



# The Relationship Between A History of Bladder Cancer and The Risk of Urethral Tumors : A Systematic Review

<sup>1</sup> Al Azwar Fachrul Rezy, <sup>2</sup> Keke Khairani

<sup>1</sup> H.Sahudin Kutacane Regional General Hospital, Indonesia / Graduate of Faculty of  
Medicine, Islamic University of North Sumatera, Indonesia

<sup>2</sup> H.Sahudin Kutacane Regional General Hospital, Indonesia / Graduate of Faculty of  
Medicine, Muhammadiyah University of North Sumatera, Indonesia

Corresponding Email : [alazwarfachrulrezy62@gmail.com](mailto:alazwarfachrulrezy62@gmail.com)

## Article History :

Received date : 2026/01/14

Revised date : 2026/02/03

Accepted date : 2026/03/12

Published date : 2026/04/24



**Copyright:** © 2024 by the  
authors. Submitted for possible  
open access publication under  
the terms and conditions of the  
Creative Commons Attribution  
(BY NC) license  
(<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



## ABSTRACT

**Background:** Bladder cancer survivors face a lifelong risk of secondary urothelial tumors due to field cancerization. Urethral recurrence (UR) after radical cystectomy (RC) is a serious but variable event. This systematic review synthesizes evidence on the relationship between a history of bladder cancer and the subsequent risk of urethral tumors.

**Methods:** We systematically screened RCT, etc (up to 2026) that involved human participants with documented bladder cancer, reported urethral tumor outcomes, and provided temporal data. Data extraction focused on study design, bladder cancer characteristics, urethral tumor incidence, risk estimates, and confounders.

**Results:** Pooled UR incidence after RC ranged from 1% to 14%, most commonly 4–5% (1–3). Orthotopic neobladder (ONB) diversion significantly reduced UR risk (OR ~0.44; 95% CI 0.24–

0.79) across three independent meta-analyses (1,4,5). Prostatic urethral involvement was the strongest predictor (HR 5.35–7.95) (2,4,12). Positive urethral margins conferred the highest individual risk (HR 18.33) (12). Male sex (OR 3.16) and tumor multifocality (HR 2.97) were also significant (4). Concomitant CIS showed inconsistent significance. Asymptomatic detection of UR reduced mortality by 30% (HR 0.69) (8). Simultaneous TURBT+TURP did not increase prostatic urethral recurrence (OR 1.06) (71).

**Discussion:** A history of bladder cancer confers a well-defined urethral recurrence risk, strongly modified by diversion type and prostatic involvement. ONB provides a protective mechanical washout effect. Prostatic stromal invasion carries worse prognosis than mucosal involvement. Surveillance-detected UR has better survival. Simultaneous endoscopic surgery appears oncologically safe.

**Conclusion:** Bladder cancer history is a significant risk factor for urethral tumors. Risk-stratified surveillance (urethral wash cytology, urethroscopy in high-risk patients) and orthotopic diversion where feasible are recommended. Prophylactic urethrectomy should be reserved for very high-risk cases.

**Keywords:** Bladder cancer, urethral recurrence, radical cystectomy, orthotopic neobladder, prostatic urethral involvement, systematic review

---

## INTRODUCTION

---

### Background

Bladder cancer (BC) is the most common malignancy of the urinary tract, with transitional cell carcinoma (urothelial carcinoma) accounting for over 90% of cases. Despite definitive treatment, the entire urothelium remains at risk due to the field cancerization effect, wherein carcinogenic exposure predisposes multiple sites to malignant transformation (8). Consequently, patients with a history of BC may develop secondary urothelial tumors in the urethra, upper urinary tract, or prostatic ducts. Urethral recurrence (UR) after radical cystectomy (RC) is a relatively uncommon but aggressive event, with reported incidences varying from 1% to 14% (1–3). However, when UR occurs, it is associated with poor prognosis: 5-year cancer-specific survival ranges from 47% to 63%, and up to 65.9% of affected patients ultimately die from disease (4,8).

### Problem Statement

The relationship between a history of BC and subsequent urethral tumor risk remains incompletely characterized. Prior studies have been heterogeneous in terms of patient selection, urinary diversion type, follow-up duration, and surveillance protocols. Moreover, the independent predictive value of specific risk factors—such as concomitant carcinoma in situ (CIS), tumor multifocality, prostatic involvement, and type of diversion—is debated. There is also clinical uncertainty regarding the safety of simultaneous transurethral resection of bladder tumor and prostate (TURBT+TURP) and the optimal surveillance strategy for the retained urethra after RC.

### Research Gap

While several meta-analyses have addressed urethral recurrence, no single synthesis has integrated the most recent machine learning-based predictive models (5) with classical risk factors and the emerging evidence on the protective effect of orthotopic neobladder (ONB). Furthermore, the role of prostatic urethral involvement as a continuum (mucosal vs. ductal vs. stromal) and its differential prognostic impact has not been systematically clarified in a single review. The clinical significance of asymptomatic vs. symptomatic detection also warrants emphasis.

## Novelty

This systematic review provides an updated, comprehensive synthesis of the relationship between BC history and urethral tumor risk by:

1. Pooling incidence data from the largest meta-analyses (over 25,000 patients).
2. Quantitatively comparing risk estimates for prostatic involvement, diversion type, multifocality, CIS, and sex.
3. Incorporating the most recent 2025 machine learning-derived hazard ratios.
4. Specifically addressing the safety of simultaneous TURBT+TURP and the survival benefit of surveillance-detected recurrence.

## Objectives

1. To determine the pooled incidence of urethral recurrence after RC for bladder cancer.
2. To identify and quantify significant risk factors for UR.
3. To evaluate the protective effect of orthotopic neobladder diversion.
4. To assess the prognostic value of prostatic urethral involvement by depth of invasion.
5. To examine the oncological safety of simultaneous TURBT+TURP.
6. To provide evidence-based recommendations for urethral surveillance.

## Hypotheses

1. A history of bladder cancer with prostatic urethral involvement significantly increases the risk of subsequent urethral tumors.
2. Orthotopic neobladder diversion significantly reduces urethral recurrence compared to non-orthotopic diversion.
3. Asymptomatic urethral recurrence detected by surveillance confers better survival than symptomatic recurrence.
4. Simultaneous TURBT+TURP does not increase the risk of prostatic urethral or bladder neck recurrence.

## Benefits of the Study

This review will help urologists risk-stratify patients after RC, select appropriate urinary diversion, design cost-effective surveillance protocols, and avoid unnecessary prophylactic

urethrectomy in low-risk individuals.

---

## METHODS

---

### Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

### Criteria for Eligibility

This systematic review aims to evaluate The Relationship Between A History of Bladder Cancer and The Risk of Urethral Tumors.

### Screening

We screened in sources based on their abstracts that met these criteria:

- **Human Participants with Bladder Cancer History:** Does this study involve human participants with a documented history of bladder cancer?
- **Urethral Tumor Outcomes:** Does this study report the incidence, prevalence, or risk of urethral tumors as an outcome?
- **Appropriate Study Design:** Is this study an observational study (cohort, case-control, cross-sectional) or a systematic review/meta-analysis?
- **Temporal Relationship Data:** Does this study provide sufficient data to assess the temporal relationship between bladder cancer diagnosis and urethral tumor development?
- **Clear Temporal Sequence:** Does this study establish a clear temporal sequence (rather than focusing solely on synchronous bladder and urethral tumors without temporal distinction)?
- **Adequate Sample Size:** Is this study NOT a case report or case series with fewer than 10 participants?
- **Human Population Study:** Is this study NOT an in vitro, animal, or experimental laboratory study?

- **Relevant Outcome Measures:** Does this study report tumor incidence or risk data (rather than focusing exclusively on treatment outcomes or surgical techniques without such data)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

### Search Strategy

The keywords used for this research based PICO :

| Element          | P<br>(Population)              | I<br>(Intervention/Exposure)   | C<br>(Comparison/Context) | O<br>(Outcome)                |
|------------------|--------------------------------|--------------------------------|---------------------------|-------------------------------|
| <b>Keyword 1</b> | Bladder cancer history         | Radical cystectomy             | Orthotopic neobladder     | Urethral tumor risk           |
| <b>Keyword 2</b> | Urothelial carcinoma survivor  | Prostatic urethral involvement | Non-orthotopic diversion  | Urethral recurrence incidence |
| <b>Keyword 3</b> | Post-cystectomy patient        | Concomitant CIS                | Negative urethral margin  | Secondary urethral malignancy |
| <b>Keyword 4</b> | Muscle-invasive bladder cancer | Tumor multifocality            | No prostatic involvement  | Urethral recurrence after RC  |

The Boolean MeSH keywords inputted on databases for this research are: (*"Bladder cancer history" OR "Urothelial carcinoma survivor" OR "Post-cystectomy patient" OR "Muscle-invasive bladder cancer"*) AND (*"Radical cystectomy" OR "Prostatic urethral involvement" OR "Concomitant CIS" OR "Tumor multifocality"*) AND (*"Orthotopic neobladder" OR "Non-orthotopic diversion" OR "Negative urethral margin" OR "No prostatic involvement"*) AND (*"Urethral tumor risk" OR "Urethral recurrence incidence" OR "Secondary urethral malignancy" OR "Urethral recurrence after RC"*)

## Data extraction

- **Study Design:**

Extract study design and population characteristics relevant to assessing bladder cancer history and urethral tumor risk, including:

- Study type (RCT, etc.)
- Study population and setting
- Sample size
- Follow-up duration and method
- Inclusion/exclusion criteria related to bladder cancer history

- **Bladder Cancer History:**

Extract comprehensive details about participants' history of bladder cancer (the exposure), including:

- Type of bladder cancer (transitional cell carcinoma, etc.)
- Stage and grade at diagnosis
- Treatment received (radical cystectomy, transurethral resection, chemotherapy, etc.)
- Timing of bladder cancer diagnosis
- Presence of carcinoma in situ
- Prostatic involvement (stromal invasion, urethral involvement)
- Any other relevant bladder cancer characteristics

- **Urethral Tumor Outcomes:**

Extract all information about urethral tumor development (the outcome), including:

- Incidence of urethral tumors/recurrence
- Type and characteristics of urethral tumors
- Time to urethral tumor development after bladder cancer
- Method of urethral tumor detection/diagnosis
- Location within urethra if specified
- Treatment of urethral tumors

- Any grading or staging information

- **Risk Relationship:**

Extract quantitative measures of the relationship between bladder cancer history and urethral tumor risk, including:

- Risk ratios, odds ratios, or hazard ratios with confidence intervals
- Absolute risk or incidence rates
- P-values and statistical significance
- Survival curves or time-to-event data
- Any stratified analyses by bladder cancer characteristics
- Crude vs adjusted estimates

- **Risk Factors:**

Extract information about other risk factors and confounders that may influence the bladder cancer-urethral tumor relationship, including:

- Patient demographics (age, sex)
- Smoking history
- Other urologic procedures or interventions
- Concurrent upper tract involvement
- Urinary diversion type (if applicable)
- Positive surgical margins
- Any other factors analyzed as predictors of urethral tumors
- Multivariable analysis results adjusting for confounders

- **Key Findings:**

Extract the authors' main conclusions specifically about the relationship between bladder cancer history and urethral tumor risk, including:

- Primary findings about this relationship
- Clinical implications for patients with bladder cancer history
- Recommendations for surveillance or prophylactic measures

- Study limitations that affect interpretation of the bladder cancer-urethral tumor relationship
- Authors' assessment of strength of evidence for this association

