematic Review and Proposal of Management Algorithm by the European Association of Urology—Young Academic Urologists: Urothelial Carcinoma Working Group

Ekaterina Laukhtina^{a,b}, Marco Moschini^c, Francesco Soria^d, David D. Andrea^a, Jeremy Yuen-Chun Teoh^e, Keiichi Mori^{a,f}, Simone Albisinni^g, Andrea Mari^h, Wojciech Krajewskiⁱ, Alessia Cimagli^j, Mohammad Abufaraj^k, Dmitry Enikeev^b, Yann Neuzillet^l, Gianluca Giannarini^m, Evangelos Xylinasⁿ, Ashish M. Kamat^o, Morgan Roupret^p, Marko Babjuk^{a,q}, J. Alfred Witjes^r, Shahrokh F. Shariat^{a,b,k,s,t,u}, Benjamin Pradere^{a,*}, European Association of Urology, Young Academic Urologists EAU-YAU: Urothelial Carcinoma Working Group, the European Association of Urology Section of Oncological Urology ESOU

^a Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; ^b Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia; ^c Department of Urology and Division of Experimental Oncology, Urological Research Institute, Vita-Salute San Raffaele, Milan, Italy; ^d Division of Urology, Department of Surgical Sciences, San Giovanni Battista Hospital, University of Studies of Torino, Torino, Italy; ^e S.H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China; ^f Department of Urology, The Jikei University School of Medicine, Tokyo, Japan; ^g Service d'Urologie, Hôpital Erasme, Université Libre de Bruxelles, Bruxelles, Belgium; ^h Department of Urology, Careggi Hospital, University of Florence, Florence, Italy; ⁱ Department of Minimally Invasive and Robotic Urology, University Center of Excellence in Urology, Wrocław Medical University, Wrocław, Poland; ^j Section of Pathological Anatomy, Marche Polytechnic University, School of Medicine, United Hospitals, Ancona, Italy; ^k Division of Urology, Department of Special Surgery, Jordan University Hospital, The University of Jordan, Amman, Jordan; ^l Department of Urology, Hôpital Foch, UVSQ-Paris-Saclay University, Suresnes, France; ^m Urology Unit, University Hospital Santa Maria della Misericordia, Udine, Italy; ⁿ Department of Urology, Bichat-Claude Bernard Hospital, Assistance Publique-Hôpitaux de Paris, Paris University, Paris, France; ^o Department of Urology, M.D. Anderson Cancer Center, University of Texas, Houston, TX, USA; ^p GRC n°5, Predictive Onco-Urology, Ap-Hp, Urology, Hôpital Pitié-Salpêtrière, Sorbonne Université, Paris, France; ^q Department of Urology, Second Faculty of Medicine, Hospital Motol, Charles University, Prague, Czech Republic; ^r Department of Urology, Radboud University, Nijmegen Heyendaal, The Netherlands; ^s Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria; ^t Department of Urology, Weill Cornell Medical College, New York, NY, USA; ^u Department of Urology, University of Texas Southwestern, Dallas, TX, USA

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Abstract

Context: Surveillance of the urethra and management of urethral recurrence (UR) after radical cystectomy (RC) is an area with poor evidence.

Objective: We aimed to summarize the available evidence and provide clinicians with practical recommendations on how to prevent and manage UR after RC for bladder cancer.

Evidence acquisition: The MEDLINE and EMBASE databases were searched during September 2021 for studies evaluating UR after RC. The primary endpoint was oncologic outcomes for patients who experienced UR depending on different surveillance and management approaches.

* Corresponding author. Department of Urology, Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Währinger Gürtel 18-20, 1090, Vienna, Austria. Tel. +33661404418.

E-mail address: benjaminpradere@gmail.com (B. Pradere).

