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Review article

Incidence, risk factors and outcomes of urethral recurrence after radical cystectomy for bladder cancer: A systematic review and meta-analysis

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Abstract

We aimed to conduct a systematic review and meta-analysis assessing the incidence and risk factors of urethral recurrence (UR) as well as summarizing data on survival outcomes in patients with UR after radical cystectomy (RC) for bladder cancer. The MEDLINE and EMBASE databases were searched in February 2021 for studies of patients with UR after RC. Incidence and risk factors of UR were the primary endpoints. The secondary endpoint was survival outcomes in patients who experienced UR. Twenty-one studies, comprising 9,435

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patients, were included in the quantitative synthesis. Orthotopic neobladder (ONB) diversion was associated with a decreased probability of UR compared to non-ONB (pooled OR: 0.44, 95% CI: 0.31−0.61, $P < 0.001$) and male patients had a significantly higher risk of UR compared to female patients (pooled OR: 3.16, 95% CI: 1.83−5.47, $P < 0.001$). Among risk factors, prostatic urethral or prostatic stromal involvement (pooled HR: 5.44, 95% CI: 3.58−8.26, $P < 0.001$; pooled HR: 5.90, 95% CI: 1.82−19.17, $P = 0.003$, respectively) and tumor multifocality (pooled HR: 2.97, 95% CI: 2.05−4.29, $P < 0.001$) were associated with worse urethral recurrence-free survival. Neither tumor stage ($P = 0.63$) nor CIS ($P = 0.72$) were associated with worse urethral recurrence-free survival. Patients with UR had a 5-year CSS that varied from 47% to 63% and an OS - from 40% to 74%; UR did not appear to be related to worse survival outcomes. Male patients treated with non-ONB diversion as well as patients with prostatic involvement and tumor multifocality seem to be at the highest risk of UR after RC. Risk-adjusted standardized surveillance protocols should be developed into clinical practice after RC.

Keywords: Urethral recurrence; Radical cystectomy; Risk factors; UR, RC

1. Introduction

Urothelial carcinoma is considered a pan-urothelial disease; therefore, the remnant urothelium remains at risk of disease recurrence after radical cystectomy (RC) for bladder cancer (BCa) [1]. The incidence of urethral recurrence (UR) after RC is reported to range from 1% to 8%, with most URs being detected in the first two postoperative years [2]. The increased use of orthotopic urinary diversion has questioned the role of prophylactic urethrectomy as well as the risk of UR and its management. Current EAU guidelines do not recommend systematic urethrectomy in all RC cases in both genders because it may then serve as the outlet for an orthotopic neobladder (ONB) and it does not have a consistent survival benefit while being associated with increased morbidity [3]. According to the AUA guidelines, clinicians must verify a negative urethral margin before offering ONB [4]. The latter also suggests that in selected patients at an increased risk of UR, urologists could consider avoiding ONB diversion. Thereby, accurate identification of patients at higher risk of UR after RC is of importance in order to improve the oncologic outcomes and avoid unnecessary urethrectomy for those who may not benefit from it.

Whereas the EAU guidelines do not specifically report risk factors for developing UR, the current AUA guidelines report tumor multiplicity, papillary pattern, carcinoma in situ (CIS), tumor at the bladder neck, prostatic urethral involvement and prostatic stromal invasion [4]. Nevertheless, the predictive value of each UR risk factor remains incomplete and controversial due to the low rate of UR reported in the literature [2,5,6]. Moreover, the survival outcomes of patients who experienced an UR are unclear as some may be salvaged with surgery alone or in combination with systemic therapy.

Therefore, we aimed to conduct a systematic review and meta-analysis assessing the incidence of UR and the risk factors associated with the risk of UR as well as summarizing data on survival outcomes in patients with UR after RC and urinary diversion.

2. Material and methods

2.1. Protocol

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses [7]. The study protocol was registered a priori on the International Prospective Register of Systematic Reviews (PROSPERO; Registration ID CRD42021236878).

2.2. Literature search

The MEDLINE and EMBASE databases were searched in February 2021 to identify studies of patients with UR after RC. A comprehensive systematic literature search was independently performed by two authors. Terms and keywords such as bladder cancer, radical cystectomy, and urethral recurrence were used to perform the search. The incidence and risk factors of UR were the primary endpoints. The secondary endpoint was survival outcomes for patients who experienced UR.

After removing duplicates, two independent reviewers screened the titles and abstracts. Any citation which either reviewer thought should be included or unclear for inclusion was identified for full text screening. Subsequently, full texts of eligible articles were reviewed for final inclusion and data extraction. Any discrepancies during the primary and secondary literature screenings were resolved by referring to the senior author.

2.3. Inclusion and exclusion criteria

We included studies that reported on the incidence and the risk factors of UR in patients treated with RC and urinary diversion. The PICO (population, intervention, control, and outcomes) in this study was the following: patients with UR after RC and urinary diversion compared to the control group of non-UR patients. The outcomes were the incidence and risk factors of UR as well as survival outcomes.