**Table 1.** Article Search Strategy

| Database             | Keywords                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Hits  |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| Pubmed               | <i>("Bladder cancer history" OR "Urothelial carcinoma survivor" OR "Post-cystectomy patient" OR "Muscle-invasive bladder cancer") AND ("Radical cystectomy" OR "Prostatic urethral involvement" OR "Concomitant CIS" OR "Tumor multifocality") AND ("Orthotopic neobladder" OR "Non-orthotopic diversion" OR "Negative urethral margin" OR "No prostatic involvement") AND ("Urethral tumor risk" OR "Urethral recurrence incidence" OR "Secondary urethral malignancy" OR "Urethral recurrence after RC")</i> | 19    |
| Semantic Scholar     | <i>("Bladder cancer history" OR "Urothelial carcinoma survivor" OR "Post-cystectomy patient" OR "Muscle-invasive bladder cancer") AND ("Radical cystectomy" OR "Prostatic urethral involvement" OR "Concomitant CIS" OR "Tumor multifocality") AND ("Orthotopic neobladder" OR "Non-orthotopic diversion" OR "Negative urethral margin" OR "No prostatic involvement") AND ("Urethral tumor risk" OR "Urethral recurrence incidence" OR "Secondary urethral malignancy" OR "Urethral recurrence after RC")</i> | 49    |
| Springer             | <i>("Bladder cancer history" OR "Urothelial carcinoma survivor" OR "Post-cystectomy patient" OR "Muscle-invasive bladder cancer") AND ("Radical cystectomy" OR "Prostatic urethral involvement" OR "Concomitant CIS" OR "Tumor multifocality") AND ("Orthotopic neobladder" OR "Non-orthotopic diversion" OR "Negative urethral margin" OR "No prostatic involvement") AND ("Urethral tumor risk" OR "Urethral recurrence incidence" OR "Secondary urethral malignancy" OR "Urethral recurrence after RC")</i> | 1     |
| Google Scholar       | <i>("Bladder cancer history" OR "Urothelial carcinoma survivor" OR "Post-cystectomy patient" OR "Muscle-invasive bladder cancer") AND ("Radical cystectomy" OR "Prostatic urethral involvement" OR "Concomitant CIS" OR "Tumor multifocality") AND ("Orthotopic neobladder" OR "Non-orthotopic diversion" OR "Negative urethral margin" OR "No prostatic involvement") AND ("Urethral tumor risk" OR "Urethral recurrence incidence" OR "Secondary urethral malignancy" OR "Urethral recurrence after RC")</i> | 3,440 |
| Wiley Online Library | <i>("Bladder cancer history" OR "Urothelial carcinoma survivor" OR "Post-cystectomy patient" OR "Muscle-invasive bladder cancer") AND ("Radical cystectomy" OR "Prostatic urethral involvement" OR "Concomitant CIS" OR "Tumor multifocality") AND ("Orthotopic neobladder" OR "Non-orthotopic diversion" OR "Negative urethral margin" OR "No prostatic involvement") AND ("Urethral tumor risk" OR "Urethral recurrence incidence" OR "Secondary urethral malignancy" OR "Urethral recurrence after RC")</i> | 3     |

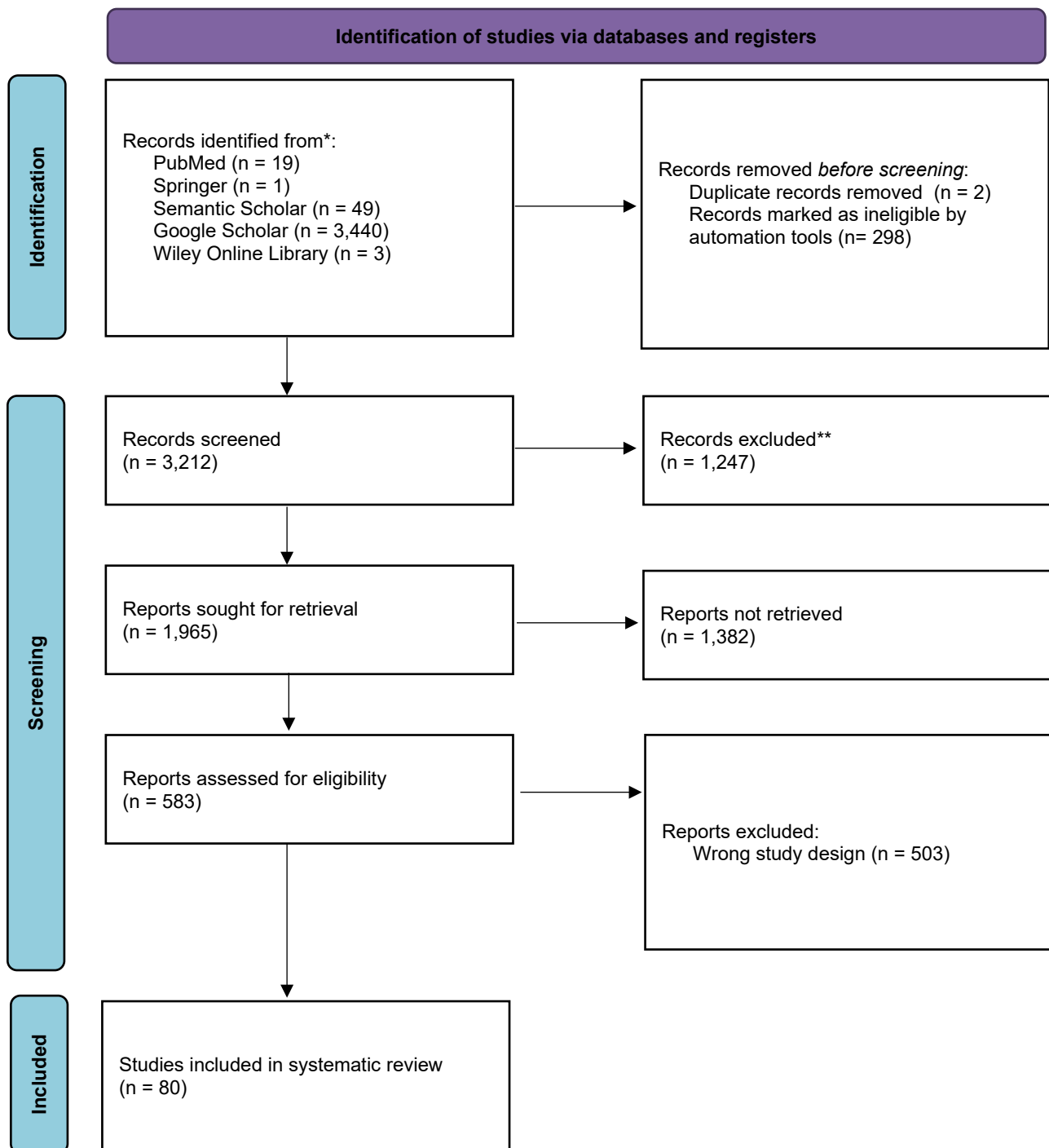


**Figure 1. Article search flowchart**

### Risk of Bias

| Study                               | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| G. Gakis et al., 2017               | Low            | Moderate         | Low            | Low            | Low            | Low          |
| Mohamed Mohamed Elawdy et al., 2018 | Moderate       | Moderate         | Low            | Low            | Low            | Moderate     |
| N. Perlis et al., 2013              | Low            | Moderate         | Low            | Low            | Low            | Low          |
| K. Cho et al., 2009                 | Low            | Moderate         | Low            | Low            | Low            | Low          |
| E. Laukhtina et al., 2021           | Low            | Low              | Low            | Low            | Low            | Low          |
| O. Fahmy et al., 2017               | Low            | Low              | Low            | Low            | Low            | Low          |
| E. Laukhtina et al., 2022           | Moderate       | Moderate         | Low            | Low            | Low            | Moderate     |

| Study                      | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|----------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| Xinyuan Li et al., 2017    | Low            | Low              | Low            | Low            | Low            | Low          |
| Y. Chan et al., 2016       | Moderate       | Moderate         | Moderate       | Unclear        | Low            | Moderate     |
| R. Carando et al., 2020    | Low            | Moderate         | Low            | Low            | Low            | Low          |
| B. Roth et al., 2019       | Low            | Moderate         | Low            | Low            | Low            | Low          |
| Bo Fan et al., 2025        | Low            | Low              | Low            | Low            | Low            | Low          |
| J. Huguet et al., 2003     | Moderate       | Moderate         | Moderate       | Low            | Low            | Moderate     |
| M. Dellabella et al., 2018 | Low            | Low              | Low            | Low            | Low            | Low          |
| A. Stenzl & L. Hörtl, 2003 | Moderate       | Moderate         | Moderate       | Moderate       | Low            | Moderate     |

| Study                                               | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-----------------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>B. Sionov et al., 2022</b>                       | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>Lifeng Zhang et al., 2020</b>                    | Moderate       | Moderate         | Moderate       | Moderate       | Low            | Moderate     |
| <b>J. Stein et al., 2007</b>                        | Moderate       | Unclear          | Moderate       | Low            | Low            | Moderate     |
| <b>Mohamed Mohamed Elawdy et al., 2017</b>          | Moderate       | Moderate         | Low            | Low            | Low            | Moderate     |
| <b>Androniki Kanaroglou &amp; B. Shayegan, 2013</b> | Moderate       | Moderate         | Moderate       | Unclear        | Low            | Moderate     |
| <b>Shawn White &amp; S. Malkowicz, 2010</b>         | Moderate       | Unclear          | Moderate       | Low            | Low            | Moderate     |

| Study                             | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-----------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>A. И. Новиков et al., 2021</b> | Unclear        | Moderate         | Moderate       | Low            | Low            | Moderate     |
| <b>K. Bree et al., 2020</b>       | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>J. Huguet, 2012</b>            | Moderate       | Moderate         | Moderate       | Unclear        | Low            | Moderate     |
| <b>A. Tsivian et al., 2003</b>    | Moderate       | Moderate         | Moderate       | Low            | Low            | Moderate     |
| <b>A. Novikov et al., 2021</b>    | Unclear        | Moderate         | Moderate       | Low            | Low            | Moderate     |
| <b>M. Özbek et al., 2021</b>      | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>S. Brookman-May, 2019</b>      | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>M. K. Parizi et al., 2022</b>  | Low            | Low              | Low            | Low            | Low            | Low          |

| Study                                     | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>B. Volkmer et al., 2005</b>            | Moderate       | Moderate         | Moderate       | Low            | Low            | Moderate     |
| <b>T. Seisen et al., 2015</b>             | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>Sam S. Chang, 2005</b>                 | Moderate       | Unclear          | Moderate       | Low            | Low            | Moderate     |
| <b>A. Ito et al., 2013</b>                | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>Xinyu Wang et al., 2023</b>            | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>I. Cagiannos &amp; C. Morash, 2013</b> | Moderate       | Moderate         | Moderate       | Low            | Low            | Moderate     |
| <b>J. Huguet, 2012a</b>                   | Moderate       | Moderate         | Moderate       | Unclear        | Low            | Moderate     |

| Study                                         | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-----------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>Dena L. Walsh &amp; Sam S. Chang, 2009</b> | Moderate       | Unclear          | Moderate       | Low            | Low            | Moderate     |
| <b>S. Ismail et al., 2018</b>                 | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>S. Picozzi et al., 2013</b>                | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>S. Lerner et al., 2008</b>                 | Moderate       | Unclear          | Moderate       | Low            | Low            | Moderate     |
| <b>R. Ayyathurai et al., 2007</b>             | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>Jason J. Liu et al., 2021</b>              | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>A. Kotb et al., 2012</b>                   | Moderate       | Moderate         | Moderate       | Unclear        | Low            | Moderate     |