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Keywords:

Urethral recurrence
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Evidence synthesis: Forty-three studies were included in the quantitative synthesis. According to the currently available literature, a tight-knitted surveillance protocol should be implemented for males treated with RC and nonorthotopic neobladder diversion as well as patients with prostatic involvement, tumor multifocality, bladder neck involvement, and concomitant carcinoma in situ. A survival benefit of a prophylactic urethrectomy has been reported only in patients at very high risk for UR based on clinical factors. Surveillance protocols were highly heterogeneous and poorly documented among included studies. Patients whose UR was diagnosed based on clinical symptoms had a poor prognosis. Only limited data were available on the comparative effectiveness of watchful waiting after RC versus clinical symptom screening as part of a follow-up strategy. However, the use of regular cytology and/or urethroscopy seems useful in select patients at high risk for UR. Despite limited data on the optimal management of UR, urethra-sparing approaches (transurethral resection of UR) seem to be an option for Ta (only) recurrences; a salvage urethrectomy with or without chemotherapy should be the standard for all others.

Conclusions: Based on the currently available literature, we have proposed an algorithm to guide the decision-making process to help identify and treat UR after RC. Given the lack of evidence on how to deal with UR and surveil patients at risk for UR, this study may invigorate research in this area of unmet need.

Patient summary: Early diagnosis and tailored management of urethral recurrence could help improve oncologic outcomes in these patients.

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1. Introduction

Urethral recurrence (UR) after radical cystectomy (RC) for bladder cancer (BCa) is a relatively rare event with a reported pooled incidence rate of 4.6% [1]. Most URs are detected within the first 2 postoperative years after RC [2]. UR was shown to be associated with several risk factors including tumor multifocality, papillary pattern, carcinoma in situ (CIS), tumor at the bladder neck, and prostatic involvement [3,4]. Prophylactic urethrectomy is nowadays rarely performed and not routinely recommended due to a lack of evidence regarding its benefits as well as the increasing use of orthotopic urinary diversion [3]. Should UR be diagnosed, there is a lack of evidence-based recommendations regarding its optimal management of the urethra during and after RC for BCa [3–5].

An evidence-based decision tree for patients with UR after RC may help overcome the clinical dilemma of such an event. A standardized risk-adjusted surveillance and treatment protocol could be of value by helping the clinician diagnose UR and management in a tailored patient-centered way.

The European Association of Urology–Young Academic Urologists (EAU-YAU); Urothelial Carcinoma Working Group has recently published a large two-part systematic review and meta-analysis assessing the incidence and risk factors of UR as well as the diagnostic estimates of frozen section analysis (FSA) in patients treated with RC for BCa [1,6]. The present systematic review aimed to provide clinicians with practical recommendations on how to detect and treat UR after RC.

2. Evidence acquisition

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [7]. The study

protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO; registration ID CRD42021271294).

The MEDLINE and EMBASE databases were searched to identify reports published up to September 2021 and evaluating UR after RC for BCa. Keywords such as “bladder cancer,” “radical cystectomy,” “urethral recurrence,” “follow-up,” “treatment,” and “urethrectomy” were used to perform the search. Initial screening was performed independently by two investigators based on the titles and abstracts of the article to identify ineligible reports. Potentially relevant reports were subjected to a full-text review, and the relevance of the reports was confirmed after the data extraction process. Any discrepancies during the primary and secondary literature screenings were resolved by referring to the senior author. The primary endpoint was oncologic outcomes for patients who experienced UR depending on different surveillance and management approaches.

The population, intervention, control, and outcomes in this study were decided by the coauthors as follows: patients with UR after RC for BCa compared with the control group of non-UR patients. The outcomes were the oncologic outcomes for patients depending on different surveillance and management approaches. We did not include studies on primary urothelial carcinoma. We excluded reviews, letters to editors, editorials, study protocols, case reports, brief correspondence, and articles not published in English. References of all papers included were scanned for additional studies of interest.

The Newcastle-Ottawa Scale was used to assess the quality of the included studies [8,9]. The scale rates based on three factors, selection (1–4 points), comparability (1–2 points), and exposure (1–3 points), with total scores ranging from 0 (lowest) to 9 (highest). The presence of confounders was determined by a consensus and review of the literature. Studies with scores of >6 were identified as “high-quality” choices.

The objective of this systematic review was to cover three important clinical questions: When should we perform a urethrectomy? How to follow the urethra after RC? How to manage UR after RC?

3. Evidence synthesis

Forty-three studies were included in the qualitative synthesis. [Supplementary Figure 1](#) summarizes the screening process of the included studies. Most of the studies included in this systematic review had a retrospective design and were identified as having a high risk of bias. The median score of all selected studies was 5 (range: 4–7).