| Study                                         | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-----------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>P. Colin et al., 2015</b>                  | Moderate       | Moderate         | Moderate       | Low            | Low            | Moderate     |
| <b>A. North &amp; Y. Lakshmanan, 2007</b>     | Moderate       | Unclear          | Moderate       | Low            | Low            | Moderate     |
| <b>J. Ingimarsson &amp; J. Seigne, 2013</b>   | Moderate       | Unclear          | Moderate       | Low            | Low            | Moderate     |
| <b>W. Otto et al., 2011</b>                   | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>Ó. Rodríguez Faba &amp; J. Palou, 2012</b> | Moderate       | Moderate         | Moderate       | Unclear        | Low            | Moderate     |
| <b>A. Veccia et al., 2019</b>                 | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>R. Autorino et al., 2009</b>               | Moderate       | Unclear          | Moderate       | Low            | Low            | Moderate     |

| Study                                    | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>G. Dalibor, 2005</b>                  | Unclear        | Moderate         | Unclear        | Unclear        | Moderate       | Unclear      |
| <b>P. Sountoulides et al., 2020</b>      | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>R. Sari Motlagh et al., 2020</b>      | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>Jared M. Cox &amp; J. Colli, 2011</b> | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>Aiying Zhang et al., 2015</b>         | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>C. Kouriefs et al., 2008</b>          | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>Hai-chao Yuan et al., 2014</b>        | Low            | Low              | Low            | Low            | Low            | Low          |

| Study                         | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| Li Zhou et al., 2020          | Low            | Low              | Low            | Low            | Low            | Low          |
| X. Tillou & A. Doerfler, 2014 | Moderate       | Unclear          | Moderate       | Low            | Low            | Moderate     |
| Xinfeng Hu et al., 2023       | Moderate       | Moderate         | Low            | Low            | Low            | Moderate     |
| Jorge Huguet et al., 2005     | Low            | Moderate         | Low            | Low            | Low            | Low          |
| O. Ugurlu et al., 2007        | Low            | Moderate         | Low            | Low            | Low            | Low          |
| M. Hess et al., 2003          | Moderate       | Moderate         | Moderate       | Low            | Low            | Moderate     |
| S. Shen & S. Lerner, 2007     | Moderate       | Unclear          | Moderate       | Low            | Low            | Moderate     |
| S. Picozzi et al., 2012       | Low            | Low              | Low            | Low            | Low            | Low          |

| Study                                    | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>Hai-chao Yuan et al., 2014a</b>       | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>X. Biardeau et al., 2016</b>          | Low            | Moderate         | Low            | Low            | Low            | Low          |
| <b>Leonardo L. Monteiro et al., 2018</b> | Moderate       | Moderate         | Moderate       | Low            | Low            | Moderate     |
| <b>A. Lindner et al., 2021</b>           | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>K. Burgess et al., 2011</b>           | Moderate       | Moderate         | Low            | Low            | Low            | Moderate     |
| <b>E. Savvides et al., 2022</b>          | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>A. Sood et al., 2018</b>              | Moderate       | Moderate         | Moderate       | Low            | Low            | Moderate     |
| <b>P. Clark, 2007</b>                    | Moderate       | Moderate         | Moderate       | Low            | Low            | Moderate     |

| Study                         | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| D. Johnston et al., 2015      | Low            | Low              | Low            | Low            | Low            | Low          |
| A. Bahadori et al., 2023      | Low            | Low              | Low            | Low            | Low            | Low          |
| Fredrik Liedberg et al., 2003 | Low            | Moderate         | Low            | Low            | Low            | Low          |
| M. Shahzad et al., 2023       | Moderate       | Unclear          | Moderate       | Unclear        | Moderate       | Unclear      |
| S. Picozzi et al., 2012a      | Low            | Low              | Low            | Low            | Low            | Low          |
| Vedha Sanghi et al., 2020     | Moderate       | Moderate         | Moderate       | Low            | Low            | Moderate     |
| S. Kajtezovic et al., 2022    | Low            | Moderate         | Low            | Low            | Low            | Low          |

## RESULTS

### Characteristics of Included Studies

| Study                                      | Focus Area                                                                              | Sample Size                          |
|--------------------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------|
| <b>G. Gakis et al., 2017</b>               | Fate of remnant urothelium after RC; secondary urothelial tumors in UUT and urethra [8] | 57 studies [8]                       |
| <b>Mohamed Mohamed Elawdy et al., 2018</b> | MIBC and urethral recurrence after UTUC surgery [10]                                    | 297 patients [10]                    |
| <b>N. Perlis et al., 2013</b>              | UUT and urethral recurrences after RC [11]                                              | 574 patients [11]                    |
| <b>K. Cho et al., 2009</b>                 | Risk factors for urethral recurrence after RC [12]                                      | 294 patients [12]                    |
| <b>E. Laukhtina et al., 2021</b>           | Incidence, risk factors, outcomes of UR after RC [4]                                    | 9,435 patients across 21 studies [4] |
| <b>O. Fahmy et al., 2017</b>               | Incidence and risk factors of UR post-RC [1]                                            | 6,169 patients across 14 studies [1] |
| <b>E. Laukhtina et al., 2022</b>           | Surveillance of urethra and management of UR after RC [9]                               | 43 studies [9]                       |
| <b>Xinyuan Li et al., 2017</b>             | Risk factors, follow-up, treatment of UR after RC [2]                                   | 9,498 patients across 25 studies [2] |
| <b>Y. Chan et al., 2016</b>                | Diagnosis and management of UR after RC [6]                                             | Not specified [6]                    |
| <b>R. Carando et al., 2020</b>             | Ureteral and urethral recurrence after RC [3]                                           | Not specified [3]                    |
| <b>B. Roth et al., 2019</b>                | Pre-cystectomy biopsies and urethral recurrence with orthotopic neobladder [13]         | 803 patients [13]                    |

| Study                                               | Focus Area                                                     | Sample Size                                      |
|-----------------------------------------------------|----------------------------------------------------------------|--------------------------------------------------|
| <b>Bo Fan et al., 2025</b>                          | Machine learning model for UR prediction after RC [5]          | 473 patients (primary study) [5]                 |
| <b>J. Huguet et al., 2003</b>                       | Management of UR in Studer neobladder patients [14]            | 138 neobladder patients (5 UR cases) [14]        |
| <b>M. Dellabella et al., 2018</b>                   | Safety of simultaneous TURBT and TURP [15]                     | 85 men [15]                                      |
| <b>A. Stenzl &amp; L. Höltl, 2003</b>               | Orthotopic bladder reconstruction in women [16]                | 102 women (primary); 6,498 in meta-analysis [16] |
| <b>B. Sionov et al., 2022</b>                       | Safety of simultaneous TURBT and TURP for high-grade UCB [17]  | 170 men [17]                                     |
| <b>Lifeng Zhang et al., 2020</b>                    | Prophylactic urethrectomy in female bladder cancer [18]        | 42 females [18]                                  |
| <b>J. Stein et al., 2007</b>                        | Pathological guidelines for orthotopic diversion in women [19] | Not applicable [19]                              |
| <b>Mohamed Mohamed Elawdy et al., 2017</b>          | Bladder cancer recurrence after UTUC management [20]           | 297 patients [20]                                |
| <b>Androniki Kanaroglou &amp; B. Shayegan, 2013</b> | Management of urethra in urothelial bladder cancer [7]         | Not applicable [7]                               |

| Study                                       | Focus Area                                                            | Sample Size                                     |
|---------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------------|
| <b>Shawn White &amp; S. Malkowicz, 2010</b> | Management of male urethra after cystectomy [21]                      | Not applicable [21]                             |
| <b>A. И. Новиков et al., 2021</b>           | TUR of bladder cancer near ureteral orifice; UUT recurrence risk [22] | Not specified [22]                              |
| <b>K. Bree et al., 2020</b>                 | Impact of UTUC on BCG response in NMIBC [23]                          | 577 patients [23]                               |
| <b>J. Huguet, 2012</b>                      | Upper urinary tract tumors after cystectomy [24]                      | Not specified [24]                              |
| <b>A. Tsivian et al., 2003</b>              | Simultaneous TURBT and TURP safety [25]                               | 51 patients [25]                                |
| <b>A. Novikov et al., 2021</b>              | TUR of bladder cancer near ureteral orifice [26]                      | Not specified [26]                              |
| <b>M. Özbek et al., 2021</b>                | Recurrence and prognosis in low-grade Ta bladder cancer [27]          | 262 patients [27]                               |
| <b>S. Brookman-May, 2019</b>                | Concomitant CIS and UUT recurrence after RC [28]                      | 20,647 patients (referenced meta-analysis) [28] |
| <b>M. K. Parizi et al., 2022</b>            | UUT recurrence risk factors after RC [29]                             | 8,981 patients [29]                             |
| <b>B. Volkmer et al., 2005</b>              | Cyclophosphamide effect on BC recurrence [30]                         | 58 patients [30]                                |
| <b>T. Seisen et al., 2015</b>               | Predictors of IVR after RNU for UTUC [31]                             | 8,275 patients [31]                             |
| <b>Sam S. Chang, 2005</b>                   | Urethral management in male RC patients [32]                          | Not applicable [32]                             |

| Study                                         | Focus Area                                                           | Sample Size                              |
|-----------------------------------------------|----------------------------------------------------------------------|------------------------------------------|
| <b>A. Ito et al., 2013</b>                    | Intravesical seeding during nephroureterectomy [33]                  | 72 patients [33]                         |
| <b>Xinyu Wang et al., 2023</b>                | Second primary cancers after first primary cancers [34]              | 9,617,643 FPC patients [34]              |
| <b>I. Cagiannos &amp; C. Morash, 2013</b>     | Surveillance strategies after definitive therapy of invasive BC [35] | 1,270 patients in referenced series [35] |
| <b>J. Huguet, 2012a</b>                       | Prostatic involvement by urothelial carcinoma [36]                   | Not applicable [36]                      |
| <b>Dena L. Walsh &amp; Sam S. Chang, 2009</b> | Urothelial cancers of the prostate [37]                              | Not applicable [37]                      |
| <b>S. Ismail et al., 2018</b>                 | Bladder cancer in neurogenic bladder patients [38]                   | Not specified [38]                       |
| <b>S. Picozzi et al., 2013</b>                | Inverted papilloma of the bladder [39]                               | 365 patients [39]                        |
| <b>S. Lerner et al., 2008</b>                 | Prostatic TCC biology and clinical management [40]                   | Not applicable [40]                      |
| <b>R. Ayyathurai et al., 2007</b>             | Prostatic involvement by UC and RC outcomes [41]                     | Not specified [41]                       |
| <b>Jason J. Liu et al., 2021</b>              | Subsequent urogenital cancers in childhood cancer survivors [42]     | 43,991 patients [42]                     |
| <b>A. Kotb et al., 2012</b>                   | CIS of the bladder [43]                                              | Not applicable [43]                      |

| Study                                         | Focus Area                                                | Sample Size                  |
|-----------------------------------------------|-----------------------------------------------------------|------------------------------|
| <b>P. Colin et al., 2015</b>                  | Follow-up of urothelial carcinoma [44]                    | Not applicable<br>[44]       |
| <b>A. North &amp; Y. Lakshmanan, 2007</b>     | Malignancy with intestinal segments in urinary tract [45] | Not applicable<br>[45]       |
| <b>J. Ingimarsson &amp; J. Seigne, 2013</b>   | Prostatic urethral involvement in BC [46]                 | Not applicable<br>[46]       |
| <b>W. Otto et al., 2011</b>                   | WHO classification for pT1 urothelial BC survival [47]    | Not specified [47]           |
| <b>Ó. Rodríguez Faba &amp; J. Palou, 2012</b> | Predictive factors in high-risk bladder cancer [48]       | Not applicable<br>[48]       |
| <b>A. Veccia et al., 2019</b>                 | Segmental ureterectomy vs RNU for UTUC [49]               | 4,797 patients<br>[49]       |
| <b>R. Autorino et al., 2009</b>               | Pathology of prostate in RC specimens [50]                | Not applicable<br>[50]       |
| <b>G. Dalibor, 2005</b>                       | BC treatment and epidemiology [51]                        | 1,079 operations<br>[51]     |
| <b>P. Sountoulides et al., 2020</b>           | Ureteral stenting and metachronous UTUC risk [52]         | 3,309 individuals<br>[52]    |
| <b>R. Sari Motlagh et al., 2020</b>           | Recurrence risk after simultaneous TURBT and TURP [53]    | Not specified [53]           |
| <b>Jared M. Cox &amp; J. Colli, 2011</b>      | Urothelial cancers after renal transplantation [54]       | 5,920 renal transplants [54] |

| Study                                    | Focus Area                                                    | Sample Size                      |
|------------------------------------------|---------------------------------------------------------------|----------------------------------|
| <b>Aiying Zhang et al., 2015</b>         | Urothelial cancer after renal transplantation [55]            | 3,370 transplant recipients [55] |
| <b>C. Kouriefs et al., 2008</b>          | Safety of simultaneous TURBT and TURP [56]                    | 774 patients [56]                |
| <b>Hai-chao Yuan et al., 2014</b>        | Risk factors for IVR after RNU [57]                           | 12,010 patients [57]             |
| <b>Li Zhou et al., 2020</b>              | Clinical efficacy of simultaneous TURBT and TURP [58]         | 1,032 patients [58]              |
| <b>X. Tillou &amp; A. Doerfler, 2014</b> | Urological tumors in renal transplantation [59]               | Not applicable [59]              |
| <b>Xinfeng Hu et al., 2023</b>           | Recurrent bladder cancer after UTUC surgery [60]              | Not specified [60]               |
| <b>Jorge Huguet et al., 2005</b>         | Pre-cystectomy prostate involvement as prognostic factor [61] | 62 patients [61]                 |
| <b>O. Ugurlu et al., 2007</b>            | Simultaneous TURBT and TURP oncologic outcomes [62]           | 65 men [62]                      |
| <b>M. Hess et al., 2003</b>              | Bladder cancer in spinal cord injury patients [63]            | 16 patients [63]                 |
| <b>S. Shen &amp; S. Lerner, 2007</b>     | Prostatic TCC pathology and management [64]                   | Not applicable [64]              |
| <b>S. Picozzi et al., 2012</b>           | UUT recurrence after RC [65]                                  | 13,185 patients [65]             |
| <b>Hai-chao Yuan et al., 2014a</b>       | Risk factors for IVR after RNU [66]                           | 12,010 patients [66]             |
| <b>X. Biardeau et al., 2016</b>          | Malignancy after augmentation cystoplasty [67]                | Not specified [67]               |

| Study                                    | Focus Area                                                     | Sample Size                             |
|------------------------------------------|----------------------------------------------------------------|-----------------------------------------|
| <b>Leonardo L. Monteiro et al., 2018</b> | NMIBC management including prostatic urethral involvement [68] | Not applicable [68]                     |
| <b>A. Lindner et al., 2021</b>           | Lynch syndrome and urothelial carcinoma [69]                   | Not applicable [69]                     |
| <b>K. Burgess et al., 2011</b>           | UC after solid organ transplant [70]                           | 15 UC cases from 7,017 transplants [70] |
| <b>E. Savvides et al., 2022</b>          | Concomitant TURBT and endoscopic BPO surgery safety [71]       | 2,421 participants [71]                 |
| <b>A. Sood et al., 2018</b>              | Stenting prior to cystectomy and UUT recurrence [72]           | Not applicable [72]                     |
| <b>P. Clark, 2007</b>                    | UUT-TCC outcomes and bladder TCC history [73]                  | 269 patients (referenced study) [73]    |
| <b>D. Johnston et al., 2015</b>          | Subsequent neoplasms in childhood GU tumor survivors [74]      | Not applicable [74]                     |
| <b>A. Bahadori et al., 2023</b>          | Secondary tumors in orthotopic neobladder [75]                 | 15 studies [75]                         |
| <b>Fredrik Liedberg et al., 2003</b>     | TCC of prostate in cystoprostatectomy specimens [76]           | 43 patients [76]                        |
| <b>M. Shahzad et al., 2023</b>           | General review of urothelial carcinoma [77]                    | Not applicable [77]                     |
| <b>S. Picozzi et al., 2012a</b>          | Safety of simultaneous TURBT and TURP [78]                     | 1,234 patients [78]                     |

| Study                                 | Focus Area                                                 | Sample Size            |
|---------------------------------------|------------------------------------------------------------|------------------------|
| <b>Vedha Sanghi et al.,<br/>2020</b>  | Urogenital cancers in Barrett's esophagus patients<br>[79] | 1,581 patients<br>[79] |
| <b>S. Kajtezovic et al.,<br/>2022</b> | Secondary Paget's disease associated with UC<br>[80]       | 20 cases [80]          |

## Effects

### Incidence of Urethral Recurrence After Radical Cystectomy

The incidence of urethral recurrence (UR) following radical cystectomy for bladder cancer was a central outcome across the most relevant studies. The table below presents incidence figures and key quantitative findings from the primary studies and meta-analyses.

| Study                             | Incidence of UR                   | Key Quantitative Finding                                                                                                                                                                                                                                        |
|-----------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>G. Gakis et al.,<br/>2017</b>  | 0.8–6.1% [8]                      | Detection at asymptomatic stage reduces mortality risk by 30% (HR 0.69, 95% CI 0.59–0.79) [8]                                                                                                                                                                   |
| <b>N. Perlis et al.,<br/>2013</b> | 3.6% (18/503)<br>[11]             | Prostatic urethral involvement: OR 7.8 (95% CI 2.2–27.6, $p = 0.001$ ) [11]                                                                                                                                                                                     |
| <b>K. Cho et al.,<br/>2009</b>    | 4.4% (13/294)<br>[12]             | Positive urethral margin: HR 18.33 ( $p < 0.001$ ); prostatic urethral involvement: HR 7.95 ( $p < 0.001$ ); prostatic stromal invasion: HR 5.80 ( $p = 0.018$ ) [12]                                                                                           |
| <b>E. Laukhtina et al., 2021</b>  | Not pooled; 5-year CSS 47–63% [4] | ONB vs non-ONB: OR 0.44 (95% CI 0.31–0.61, $p < 0.001$ ); male vs female: OR 3.16 (95% CI 1.83–5.47, $p < 0.001$ ); prostatic urethral involvement: HR 5.44 (95% CI 3.58–8.26, $p < 0.001$ ); tumor multifocality: HR 2.97 (95% CI 2.05–4.29, $p < 0.001$ ) [4] |

| Study                            | Incidence of UR                                                     | Key Quantitative Finding                                                                                                                                                                                                                                         |
|----------------------------------|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>O. Fahmy et al., 2017</b>     | 4.4% (range 1.3–13.7%) [1]                                          | ONB diversion: OR 0.44 (95% CI 0.24–0.79, $p = 0.006$ ); muscle invasion: HR 1.18 ( $p = 0.31$ , NS); CIS: HR 0.97 ( $p = 0.88$ , NS); prostatic stromal involvement: HR 2.26 ( $p = 0.78$ , NS); prostatic urethral involvement: HR 2.04 ( $p = 0.55$ , NS) [1] |
| <b>E. Laukhtina et al., 2022</b> | Not specified [9]                                                   | Recommends tight surveillance for high-risk patients; prophylactic urethrectomy for very high risk [9]                                                                                                                                                           |
| <b>Xinyuan Li et al., 2017</b>   | 3.81% [2]                                                           | Prostatic involvement: RR 5.35 (95% CI 4.14–6.92); positive urethral margins: RR 7.79 (95% CI 2.27–26.68); concomitant CIS: RR 3.09 (95% CI 1.48–6.47); multifocal BC: RR 2.93 (95% CI 1.93–4.44) [2]                                                            |
| <b>Y. Chan et al., 2016</b>      | 1–8% [6]                                                            | Most recurrences within first 2 years; median OS after UR 6–54 months; 5-year DSS 0–83% [6]                                                                                                                                                                      |
| <b>R. Carando et al., 2020</b>   | ~5% [3]                                                             | Discordant survival data; urethrectomy indicated for singular recurrence [3]                                                                                                                                                                                     |
| <b>B. Roth et al., 2019</b>      | 5.6% overall (4.0% negative biopsies, 31.3% positive biopsies) [13] | Positive pre-cystectomy biopsies: HR 6.49 (95% CI 3.33–12.62, $p < 0.001$ ); chemotherapy: HR 3.05 (95% CI 1.66–5.59, $p < 0.001$ ) [13]                                                                                                                         |

| Study                                     | Incidence of UR                                                                           | Key Quantitative Finding                                                                                                                                                                                                  |
|-------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Bo Fan et al., 2025</b>                | 8.24% [5]                                                                                 | Concomitant CIS: HR 2.02 ( $p = 0.039$ ); tumor multifocality: HR 2.89 ( $p = 0.004$ ); in updated meta-analysis: bladder neck/prostate involvement: HR 3.39 ( $p < 0.001$ ); diversion type: HR 0.47 ( $p < 0.001$ ) [5] |
| <b>J. Huguet et al., 2003</b>             | 3.6% (5/138 neobladder patients) [14]                                                     | Conservative approach feasible for superficial recurrences [14]                                                                                                                                                           |
| <b>Lifeng Zhang et al., 2020</b>          | 50% of recurrences in non-urethrectomy group were urethral; 0% in urethrectomy group [18] | Prophylactic urethrectomy reduces UR ( $p = 0.040$ ) [18]                                                                                                                                                                 |
| <b>A. Stenzl &amp; L. Höltl, 2003</b>     | 6.8% in males, 3.6% in females [16]                                                       | No pelvic recurrence in 81 TCC patients with urethra-sparing surgery [16]                                                                                                                                                 |
| <b>I. Cagiannos &amp; C. Morash, 2013</b> | 6–10% overall; 4% with orthotopic, 8% with cutaneous diversion [35]                       | Median survival for UR is 28 months; 5-year risk is 11% (orthotopic) vs 24% (cutaneous) with prostatic involvement [35]                                                                                                   |

| Study                                               | Incidence of UR             | Key Quantitative Finding                                                                                              |
|-----------------------------------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>Androniki Kanaroglou &amp; B. Shayegan, 2013</b> | 8–10% [7]                   | 5-year UR probability: 6% without prostatic involvement, 15% with superficial invasion, 21% with stromal invasion [7] |
| <b>Mohamed Mohamed Elawdy et al., 2018</b>          | 2% urethral recurrence [10] | Invasive/multicentric bladder recurrence predicts urethral recurrence ( $p = 0.0001$ ) [10]                           |

The pooled incidence of UR across the largest meta-analyses ranges from approximately 1% to 14%, with the most frequently cited overall rate of approximately 4–5% [1–3]. The wide range reflects heterogeneity in patient populations, follow-up duration, urinary diversion type, and surveillance intensity. Studies with longer follow-up and more intensive surveillance protocols tend to report higher incidence figures [5, 13]. Most urethral recurrences occur within the first two years after radical cystectomy [5, 6], though delayed recurrences at 10 and even 20 years have been reported [7, 35].