3.1. Prediction of UR

3.1.1. How to assess patients at risk for UR?

The prevalence of UR in patients who undergo RC for BCa is low. Some patients are at higher risk for UR. Therefore, a risk-adjusted follow-up scheme could be useful. Previous meta-analyses reported that male patients treated with nonorthotopic neobladder (non-ONB) diversion, prostatic involvement, tumor multifocality, concomitant CIS, and positive urethral margins were at increased risk for UR [1,10]. In addition, the guidelines by the American Urological Association suggested papillary pattern and bladder neck involvement as risk factors for UR after RC [5]. In women, the urethra is commonly removed if non-ONB

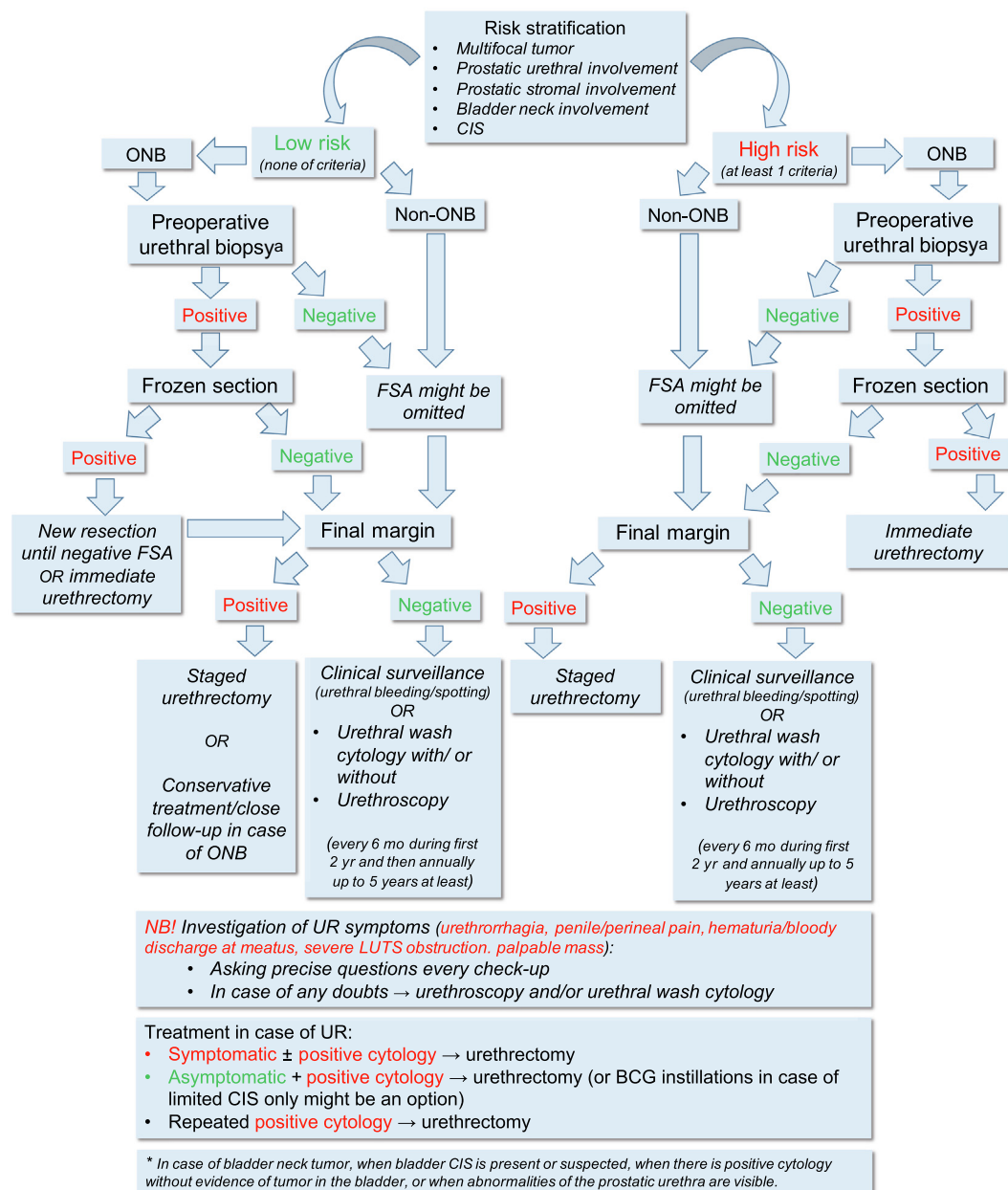


Fig. 1 – Algorithm for decision-making process regarding the follow-up of the urethra and management of urethral recurrence after radical cystectomy for bladder cancer. BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; FSA = frozen section analysis; LUTS = lower urinary tract symptoms; ONB = orthotopic neobladder; UR = urethral recurrence.

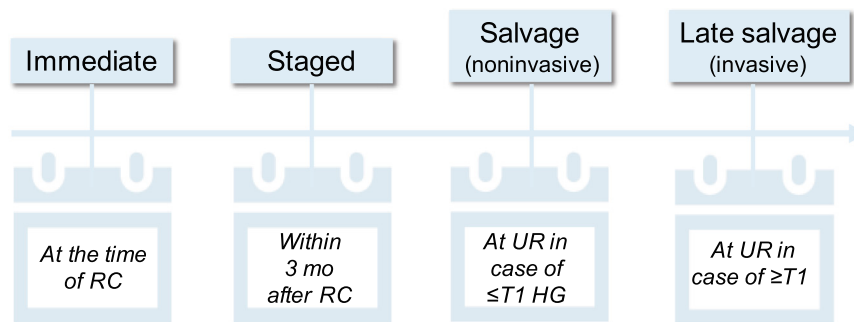


Fig. 2 – Type of urethrectomy according to its timing and disease stage. HG = high grade; RC = radical cystectomy; UR = urethral recurrence.

diversion is performed. Generally, there is a very low UR rate in female patients. Nevertheless, bladder neck invasion and anterior vaginal wall involvement are risk factors for UR in women [2,10]. In men, a preoperative urethra biopsy remains recommended in case of a bladder neck tumor, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumor in the bladder, or when abnormalities of the prostatic urethra are visible [5].

Therefore, according to the currently available literature, a preoperative patient risk classification should be used to determine which patients are at increased risk for UR, how to manage the urethra at the time of RC, how to surveil it after RC, and how to manage the different types of UR. As previously proposed, patients at high risk for UR are defined by the presence of at least one of these criteria (see Fig. 1): prostatic involvement, tumor multifocality, bladder neck involvement, and concomitant CIS in the bladder.

3.1.2. Should frozen section be performed?

Although the accuracy and prognostic benefit of an FSA during RC remain controversial [11], we recently reported high diagnostic performance for an FSA of urethral margin during RC, with pooled sensitivity and specificity of 83% and 95%, respectively [6]. To date, an intraoperative FSA is recommended before performing an ONB, especially in case of a positive preoperative urethral biopsy [4,5]. A positive distal urethral FSA may change the treatment strategy (eg, no ONB or/and immediate urethrectomy at the time of RC) as well as patient counseling. Nevertheless, even in cases of risk factors and intraoperative suspicions, if the FSA of the distal urethra is negative, an ONB diversion can be executed [12].

Based on the available literature, it appears that in the absence of risk factors for UR, an FSA could be omitted, especially when a non-ONB diversion is planned. Nevertheless, in case of a planned ONB, an FSA may help ensure a cancer-free anastomosis in patients planned for an ONB diversion. Moreover, in the case of risk factors, an intraoperative FSA can help determine the real need for an immediate versus a staged urethrectomy versus no urethrectomy (Fig. 1).

3.1.3. When should we perform a urethrectomy?

In case of a positive urethral FSA and/or risk factors for UR, a urethrectomy can be performed at the time of RC (Figs. 1 and 2), but it could also be postponed to a secondary proce-