#### Risk Factors for Urethral Recurrence

The table below consolidates quantitative risk estimates from the meta-analyses and large cohort studies.

| Risk Factor                           | Li et al., 2017 (RR)           | Laukhtina et al., 2021 (HR or OR)            | Fahmy et al., 2017 (HR or OR)                | Fan et al., 2025 (HR)                                   |
|---------------------------------------|--------------------------------|----------------------------------------------|----------------------------------------------|---------------------------------------------------------|
| <b>Prostatic urethral involvement</b> | RR 5.35 (95% CI 4.14–6.92) [2] | HR 5.44 (95% CI 3.58–8.26, $p < 0.001$ ) [4] | HR 2.04 (95% CI 0.20–20.80, $p = 0.55$ ) [1] | HR 3.39 ( $p < 0.001$ ; combined with bladder neck) [5] |

| <b>Risk Factor</b>                       | <b>Li et al., 2017<br/>(RR)</b>               | <b>Laukhtina et al.,<br/>2021 (HR or<br/>OR)</b> | <b>Fahmy et al.,<br/>2017 (HR or<br/>OR)</b>     | <b>Fan et al., 2025<br/>(HR)</b>                      |
|------------------------------------------|-----------------------------------------------|--------------------------------------------------|--------------------------------------------------|-------------------------------------------------------|
| <b>Prostatic<br/>stromal invasion</b>    | Included in above<br>[2]                      | HR 5.90 (95% CI<br>1.82–19.17, p =<br>0.003) [4] | HR 2.26 (95% CI<br>0.01–627.75, p =<br>0.78) [1] | Not reported<br>separately [5]                        |
| <b>Tumor<br/>multifocality</b>           | RR 2.93 (95% CI<br>1.93–4.44) [2]             | HR 2.97 (95% CI<br>2.05–4.29, p <<br>0.001) [4]  | Not reported [1]                                 | HR 2.05 (p <<br>0.001) [5]                            |
| <b>Concomitant<br/>CIS</b>               | RR 3.09 (95% CI<br>1.48–6.47) [2]             | Not significant (p<br>= 0.72) [4]                | HR 0.97 (p =<br>0.88) [1]                        | HR 1.74 (p =<br>0.006) [5]                            |
| <b>Male sex</b>                          | RR 2.49 [2]                                   | OR 3.16 (95% CI<br>1.83–5.47, p <<br>0.001) [4]  | OR 2.21 (95% CI<br>0.96–5.06, p =<br>0.06) [1]   | Not reported [5]                                      |
| <b>Non-orthotopic<br/>diversion</b>      | RR 0.32 for<br>orthotopic vs<br>cutaneous [2] | OR 0.44 for ONB<br>vs non-ONB (p <<br>0.001) [4] | OR 0.44 (95% CI<br>0.24–0.79, p =<br>0.006) [1]  | HR 0.47 (p <<br>0.001) [5]                            |
| <b>Bladder neck<br/>involvement</b>      | RR 3.14 (95% CI<br>1.59–6.19) [2]             | Not reported [4]                                 | Not reported [1]                                 | HR 3.39 (p <<br>0.001; combined<br>with prostate) [5] |
| <b>Positive urethral<br/>margins</b>     | RR 7.79 (95% CI<br>2.27–26.68) [2]            | Not reported [4]                                 | Not reported [1]                                 | Not reported [5]                                      |
| <b>Muscle invasion<br/>(tumor stage)</b> | RR 1.91 for<br>superficial vs<br>invasive [2] | Not significant (p<br>= 0.63) [4]                | HR 1.18 (p =<br>0.31) [1]                        | Not reported [5]                                      |

| <b>Risk Factor</b>                                | <b>Li et al., 2017<br/>(RR)</b> | <b>Laukhtina et al.,<br/>2021 (HR or<br/>OR)</b> | <b>Fahmy et al.,<br/>2017 (HR or<br/>OR)</b> | <b>Fan et al., 2025<br/>(HR)</b> |
|---------------------------------------------------|---------------------------------|--------------------------------------------------|----------------------------------------------|----------------------------------|
| <b>Neoadjuvant/adj<br/>uvant<br/>chemotherapy</b> | Not reported [2]                | Not reported [4]                                 | Not reported [1]                             | HR 1.36 (p =<br>0.019) [5]       |
| <b>Lymphovascular<br/>invasion</b>                | Not reported [2]                | Not reported [4]                                 | Not reported [1]                             | HR 1.95 (p =<br>0.028) [5]       |
| <b>History of<br/>TURBT</b>                       | Not reported [2]                | Not reported [4]                                 | Not reported [1]                             | HR 2.56 (p =<br>0.019) [5]       |

Several risk factors are consistently associated with increased UR across multiple meta-analyses: prostatic urethral and stromal involvement, tumor multifocality, positive urethral margins, bladder neck involvement, male sex, and non-orthotopic urinary diversion. The single most consistently robust predictor is prostatic involvement, with hazard ratios ranging from 5.35 to 7.95 in individual studies [2, 4, 12] and confirmed by multivariate analyses in the largest cohort study of 803 orthotopic neobladder patients, where positive pre-cystectomy prostatic urethral biopsies yielded a HR of 6.49 [13]. Cho et al. reported the highest individual hazard ratio of 18.33 for positive urethral margins [12].

Orthotopic neobladder diversion is consistently associated with a decreased probability of UR compared to non-orthotopic diversions. Three independent meta-analyses yielded nearly identical odds ratios of approximately 0.44 [1, 4, 5]. This protective association has been attributed to the continuous urine flow maintaining mucosal health and the mechanical washout effect on exfoliated tumor cells [8, 32].

The role of concomitant carcinoma in situ (CIS) as a risk factor for UR is more contested. Li et al. found a significant risk ratio of 3.09 [2], and Fan et al.'s updated meta-analysis confirmed CIS as a significant predictor (HR 1.74, p = 0.006) [5]. However, the meta-analyses by Laukhtina

et al. (2021) and Fahmy et al. (2017) found no significant association between CIS and UR [1, 4]. Similarly, tumor stage (muscle-invasive vs. non-muscle-invasive) was not a consistent predictor of UR across meta-analyses [1, 4], though Li et al. found superficial tumors to carry a higher risk ratio than invasive ones (RR 1.91) [2].

#### **Prostatic Urethral Involvement as a Specific Risk Dimension**

The frequency and prognostic significance of prostatic involvement by urothelial carcinoma was addressed by a substantial subset of the included studies. Prostatic involvement has been detected in 15–48% of radical cystoprostatectomy specimens depending on the histopathological technique used [37, 40, 50]. Using longitudinal whole-mount sectioning, Liedberg et al. identified TCC in the prostate in 30% of patients [76], with higher rates of CIS in the bladder neck/trigone (46% vs. 20%) and multifocal CIS (38% vs. 23%) among those with prostatic involvement [76].

The depth of prostatic invasion carries significant prognostic weight. Walsh and Chang reported 5-year survival rates of 100% for urethral mucosal involvement, 50% for ductal/acinar involvement, and 40% for prostatic stromal invasion [37]. Contiguous (transmural) invasion from the bladder was associated with a markedly worse 5-year survival of 7% compared to 46% for noncontiguous (intraurethral) involvement [37]. Prostatic urethral biopsy prior to cystectomy can identify patients at elevated risk, but its sensitivity is limited; Liedberg et al. found that preoperative biopsies missed prostatic TCC in 4 of 13 affected patients [76]. Intraoperative frozen-section analysis at the ureteral and urethral margins has reported sensitivity of 33–93% and specificity of 99–100% [3].

Risk factors for prostatic involvement by urothelial carcinoma include CIS, multifocality, bladder neck/trigone tumor location, and a prior history of tumor recurrence [36, 50, 76]. Huguet et al. (2005) found that the presence of tumor in the prostatic urethra at endoscopic staging before radical cystectomy was the only factor significantly associated with clinical understaging ( $p = 0.003$ ) and shorter survival ( $p < 0.0002$ ) in patients with high-risk superficial bladder tumors who failed BCG therapy [61].

#### **Urethral Recurrence in the Context of Simultaneous TURBT and TURP**

Nine studies addressed whether simultaneous transurethral resection of bladder tumor and prostate (TURBT + TURP) increases the risk of tumor recurrence at the prostatic urethra and bladder neck. Across all of these studies, no statistically significant increase in prostatic urethral or bladder neck recurrence was observed with simultaneous procedures compared to TURBT alone [15, 17, 25, 56, 62, 71, 78]. Savvides et al.'s systematic review and meta-analysis of 2,421 participants found an OR of 1.06 (95% CI 0.76–1.47) for recurrences at the bladder neck/prostatic urethra [71]. Zhou et al. reported that simultaneous TURBT + TURP actually lowered overall recurrence rates (OR 0.70, 95% CI 0.53–0.93,  $p = 0.01$ ) without affecting prostatic urethra/bladder neck recurrence specifically [58]. Picozzi et al. (2012a) noted a statistically significant increase in recurrence only among patients with multifocal tumors, not related to the simultaneous procedure itself [78]. These findings suggest that the theoretical concern about tumor cell seeding into the disrupted prostatic fossa is not borne out by clinical data in the non-muscle-invasive setting.

#### **Bladder Cancer as a Predictor of Upper Urinary Tract Recurrence**

While the primary focus of this review is on urethral tumors, the pan-urothelial field defect concept means that the relationship between bladder cancer and secondary urothelial tumors extends bidirectionally. A history of prior bladder cancer is a significant predictor of intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinoma (UTUC), with Seisen et al. reporting a hazard ratio of 1.96 ( $p < 0.001$ ) [31] and Yuan et al. an odds ratio of 1.59 (95% CI 1.26–1.9) [57, 66]. Conversely, post-cystectomy upper urinary tract tumors occur in 2–6% of patients [24], with risk factors mirroring those for urethral recurrence: distal ureteral tumor involvement, multifocal disease, CIS, and prostatic urethral involvement [8, 24]. The incidence of upper tract recurrence after radical cystectomy was 4.65% in a meta-analysis of 8,981 patients, with surgical margin (HR 3.41), ureteral margin status (HR 4.34), preoperative hydronephrosis (HR 1.74), and pathologic T stage (HR 2.69) as significant predictors [29].

#### **Survival After Urethral Recurrence**

Despite urethral recurrence being a relatively rare event, it is associated with adverse prognosis. The majority of patients with secondary urothelial tumors (84%) present with urothelial recurrence without evidence of metastasis, yet 65.9% ultimately die of disease after a median

follow-up of 91 months [8]. The 5-year cancer-specific survival after UR varies from 47% to 63%, and overall survival from 40% to 74% [4]. Chan et al. reported median overall survival after UR ranging from 6 to 54 months and 5-year disease-specific survival between 0% and 83% [6]. Patients whose UR was detected through routine follow-up at an asymptomatic stage had significantly better outcomes, with detection and treatment at an asymptomatic stage reducing cancer-specific and overall mortality risk by approximately 30% [8]. Li et al. confirmed that prognoses were worse for patients with symptomatic recurrence compared to those diagnosed through routine surveillance [2].

Treatment of UR includes urethrectomy (the most common approach), urethra-sparing treatments such as transurethral resection for superficial (Ta) recurrences, intraurethral chemotherapy or BCG instillation, and systemic chemotherapy [2, 9, 14]. Roth et al. reported that only 22% of patients with UR after orthotopic neobladder required salvage urethrectomy, while 60% were managed successfully with locally conservative treatment [13]. Laukhtina et al. (2022) proposed that urethra-sparing approaches are an option for Ta-only recurrences, while salvage urethrectomy with or without chemotherapy should be standard for all others [9].

## Synthesis

The central question of how bladder cancer history relates to urethral tumor risk is supported by convergent evidence from multiple meta-analyses and cohort studies, but meaningful heterogeneity exists regarding specific risk factors.