dure according to final pathology examination. In the biggest study based on the Surveillance, Epidemiology, and End Results database including 195 men who underwent either an immediate/staged (within 6 wk after RC) or a delayed (>6 wk after RC) urethrectomy, Nelles et al. [13] failed to find any significant differences in outcomes between an immediate and a delayed urethrectomy; the latter was performed mostly during the early stages of UR. Spiess et al. [14] found similar oncologic outcomes in patients who underwent an immediate or a staged urethrectomy (median time from cystectomy to urethrectomy: 16 wk). However, a survival benefit of a prophylactic urethrectomy has been reported for patients at very high risk for UR (eg, multiple tumors and/or concomitant CIS) [15]. Therefore, the decision to perform an immediate urethrectomy should be based on a preoperative rigorous assessment of patients' risk factors for UR to either potentially plan an intraoperative FSA to validate or not (if positive) the need for an immediate urethrectomy, or check the final pathology for further factors to help decide regarding an early urethrectomy, especially in case of a non-ONB diversion [16]. In any case of positive surgical margin of the urethra on final pathology examination, a complete urethrectomy should be performed within 3 mo after the RC.

Two main urethrectomy approaches are described: the prepubic and the perineal approach. Compared with a perineal urethrectomy, the prepubic approach is associated with a lower risk of severe complications, with shorter operative time and hospital length of stay [17,18]. A partial urethrectomy (at least to the bulbous portion) has been suggested as an option, but a total urethrectomy remains the standard of care for patients at high risk for UR until strong evidence arises to support a risk-based segmental urethrectomy [19].

Spiess et al. [14] did not find any differences in surgical morbidity for patients who underwent an immediate versus a staged urethrectomy (performed within a median period of 16 wk based on RC pathologic features). Typical postoperative complications after a urethrectomy are generally manageable such as genital hematoma but can also be more serious such as deep venous thrombosis [20]. Neurovascular bundle preservation could help improve postoperative potency [21], but quality data regarding risks, benefits, technique, and alternatives are still missing. Data on psychological or quality of life impact of patients who underwent a urethrectomy are missing.

3.1.4. Follow-up of patients at risk

Follow-up protocols are highly heterogeneous and rarely described among the published studies. Among the proposed tests are physical examination, urethral wash cytology, urethroscopy, pelvic computed tomography, pelvic magnetic resonance imaging, and ultrasound [22–37]. Most articles also reported on the assessment for clinical symptoms during each follow-up consultation. The cumulative data supported a close-knit surveillance protocol for patients at high risk for UR, at least for the first years. According to available data, the median time to UR after RC ranges from 8 [38] to 33 mo [39], suggesting the surveillance duration to be most valuable within the first 3–5 yr.

3.2. Management of UR

3.2.1. Diagnostic of UR

3.2.1.1. Clinical symptoms At the time of clinical symptoms or/and signs, the UR is, usually, already at an advanced stage [31,40] with poor oncologic prognosis [41], specifically when compared with patients who had their UR diagnosed with cytology but did not yet have symptoms [31]. Classic symptoms of UR are urethrorrhagia or penile/perineal pain. Clinical signs include blood at the meatus/hematuria, a palpable mass of the urethra, or obstructive lower urinary tract symptoms in patients with an ONB such as weak flow, sensation of not emptying, and overflow incontinence [24]. A retrospective study confirmed the worse oncologic outcomes of patients who presented with symptomatic UR (ie, lower 5-yr cancer-specific survival of 41% vs 80%; $p < 0.001$) compared with patients who had their UR diagnosed based on cytology [24]. Patients presenting with clinical signs and/or symptoms exhibit metastases more frequently than those with asymptomatic UR diagnosed by cytology [23]. Clinical examination and search for symptoms should be performed at each consultation.

3.2.1.2. Cytology Urethral wash cytology has been recommended for monitoring of recurrences in the remnant urothelium after RC [42]. The reliability, reproductivity, and performance of cytology are generally highly variable [43]. The follow-up schedule (ie, start and finish, and frequency) for the urethra has not been studied sufficiently to enable evidence-based recommendations regarding the intervals for wash cytology in patients with incontinent urinary diversion and voided cytology for those with an ONB. Hickey et al. [44] reported that urethral wash cytology performed every 6 mo for the rest of the patient's life may help detect all URs in due time. Varol et al. [45] advocated biannual assessment for the first 2 yr and annually thereafter, which was confirmed by Giannarini et al. [29]. Nevertheless, the use of urethral cytology during follow-up seems not to be necessary for every RC patient [46,47]. Therefore, to avoid unnecessary examinations, some authors proposed to use urethral wash cytology during follow-up only in patients at increased risk for UR [48]. Based on the cumulative data of the literature and experience of the authors, we propose using urethral wash cytology in high-risk patients on a biannual schedule during the first 2 yr and then annually up to 5 yr after RC (see Fig. 1).