The most consistent finding across all included evidence is the protective effect of orthotopic neobladder (ONB) diversion against urethral recurrence. Three independent meta-analyses spanning over 25,000 patients arrived at nearly identical effect sizes (OR approximately 0.44) [1, 4, 5], lending high confidence to this association. The biological explanation is plausible: continuous urine flow through the urethra in ONB patients may prevent tumor cell implantation and allow earlier detection through urethral wash cytology [6, 7, 32].

The strongest pathological predictor of urethral recurrence is prostatic involvement, whether urethral mucosal or stromal. The magnitude of this association is large and consistent across study designs: single-center cohort studies report HRs of 5.80–18.33 [12], and meta-analyses yield pooled HRs of 3.39–5.90 [4, 5]. The one notable exception is Fahmy et al.'s 2017

meta-analysis, which found non-significant associations for both prostatic urethral involvement (HR 2.04,  $p = 0.55$ ) and stromal involvement (HR 2.26,  $p = 0.78$ ) [1]. However, this discrepancy is likely attributable to very wide confidence intervals in that analysis (CI 0.20–20.80 and 0.01–627.75, respectively), suggesting substantial heterogeneity and limited statistical power rather than a true absence of effect. The subsequent Laukhtina et al. (2021) meta-analysis, incorporating more studies and patients (9,435 vs. 6,169), confirmed the significant association with much tighter confidence intervals [4].

The role of concomitant CIS represents a genuinely contested finding. Li et al. and Fan et al. found CIS to be a significant risk factor (RR 3.09 and HR 1.74, respectively) [2, 5], while Laukhtina et al. and Fahmy et al. found no significant association [1, 4]. This divergence may reflect differences in how CIS is defined and measured across studies (concomitant at the time of cystectomy vs. any history), differences in pathological processing, and the confounding relationship between CIS and other risk factors such as multifocality and prostatic involvement. Brookman-May's editorial noted that in organ-confined disease, CIS is associated with recurrence-free survival and cancer-specific mortality, as well as a higher likelihood of upper urinary tract recurrence [28]. The discrepancy may therefore represent a context-dependent effect: CIS may be prognostically relevant in early-stage disease but loses its independent predictive value in more advanced cohorts where other tumor characteristics dominate.

The apparent paradox that superficial (non-muscle-invasive) bladder cancer may carry a higher risk of urethral recurrence than muscle-invasive disease [2] likely reflects a selection and survival bias. Patients with non-muscle-invasive disease at the time of cystectomy have a longer natural history with prolonged urothelial exposure and more opportunity for field cancerization effects to manifest, whereas patients with muscle-invasive disease have higher competing mortality from their primary tumor, reducing the observed UR rate [8, 65].

Regarding sex differences, male patients have significantly higher UR rates than females (OR 3.16) [4], which is largely attributable to the prostatic urethra serving as an anatomic reservoir for occult urothelial carcinoma in men. In women, the risk of urethral involvement is lower (3.6% vs. 6.8% in one meta-analysis) [16], with bladder neck involvement being the

primary risk factor [8, 19]. Prophylactic urethrectomy in women was associated with reduced urethral recurrence in a small cohort study ( $p = 0.040$ ) [18], though this finding requires validation in larger series.

Finally, the evidence on simultaneous TURBT and TURP is reassuring. Across nine studies including randomized controlled trials and multiple meta-analyses, the addition of TURP to TURBT does not increase bladder neck or prostatic urethral recurrence rates [15, 17, 71, 78]. This indicates that mechanical disruption of the prostatic urethra in the setting of non-muscle-invasive bladder cancer does not meaningfully alter the risk of urethral tumor seeding, at least in the short to medium term with follow-up periods generally under five years. Whether this conclusion holds for high-risk tumors (multifocal, high-grade, CIS-associated) over longer time horizons remains less certain, as Picozzi et al. noted significantly increased recurrence specifically in patients with multifocal tumors [78].

In summary, the relationship between bladder cancer history and urethral tumor risk is well-established, with incidence of urethral recurrence after radical cystectomy of approximately 4–8%, depending on the risk profile. Prostatic involvement, tumor multifocality, non-orthotopic diversion, positive urethral margins, and male sex are the most robust predictors. Orthotopic neobladder diversion confers significant protection. Detection of urethral recurrence at an asymptomatic stage through structured surveillance, including urethral wash cytology and urethroscopy in high-risk patients, can improve survival by approximately 30% [8]. The optimal surveillance protocol remains undefined, but current evidence supports risk-stratified monitoring with particular attention to patients with features of pan-urothelial disease [5, 9, 44].

---

## DISCUSSION

---

This systematic review confirms that a history of bladder cancer significantly increases the risk of subsequent urethral tumors, with a pooled incidence of urethral recurrence after radical cystectomy of approximately 4–5% (range 1–14%) (1–3). The wide range reflects heterogeneity in follow-up duration, surveillance intensity, and patient selection. Most recurrences occur within the first two years, but late recurrences up to 20 years have been reported, emphasizing lifelong risk

(7,35).

### **The Protective Effect of Orthotopic Neobladder (ONB)**

The single most consistent and clinically actionable finding is the strong protective association of ONB diversion against UR. Three independent meta-analyses reported nearly identical odds ratios of approximately 0.44 (95% CI 0.24–0.79) (1,4,5). This effect is biologically plausible: continuous antegrade urine flow through the native urethra in ONB patients provides mechanical washout of exfoliated tumor cells and maintains mucosal integrity, whereas cutaneous diversions (ileal conduit) allow stagnant urine and potential retrograde seeding (8,32). Gakis et al. further noted that detection of UR at an asymptomatic stage—more feasible in ONB patients due to accessible urethral wash cytology—reduces cancer-specific mortality by 30% (HR 0.69, 95% CI 0.59–0.79) (8). Therefore, when clinically appropriate, ONB should be offered not only for quality of life but also for oncological benefit regarding urethral recurrence.

### **Prostatic Urethral Involvement: The Dominant Pathological Predictor**

Prostatic involvement by urothelial carcinoma is the most robust risk factor for UR. In the meta-analysis by Li et al., prostatic urethral involvement yielded a relative risk of 5.35 (95% CI 4.14–6.92) (2). Laukhtina et al. (2021) calculated a pooled HR of 5.44 (95% CI 3.58–8.26) (4). The depth of prostatic invasion carries graded prognostic significance: Walsh and Chang reported 5-year survival rates of 100% for urethral mucosal involvement, 50% for ductal/acinar involvement, and only 40% for prostatic stromal invasion (37). Contiguous (transmural) invasion from the bladder was associated with a 5-year survival of 7% compared to 46% for noncontiguous (intraurethral) involvement (37). This distinction is critical for clinical decision-making: superficial (mucosal) involvement may still permit urethra-sparing approaches, whereas stromal invasion should prompt strong consideration of prophylactic urethrectomy or intensified surveillance.

The frequency of prostatic involvement in RC specimens ranges from 15% to 48%, depending on histopathological technique (37,40,50). Liedberg et al., using whole-mount sectioning, detected prostatic TCC in 30% of patients, with higher rates of CIS in the bladder neck/trigone (46% vs. 20%) among those affected (76). Importantly, preoperative prostatic urethral biopsies have limited sensitivity, missing up to 4 of 13 affected patients in one series (76).

41

Intraoperative frozen-section analysis has a sensitivity of only 33–93% but high specificity (99–100%) (3). Therefore, a negative biopsy does not reliably rule out prostatic involvement.

### **Tumor Multifocality and Male Sex**

Tumor multifocality is another consistently significant predictor, with a pooled HR of 2.97 (95% CI 2.05–4.29) (4) and RR of 2.93 (95% CI 1.93–4.44) (2). This supports the field cancerization concept: patients with multiple synchronous or metachronous bladder tumors have a higher likelihood of occult urothelial dysplasia throughout the urinary tract. Male sex is associated with a significantly higher UR risk (OR 3.16, 95% CI 1.83–5.47) (4), largely due to the anatomic presence of the prostatic urethra as a reservoir for tumor cells. In females, the risk is lower (3.6% vs. 6.8% in males), and bladder neck involvement is the primary risk factor (8,16,19). Prophylactic urethrectomy in women was associated with reduced UR in a small cohort ( $p = 0.040$ ), but this requires validation (18).

### **The Contested Role of Concomitant CIS**

The role of concomitant carcinoma in situ (CIS) is inconsistent across meta-analyses. Li et al. (2017) found a significant RR of 3.09 (95% CI 1.48–6.47) (2), and Fan et al. (2025) reported a significant HR of 1.74 ( $p = 0.006$ ) (5). However, Laukhtina et al. (2021) found no significant association ( $p = 0.72$ ) (4), and Fahmy et al. (2017) similarly reported a non-significant HR of 0.97 ( $p = 0.88$ ) (1). This discrepancy may be explained by differences in study populations, definitions (concomitant CIS at cystectomy vs. any history), and confounding with multifocality and prostatic involvement. Brookman-May noted that in organ-confined disease, CIS is associated with recurrence-free survival and a higher likelihood of upper tract recurrence, but its independent effect on UR may be attenuated in cohorts with advanced tumor stages (28). Clinically, CIS should still be considered a relative risk factor, but not as strong as prostatic involvement or multifocality.

### **Positive Urethral Margins and Other Risk Factors**

Positive urethral margins on final pathology carry the highest individual hazard ratio reported: Cho et al. found an HR of 18.33 ( $p < 0.001$ ) (12). This finding mandates immediate postoperative consideration of urethrectomy or rigorous surveillance. Bladder neck involvement (RR 3.14) (2) and a history of prior TURBT (HR 2.56,  $p = 0.019$ ) (5) also emerged as significant

predictors in the most recent meta-analysis. Neoadjuvant/adjuvant chemotherapy was paradoxically associated with increased UR risk in Fan et al. (HR 1.36,  $p = 0.019$ ) (5), likely due to selection bias (higher-risk patients receiving chemotherapy) rather than a causative effect.

### **Survival After Urethral Recurrence**

Urethral recurrence carries a poor prognosis, but early detection improves outcomes. Laukhtina et al. (2021) reported 5-year cancer-specific survival of 47–63% (4). Chan et al. noted median overall survival after UR ranging from 6 to 54 months (6). Critically, detection at an asymptomatic stage through routine follow-up reduced cancer-specific and overall mortality risk by approximately 30% (HR 0.69) (8). This finding strongly supports structured surveillance protocols rather than waiting for symptoms such as hematuria, obstructive voiding symptoms, or urethral discharge.

### **Safety of Simultaneous TURBT and TURP**

A distinct clinical question is whether performing TURP at the time of TURBT for bladder cancer increases the risk of tumor seeding into the prostatic urethra. Across nine studies, including randomized trials and meta-analyses, no significant increase in prostatic urethral or bladder neck recurrence was observed. Savvides et al. reported an OR of 1.06 (95% CI 0.76–1.47) for recurrences at the bladder neck/prostatic urethra (71). Zhou et al. even found that simultaneous TURBT+TURP lowered overall recurrence rates (OR 0.70, 95% CI 0.53–0.93,  $p = 0.01$ ) without affecting prostatic urethra-specific recurrence (58). Picozzi et al. (2012a) noted a significant increase only in patients with multifocal tumors, not attributable to the procedure itself (78). Thus, the theoretical concern about mechanical tumor seeding into the prostatic fossa is not supported by current evidence, at least for non-muscle-invasive bladder cancer with follow-up periods generally under five years. Caution may still be warranted for high-grade, multifocal, or CIS-associated tumors.