3.2.1.3. Urethroscopy The value of urethroscopy for the detection of UR during follow-up after RC remains underin-

vestigated. Yamashita et al. [33] showed better detection of early UR after RC during follow-up with urethroscopy than that with wash urethral cytology alone. Therefore, in line with international guidelines [3], we suggest that urethroscopy should be performed in high-risk patients, even in case of a non-ONB diversion, every 6 mo in the 1st year after RC and then once a year for the ensuing 5 yr at least (see Fig. 1).

3.2.2. Treatment of UR

3.2.2.1. Salvage urethrectomy Despite the absence of clear recommendations for the management of UR after RC, salvage urethrectomy appears to be the treatment of choice in the absence of synchronous metastases. However, the small number of patients in the published retrospective studies makes an assessment of the efficacy of this approach difficult [39,46,49]. In general, a salvage urethrectomy can be performed safely in most patients with UR [50]. Predictive factors of survival after a salvage urethrectomy in patients without metastases (and other sites of recurrence) include the stage of urethral disease at recurrence [49], the histologic stage of the RC specimen [46], and whether a complete surgical resection was possible [39]. In case of UR in ONB patients, noncontinent cutaneous urinary diversion is a main option.

3.2.2.2. Urethra-sparing treatment Conservative treatment of UR is an option that might be discussed in the case of small, low-grade tumors. Three studies reported transurethral resection as an effective treatment for low-grade UR [32,51,52]. Intraurethral chemotherapy or bacillus Calmette-Guérin (BCG) has also been suggested based on data in non-muscle-invasive BCa; however, the data are inconclusive with regard to efficacy and adverse events. Indeed, in a small exploratory series, three cases were treated with intraurethral instillation of 5-fluorouracil, but only one (with low-grade pTa) did not experience disease recurrence after 7 yr of follow-up; the others died of metastatic disease within 1 yr [49]. Similarly, Varol et al. [45] reported treatment with BCG instillations in ten ONB patients with efficacy of 83% in the case of CIS only; it was, however, ineffective in patients with either papillary or invasive carcinoma. Therefore, BCG therapy seems to have no benefit as a urethra-sparing strategy except in patients with CIS only. Among other treatment options, radiotherapy and systemic chemotherapy were performed in small case series with variable results [39].

Overall, due to the lack of long-term data and the small size of the published studies, urethra-sparing strategies can be considered only as an inferior alternative to a complete urethrectomy in well-informed patients who harbor TaLG disease. It can be amended with adjuvant intravesical BCG instillations (of unknown length and frequency) in highly selected cases with CIS only.

3.3. Discussion and perspectives

The surveillance of the urethra and management of UR after RC remain poorly investigated in the postoperative management of BCa patients; the lack of awareness of this recurrence site often leads to late diagnosis with detrimental prognosis. Our systematic review found that the available data are mainly retrospective based on small heterogeneous

cohorts, resulting in very low-quality evidence. Therefore, to improve clinicians' awareness and to help them in clinical decision-making and patient counseling for the management of UR after RC, we proposed an evidence-based algorithm to allow for early diagnose and effective treatment of UR (Fig. 1).

First, risk stratification based on tumor multifocality, prostatic involvement, bladder neck involvement, presence of CIS, and sex can help identify each patient's individual risk for UR (ie, low and high risk for UR). An intraoperative FSA of the distal urethra should be performed in high-risk patients. In case of a positive FSA, an immediate urethrectomy should be considered together with the abortion of an ONB should it have been planned. In case of a positive final pathologic margin, a urethrectomy could be performed within 3 mo (staged urethrectomy; Table 1).

Despite the lack of investigation regarding urethral wash cytology in the surveillance of the urethra after RC, specifically when it comes to its effectiveness compared with clinical symptom screening, we recommend the use of regular cytology and/or urethroscopy during the surveillance in selected high-risk patients to make earlier detection possible. Finally, the standard of care for persistent cancer (ie, pathology positive) or UR should be a urethrectomy. Owing to a lack of data on urethra-sparing approaches, this option should not be proposed routinely, but it remains an option for noninvasive small-size recurrences in selected well-informed patients. The utility of local or systemic chemo- and immunotherapy or that of radiation therapy remains without any evidence.