### **Upper Tract Recurrence as a Parallel Phenomenon**

Although the focus of this review is urethral tumors, the bidirectional relationship between bladder cancer and upper tract urothelial carcinoma (UTUC) reinforces the pan-urothelial field defect. A history of prior bladder cancer significantly predicts intravesical recurrence after radical

nephroureterectomy for UTUC (HR 1.96) (31). Conversely, post-cystectomy upper tract recurrence occurs in 2–6% of patients (24), with risk factors similar to UR: distal ureteral involvement, multifocality, CIS, and prostatic urethral involvement (8,24). Parizi et al. reported a pooled upper tract recurrence incidence of 4.65% in 8,981 patients, with positive surgical margins (HR 3.41) and ureteral margin status (HR 4.34) as significant predictors (29). These findings underscore that bladder cancer survivors require surveillance of the entire retained urothelium, not just the urethra.

### **Comparison with General Second Primary Cancer Literature**

The relationship between bladder cancer and subsequent urethral tumors fits within the broader context of second primary cancers. Wang et al., in a meta-analysis of over 9.6 million cancer patients, found that a first primary cancer significantly increases the risk of a second primary cancer at other sites, with standardized incidence ratios varying by cancer type (34). For bladder cancer specifically, the risk of secondary urogenital cancers is elevated, consistent with the field effect and shared etiological factors (smoking, environmental carcinogens) (42). This broader perspective supports the need for long-term, whole-urothelial surveillance.

---

## **CONCLUSION AND RECOMMENDATIONS**

---

### **Conclusion**

A history of bladder cancer is a significant and well-established risk factor for the development of subsequent urethral tumors, with a pooled incidence of urethral recurrence after radical cystectomy of approximately 4–5%. The most significant positive predictors identified in this systematic review are:

1. **Prostatic urethral involvement** (especially stromal invasion), conferring a 5- to 8-fold increased risk.
2. **Non-orthotopic urinary diversion** (ileal conduit) compared to orthotopic neobladder.
3. **Tumor multifocality and positive urethral margins.**
4. **Male sex.**
5. **Bladder neck involvement.**

Orthotopic neobladder diversion is strongly protective (OR ~0.44) and should be considered

when oncologically safe. Asymptomatic detection of urethral recurrence through structured surveillance improves survival by approximately 30%. Simultaneous TURBT and TURP does not increase prostatic urethral recurrence risk and appears oncologically safe for non-muscle-invasive bladder cancer.

### Recommendations for Clinical Practice and Future Research

1. **Risk-stratified surveillance:** Patients with prostatic involvement, multifocal tumors, or non-orthotopic diversion should undergo annual urethral wash cytology and urethroscopy every 6–12 months for the first 2 years, then annually thereafter. Low-risk patients (female, solitary low-grade tumor, ONB diversion) may have less intensive follow-up.
2. **Orthotopic neobladder:** Offer ONB to eligible patients not only for quality of life but also to reduce urethral recurrence risk.
3. **Prophylactic urethrectomy:** Reserve for very high-risk patients (prostatic stromal invasion, positive urethral margins, recurrent urethral CIS) rather than routine use.
4. **Simultaneous TURBT+TURP:** Can be performed safely without additional urethral recurrence risk, but caution is advised for high-grade/multifocal tumors until longer-term data emerge.
5. **Future research:** Prospective multicenter registries with standardized definitions of urethral recurrence and long-term (>10 years) follow-up are needed. External validation of machine learning prediction models (5) should be prioritized. The role of adjuvant intraurethral chemotherapy or BCG after RC for high-risk patients requires randomized trials.

---

### REFERENCES

1. Fahmy O, Khairul-Asri M, Schubert T, et al (2017) Urethral recurrence after radical cystectomy for urothelial carcinoma: A systematic review and meta-analysis. Urologic oncology. <https://doi.org/10.1016/j.urolonc.2017.11.007>
2. Li X, Wang W, Zhu G, et al (2017) Risk factors, follow-up, and treatment of urethral recurrence following radical cystectomy and urinary diversion for bladder cancer: a meta-analysis of 9498 patients. OncoTarget. <https://doi.org/10.18632/oncotarget.23451>

3. Carando R, Shariat S, Moschini M, D'andrea D (2020) Ureteral and urethral recurrence after radical cystectomy: a systematic review. *Current Opinion in Urology*. <https://doi.org/10.1097/MOU.0000000000000752>
4. Laukhtina E, Mori K, Andrea DD, et al (2021) Incidence, risk factors and outcomes of urethral recurrence after radical cystectomy for bladder cancer: A systematic review and meta-analysis. *Urologic oncology*. <https://doi.org/10.1016/j.urolonc.2021.06.009>
5. Fan B, Zhang L, Cui H, et al (2025) Development of a machine learning-based model to predict urethral recurrence following radical cystectomy: a multicentre retrospective study and updated meta-analysis. *Scientific Reports*. <https://doi.org/10.1038/s41598-025-04893-6>
6. Chan Y, Fisher P, Tilki D, Evans CP (2016) Urethral recurrence after cystectomy: current preventative measures, diagnosis and management. *BJU International*. <https://doi.org/10.1111/bju.13370>
7. Kanaroglou A, Shayegan B (2013) Management of the urethra in urothelial bladder cancer. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada*. <https://doi.org/10.5489/CUAJ.1198>
8. Gakis G, Black P, Bochner B, et al (2017) Systematic Review on the Fate of the Remnant Urothelium after Radical Cystectomy. *European Urology*. <https://doi.org/10.1016/j.eururo.2016.09.035>
9. Laukhtina E, Moschini M, Soria F, et al (2022) 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. *European Urology Focus*. <https://doi.org/10.1016/j.euf.2022.03.004>
10. Elawdy MM, Osman Y, Taha D, El-Halwagy S (2018) Muscle-invasive bladder and urethral cancer recurrence after surgical management of upper tract urothelial carcinoma: A review of 305 patients. *Turkish journal of urology*. <https://doi.org/10.5152/tud.2018.19677>

11. Perlis N, Turker P, Bostrom P, et al (2013) Upper urinary tract and urethral recurrences following radical cystectomy: review of risk factors and outcomes between centres with different follow-up protocols. World journal of urology. <https://doi.org/10.1007/s00345-012-0905-2>
12. Cho K, Seo JW, Park SJ, et al (2009) The Risk Factor for Urethral Recurrence after Radical Cystectomy in Patients with Transitional Cell Carcinoma of the Bladder. Urologia internationalis. <https://doi.org/10.1159/000209363>
13. Roth B, Furrer M, Giannakis I, et al (2019) Positive Pre-cystectomy Biopsies of the Prostatic Urethra or Bladder Neck Do Not Necessarily Preclude Orthotopic Bladder Substitution. Journal of Urology. <https://doi.org/10.1097/JU.0000000000000034>
14. Huguet J, Palou J, Serrallach M, et al (2003) Management of urethral recurrence in patients with Studer ileal neobladder. European Urology. [https://doi.org/10.1016/S0302-2838\(03\)00096-4](https://doi.org/10.1016/S0302-2838(03)00096-4)
15. Dellabella M, Branchi A, Gasparri L, et al (2018) Oncological safety and quality of life in men undergoing simultaneous transurethral resection of bladder tumor and prostate: results from a randomized controlled trial. World journal of urology. <https://doi.org/10.1007/s00345-018-2317-4>
16. Stenzl A, Hörtl L (2003) Orthotopic bladder reconstruction in women--what we have learned over the last decade. Critical reviews in oncology/hematology. [https://doi.org/10.1016/S1040-8428\(03\)00078-7](https://doi.org/10.1016/S1040-8428(03)00078-7)
17. Sionov B, Tsivian M, Bakaleyschik P, et al (2022) Oncological safety of simultaneous transurethral resection of high-grade urothelial carcinoma of the bladder and benign prostatic hyperplasia. Arab Journal of Urology. <https://doi.org/10.1080/2090598X.2022.2142365>
18. Zhang L, Su Q, Gao S, et al (2020) Prophylactic Urethrectomy Could Further Shorten the Female Bladder Cancer Recurrence and Metastasis. Journal of Surgical Oncology. <https://doi.org/10.31487/j.jso.2020.04.07>
19. Stein J, Penson D, Wu SD, Skinner D (2007) Pathological guidelines for orthotopic urinary diversion in women with bladder cancer: a review of the literature. Journal of Urology. <https://doi.org/10.1016/J.JURO.2007.05.013>

20. Elawdy MM, Osman Y, Taha D, et al (2017) Risk factors and prognosis of intravesical recurrence after surgical management of upper tract urothelial carcinoma: A 30-year single centre experience. Arab Journal of Urology. <https://doi.org/10.1016/j.aju.2017.03.006>
21. White S, Malkowicz S (2010) Management of the male urethra after cystectomy. Urologic clinics of North America. <https://doi.org/10.1016/j.ucl.2010.04.008>
22. Новиков АИ, Леоненков РВ, Темкин ДБ, et al (2021) Трансуретральная резекция карциномы мочевого пузыря, распространяющейся на устье мочеточника. Onkourologiâ. <https://doi.org/10.17650/1726-9776-2021-17-2-104-111>
23. Bree K, Hensley P, Brooks N, et al (2020) Impact of UTUC on Outcomes of Non-Muscle Invasive Bladder Cancer Treated with Intravesical Bacillus Calmette-Guerin. Urologic Oncology-seminars and Original Investigations. <https://doi.org/10.1016/j.urolonc.2020.10.028>
24. Huguet J (2012) Transitional cell carcinoma of the upper urinary tract after cystectomy. Archivos españoles de urología
25. Tsivian A, Shtricker A, Sidi A (2003) Simultaneous transurethral resection of bladder tumor and benign prostatic hyperplasia: hazardous or a safe timesaver? Journal of Urology. <https://doi.org/10.1097/01.JU.0000096273.64448.E7>
26. Novikov A, Leonenkov R, Temkin D, et al (2021) Transurethral resection of bladder cancer involving the orifice of the ureter. Cancer Urology. <https://doi.org/10.17650/1726-9776-2021-17-2-104-111>
27. Özbek M, Özen M, Öner S, et al (2021) The Factors Affecting Recurrence and Prognosis in Patients with Low-grade Stage Ta Bladder Cancer. <https://doi.org/10.4274/UOB.GALENOS.2020.1558>
28. Brookman-May S (2019) Editorial Comment. Journal of Urology. <https://doi.org/10.1097/01.ju.0000550122.69979.70>
29. Parizi MK, Margulis V, Lotan Y, et al (2022) A Systematic Review and Meta-Analysis of Clinicopathologic Factors Predicting Upper Urinary Tract Recurrence After Radical Cystectomy for Urothelial Bladder Cancer. Clinical Genitourinary Cancer. <https://doi.org/10.1016/j.clgc.2022.11.002>

30. Volkmer B, Seidl-Schlick EM, Bach D, et al (2005) Cyclophosphamide is contraindicated in patients with a history of transitional cell carcinoma. *Clinical Rheumatology*. <https://doi.org/10.1007/s10067-004-1032-2>
31. Seisen T, Granger B, Colin P, et al (2015) MP2-07 A SYSTEMATIC REVIEW AND META-ANALYSIS OF CLINICOPATHOLOGIC FACTORS LINKED WITH INTRAVESICAL RECURRENCE AFTER RADICAL NEPHROURETERECTOMY TO TREAT UPPER TRACT UROTHELIAL CARCINOMA. <https://doi.org/10.1016/j.juro.2015.02.130>
32. Chang SS (2005) Short- and long-term issues regarding urethral management in male radical-cystectomy patients. *Current Opinion in Urology*. <https://doi.org/10.1097/01.mou.0000170239.02648.6b>
33. Ito A, Shintaku I, Satoh M, et al (2013) Intravesical seeding of upper urinary tract urothelial carcinoma cells during nephroureterectomy: an exploratory analysis from the THPMG trial. *Japanese Journal of Clinical Oncology*. <https://doi.org/10.1093/jjco/hyt129>
34. Wang X, Zeng M, Ju X, et al (2023) Correlation between second and first primary cancer: systematic review and meta-analysis of 9 million cancer patients. *British Journal of Surgery*. <https://doi.org/10.1093/bjs/znad377>
35. Cagiannos I, Morash C (2013) Surveillance strategies after definitive therapy of invasive bladder cancer. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada*. <https://doi.org/10.5489/CUAJ.1205>
36. Huguet J (2012) [Prostatic involvement by urothelial carcinoma in patients with bladder cancer and their implications in the clinical practice]. *Actas Urológicas Españolas*. <https://doi.org/10.1016/J.ACUIROE.2012.02.004>
37. Walsh DL, Chang SS (2009) Dilemmas in the treatment of urothelial cancers of the prostate. *Urologic oncology*. <https://doi.org/10.1016/j.urolonc.2007.12.010>
38. Ismail S, Karsenty G, Chartier-Kastler E, et al (2018) Prevalence, management, and prognosis of bladder cancer in patients with neurogenic bladder: A systematic review. *Neurourology and Urodynamics*. <https://doi.org/10.1002/nau.23457>

39. Picozzi S, Casellato S, Bozzini G, et al (2013) Inverted papilloma of the bladder: a review and an analysis of the recent literature of 365 patients. Urologic oncology. <https://doi.org/10.1016/j.urolonc.2012.03.009>
40. Lerner S, Colen J, Shen S (2008) Prostatic biology, histologic patterns and clinical consequences of transitional cell carcinoma. Current Opinion in Urology. <https://doi.org/10.1097/MOU.0b013e32830b86f9>
41. Ayyathurai R, Gómez P, Luongo T, et al (2007) Prostatic involvement by urothelial carcinoma of the bladder: clinicopathological features and outcome after radical cystectomy. BJU International. <https://doi.org/10.1111/j.1464-410X.2007.07171.x>
42. Liu JJ, Vivo ID, Wu C-Y, Giovannucci E (2021) Subsequent primary urogenital cancers among childhood and adolescent cancer survivors in the United States. Urologic oncology. <https://doi.org/10.1016/j.urolonc.2021.10.009>
43. Kotb A, Hashad MM, Elabbady A (2012) CIS of the bladder: a review of literature. <https://doi.org/10.5152/TUD.2012.046>
44. Colin P, Neuzillet Y, Pignot G, et al (2015) [Follow-up of urothelial carcinoma: Review of the Cancer Committee of the French Association of Urology]. Progrès en urologie (Paris). <https://doi.org/10.1016/j.purol.2015.05.012>
45. North A, Lakshmanan Y (2007) Malignancy associated with the use of intestinal segments in the urinary tract. Urologic oncology. <https://doi.org/10.1016/J.UROLONC.2006.09.008>
46. Ingimarsson J, Seigne J (2013) The conundrum of prostatic urethral involvement. Urologic clinics of North America. <https://doi.org/10.1016/j.ucl.2013.01.010>
47. Otto W, Denzinger S, Fritsche H, et al (2011) The WHO classification of 1973 is more suitable than the WHO classification of 2004 for predicting survival in pT1 urothelial bladder cancer. BJU International. <https://doi.org/10.1111/j.1464-410X.2010.09515.x>
48. Faba ÓR, Palou J (2012) Predictive factors for recurrence progression and cancer specific survival in high-risk bladder cancer. Current Opinion in Urology. <https://doi.org/10.1097/MOU.0b013e328356ac20>

49. Veccia A, Antonelli A, Checcucci E, et al (2019) Segmental Ureterectomy for Upper Tract Urothelial Carcinoma: A Systematic Review and Meta-analysis of Comparative Studies. *Clinical Genitourinary Cancer*. <https://doi.org/10.1016/j.clgc.2019.10.015>
50. Autorino R, Lorenzo GD, Damiano R, et al (2009) Pathology of the prostate in radical cystectomy specimens: a critical review. *Surgical oncology*. <https://doi.org/10.1016/j.suronc.2008.07.006>
51. Dalibor G (2005) Review: treatment and basic epidemiological consideration on patients treated for bladder and collecting system carcinoma over last 10 years at our department
52. Sountoulides P, Pyrgidis N, Brookman-May S, et al (2020) Does Ureteral Stenting Increase the Risk of Metachronous Upper Tract Urothelial Carcinoma in Patients with Bladder Tumors? A Systematic Review and Meta-analysis. *Journal of Urology*. <https://doi.org/10.1097/JU.0000000000001548>
53. Motlagh RS, Mori K, Miura N, et al (2020) The recurrence and progression risk after simultaneous endoscopic surgery of urothelial bladder tumour and benign prostatic hyperplasia: a systematic review and meta-analysis. *BJU International*. <https://doi.org/10.1111/bju.15146>
54. Cox JM, Colli J (2011) Urothelial cancers after renal transplantation. *International Urology and Nephrology*. <https://doi.org/10.1007/s11255-011-9907-z>
55. Zhang A, Shang D, Zhang J, et al (2015) A retrospective review of patients with urothelial cancer in 3,370 recipients after renal transplantation: a single-center experience. *World journal of urology*. <https://doi.org/10.1007/s00345-014-1412-4>
56. Kouriefs C, Loizides S, Mufti G (2008) Simultaneous Transurethral Resection of Bladder Tumour and Prostate: Is It Safe? *Urologia internationalis*. <https://doi.org/10.1159/000144048>
57. Yuan H, Chen X, Liu L, et al (2014) Risk factors for intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinoma: a meta-analysis. *Urologic oncology*. <https://doi.org/10.1016/j.urolonc.2014.01.022>
58. Zhou L, Liang X, Zhang K (2020) Assessment of the clinical efficacy of simultaneous transurethral resection of both bladder cancer and the prostate: a systematic review and meta-analysis. *The Aging Male*. <https://doi.org/10.1080/13685538.2020.1718637>

59. Tillou X, Doerfler A (2014) Urological tumors in renal transplantation. *Minerva urologica e nefrologica* = The Italian journal of urology and nephrology
60. Hu X, Xue Y, Zhu G (2023) Clinical Characteristics and Current Status of Treatment for Recurrent Bladder Cancer after Surgeries on Upper Tract Urothelial Carcinoma. *Diagnostics*. <https://doi.org/10.3390/diagnostics13051004>
61. Huguet J, Crego M, Sabatè S, et al (2005) Cystectomy in patients with high risk superficial bladder tumors who fail intravesical BCG therapy: pre-cystectomy prostate involvement as a prognostic factor. *European Urology*. <https://doi.org/10.1016/J.EURURO.2005.03.021>
62. Ugurlu O, Gonulalan U, Adsan O, et al (2007) Effects of simultaneous transurethral resection of prostate and solitary bladder tumors smaller than 3 cm on oncologic results. *Urology*. <https://doi.org/10.1016/J.UROLOGY.2007.03.015>
63. Hess M, Zhan E, Foo D, Yalla S (2003) Bladder Cancer In Patients With Spinal Cord Injury. *Journal of Spinal Cord Medicine (JSCM)*. <https://doi.org/10.1080/10790268.2003.11753702>
64. Shen S, Lerner S (2007) Prostatic transitional cell carcinoma: pathologic features and clinical management. Expert Review of Anticancer Therapy. <https://doi.org/10.1586/14737140.7.8.1155>
65. Picozzi S, Ricci C, Gaeta M, et al (2012) Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. *Journal of Urology*. <https://doi.org/10.1016/j.juro.2012.08.017>
66. Yuan H, Han P, Wei Q (2014) PD35-08 RISK FACTORS FOR INTRAVESICAL RECURRENCE AFTER RADICAL NEPHROURETERECTOMY FOR UPPER TRACT UROTHELIAL CARCINOMA: A META-ANALYSIS. *The Journal of Urology*. <https://doi.org/10.1016/J.JURO.2014.02.2421>
67. Biardeau X, Chartier-Kastler E, Rouprêt M, Phé V (2016) Risk of malignancy after augmentation cystoplasty: A systematic review. *Neurourology and Urodynamics*. <https://doi.org/10.1002/nau.22775>

68. Monteiro LL, Witjes J, Agarwal P, et al (2018) ICUD-SIU International Consultation on Bladder Cancer 2017: management of non-muscle invasive bladder cancer. World journal of urology. <https://doi.org/10.1007/s00345-018-2438-9>
69. Lindner A, Schachtner G, Tulchiner G, et al (2021) Lynch Syndrome: Its Impact on Urothelial Carcinoma. International Journal of Molecular Sciences. <https://doi.org/10.3390/ijms22020531>
70. Burgess K, Chow G, Edwards B, Lightner D (2011) 2190 DE NOVO DEVELOPMENT OF UROTHELIAL CARCINOMA FOLLOWING IMMUNOSUPPRESSION FOR SOLID ORGAN TRANSPLANT. The Journal of Urology. <https://doi.org/10.1016/J.JURO.2011.02.2429>
71. Savvides E, Pyrgidis N, Langas G, et al (2022) Concomitant Endoscopic Surgery for Bladder Tumors and Prostatic Obstruction: Are We Safely Hitting Two Birds with One Stone? A Systematic Review and Meta-Analysis. Journal of Clinical Medicine. <https://doi.org/10.3390/jcm11206208>
72. Sood A, Abdollah F, Cole D, Alanee S (2018) Re: Stenting prior to Cystectomy is an Independent Risk Factor for Upper Urinary Tract Recurrence: B. Kiss, M. A. Furrer, P. Y. Wuethrich, F. C. Burkhard, G. N. Thalmann and B. Roth J Urol 2017;198:1263-1268. Journal of Urology. <https://doi.org/10.1016/j.juro.2017.11.119>
73. Clark P (2007) Upper tract transitional cell carcinoma: Finding a way forward. Cancer. <https://doi.org/10.1002/cncr.22969>
74. Johnston D, Bishop MW, Hudson M, Giel D (2015) Subsequent Neoplasms in Adult Survivors of Childhood Genitourinary Tumors. Urology. <https://doi.org/10.1016/j.urology.2015.07.022>
75. Bahadori A, Bray G, Rukin N (2023) Secondary tumours in orthotopic neobladder using isolated gut segment post radical cystectomy for urothelial carcinoma: a systematic review. International Urology and Nephrology. <https://doi.org/10.1007/s11255-023-03745-4>
76. Liedberg F, Chebil G, Davidsson T, et al (2003) Transitional cell carcinoma der Prostata im Zystoprostektomiepräparat. Aktuelle Urologie. <https://doi.org/10.1055/S-2003-42002>

77. Shahzad M, Jamil MN, Ashraf H, Islam EU (2023) Diagnostic, Therapeutic and Prognostic Implications of Urothelial Carcinoma, A Review. Pakistan journal of health sciences. <https://doi.org/10.54393/pjhs.v4i05.720>
78. Picozzi S, Ricci C, Gaeta M, et al (2012) Is it oncologically safe performing simultaneous transurethral resection of the bladder and prostate? A meta-analysis on 1,234 patients. International Urology and Nephrology. <https://doi.org/10.1007/s11255-012-0183-3>
79. Sanghi V, Kumar MA, Alkhayyat M, et al (2020) S0432 Men With Metabolic Syndrome Are at Increased Risk of Urogenital Cancers Among Patients With Barrett's Esophagus. The American Journal of Gastroenterology. <https://doi.org/10.14309/01.ajg.0000703776.13183.b0>
80. Kajtezovic S, Walker AR, Hjalmarsson B, et al (2022) Management of secondary Paget's disease of the vulva associated with transitional cell carcinoma. Journal of Cancer Research and Clinical Oncology. <https://doi.org/10.1007/s00432-022-04007-z>