This systematic review highlights the need for further evaluation, especially regarding the following: (1) improve-

ment of UR risk stratification; (2) which patient requires an immediate or a staged urethrectomy and to what extent (segmental versus subtotal versus total); (3) reliability and frequency of urethral wash cytology and/or urethroscopy in a risk-adjusted surveillance protocol; (4) in case of UR alone, when we should consider urethra-sparing treatment versus salvage urethrectomy; and (5) in case of UR alone, whether there is any benefit to combining systemic therapy with a salvage urethrectomy.

Understanding of the clinical natural history and underlying biology of UR might help design appropriate surveillance protocols based on risk factors including extended clinicopathologic features (eg, lymphovascular invasion, variant histology, neoadjuvant chemotherapy, etc.) related to UR. Indeed, some adverse pathologic features such as lymphovascular invasion, molecular subtypes, and variant histology have been shown to be associated with more aggressive disease in UC [53–58]. These may also lead to increased high risk for UR to help guide the type and extent of local only versus local plus systemic therapy.

The main strength of the present study is that, to our knowledge, it is the first to propose a practical algorithm to identify and manage UR after RC based on currently available literature using a three-step systematic review approach. However, there are several potential limitations to our study that should be mentioned. The main limitation was the retrospective design of the majority of included studies as well as their small sample sizes, implying a low level of evidence for our suggested recommendations and algorithm. Owing to the heterogeneity of patient populations in terms of inclusion criteria and clinicopathologic features, meta-analyses on surveillance approaches and UR management were not feasible.

4. Conclusions

Based on the currently available literature, we propose an algorithm to support the decision-making process in order to facilitate/improve the identification/detection and then management of a UR after RC. Given the lack of evidence on this topic, awareness of the problem and surveillance in high-risk patients for possible UR are necessary to improve postoperative management and survival of BCa patients. This study should attract the attention of the urologic community in order to stimulate research in this unknown, poorly understood disease space.

Author contributions: Ekaterina Laukhtina had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pradere, Shariat.

Acquisition of data: Laukhtina, Pradere.

Analysis and interpretation of data: Laukhtina, Pradere, Shariat.

Drafting of the manuscript: Laukhtina, Pradere.

Critical revision of the manuscript for important intellectual content: Moschini, Soria, D'Andrea, Teoh, Mori, Albisinni, Mari, Krajewski, Cimadamore, Abufaraj, Enikeev, Neuzillet, Giannarini, Xylinas, Kamat, Roupret, Babjuk, Witjes, Shariat.

Statistical analysis: None.

Obtaining funding: None.

Administrative, technical, or material support: None.

Table 1 – Summary of evidence for follow-up of the urethra and management of urethral recurrence after radical cystectomy for bladder cancer

Summary of evidence	Level of evidence
Risk stratification based on tumor multifocality, prostatic involvement, bladder neck involvement, presence of CIS, and sex can help identify each patient's individual risk for UR.	2a
FSA of urethral margin during RC showed high diagnostic performance.	2a
Even in cases of risk factors and intraoperative suspicions, if the FSA of the distal urethra is negative, an ONB diversion can be executed.	3b
In case of a positive FSA, an immediate urethrectomy should be considered.	2a
A survival benefit for prophylactic urethrectomy has been reported only in patients at a very high risk for UR based on clinical factors.	2b
In case of a positive final pathological margin, urethrectomy could be performed within 3 mo after RC (staged urethrectomy).	2a
Patients whose UR was diagnosed based on clinical symptoms have a poor prognosis.	2b
In selected high-risk patients, the use of regular cytology and/or urethroscopy during the surveillance allow earlier detection of UR.	3a
In case of UR, the standard of care should be a urethrectomy.	3a
Urethra-sparing approaches remain an option for noninvasive small size recurrences in selected patients.	4
CIS = carcinoma in situ; FSA = frozen section analysis; ONB = orthotopic neobladder; RC = radical cystectomy; UR = urethral recurrence.	

Supervision: Shariat, Pradere.

Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euf.2022.03.004>.

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