We excluded reviews, letters to editors, editorials, animal studies, study protocols, case reports, meeting abstracts, replies from authors, brief correspondence, and articles not published in English. References of all papers included were scanned for additional studies of interest.

2.4. Data extraction

Two investigators independently extracted the following information from the included articles: first author's name, number of the patients who underwent RC, incidence of UR, sex, sex of UR cases, type of urinary diversion, type of diversion in UR cases, time to UR, duration of follow-up, survival outcomes. The hazard ratios (HR) and 95% confidence intervals (95% CIs) for the following factors associated with urethral recurrence-free survival (RFS) based on multivariate analysis were retrieved: bladder cancer stage, CIS presence, prostatic urethral involvement, prostatic stromal involvement, and tumor multifocality. All discrepancies regarding data extraction were resolved by consensus with the committee of investigators.

2.5. Quality assessment

The Newcastle−Ottawa Scale was used to assess the quality of the included studies in accordance with the Cochrane Handbook for systematic reviews of interventions or included non-randomized studies [8,9]. The scale rates following three factors: Selection (1−4 points), Comparability (1−2 points) and Exposure (1−3 points), with total scores ranging from 0 (lowest) to 9 (highest). The presence of confounders was determined by consensus and review of the literature. Studies with scores of more than 6 were identified as "high-quality" choices.

2.6. Statistical analyses

First, for studies reporting urethral RFS, forest plots were used to assess the HRs and 95% CIs to describe the relationships between the incidence of UR and the risk factors. Second, forest plots were used as the summary variables for dichotomous outcomes and to describe the relationships between incidence of UR and sex, diversion type, diversion type in male patients. Dichotomous variables are presented as proportions and compared with odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated using Cochrane's Q test and the I2 statistic. Significant heterogeneity was indicated by a $P < 0.05$ in Cochrane's Q tests and a ratio >50% in I^2 statistics. We used fixed effects models for calculation non-heterogeneous results. Random effect models were used in cases of heterogeneity. Publication bias was assessed with funnel plots. All statistical analyses were performed using Review Manager 5.3 Software (RevMan; The Cochrane Collaboration, Oxford, UK); the statistical significance level was set at $P < 0.05$.

3. Results

The literature search identified 864 unique references. Among them, 108 records were removed due to duplication, and 705 articles were excluded due to unrelated outcomes during the screening process (Supplementary Fig. 1). Of the 51 full-text articles assessed for eligibility, 14 were excluded based on the selection criteria.

Thirty-seven studies were included in the qualitative synthesis [10−46]. Table 1 summarizes the characteristics of the included studies. Twenty-one studies, comprising 9,435 patients, were included in the quantitative synthesis [12−18,20,21,27−29,31,34−40,46]. Across included studies, all cystectomies were performed for urothelial carcinoma. Most of the studies mentioned that UR was histological confirmed. The associations between incidence of UR and sex/diversion types as well as the associations between urethral RFS and risk factors such as bladder cancer stage, CIS presence, prostatic urethral involvement, prostatic stromal involvement, and tumor multifocality were analyzed.

Most of the studies included in this meta-analysis were identified as having a high-risk of bias according to Newcastle−Ottawa Scale. The median score and range of all selected studies was 5 (4−7).

3.1. Incidence

The incidence of UR after RC varied from 0.8% [24] to 13.7% [37]. Pooled incidence rate was 4.6%. Median time to UR ranged from 8 [33] to 33 months [40] after RC.

3.1.1. Gender

Nine studies provided data on the association between sex and the incidence of UR in patients treated with RC [13,14,17,20,31,36,37,39,40]. The forest plot (Fig. 1A) revealed that male patients have a significantly higher risk of UR compared to their female counterparts (pooled OR: 3.16, 95% CI: 1.83−5.47, $P < 0.001$). The Cochrane's Q test ($P = 0.41$) and I2 test (I2 = 3%) revealed no significant heterogeneity among trials.

3.1.2. Diversion type

Ten studies provided data on the association between the incidence of UR in patients treated with RC and the type of urinary diversion [12,13,15,18,20,21,29,31,35,46]. The forest plot (Fig. 1B) revealed that ONB diversion was associated with a decreased probability of UR compared to non-ONB (pooled OR: 0.44, 95% CI: 0.31−0.61, $P < 0.001$). The Cochrane's Q test ($P = 0.08$) and I2 test (I2 = 42%) revealed no significant heterogeneity among trials. The

Table 1
Characteristics of included studies reporting incidence, risk factors and outcomes of urethral recurrence after radical cystectomy

Author, publication year	Number of patients (UR patients / total sample size)	Gender (male/ female) in total (UR) patients	Type of diversion (ONB / non-ONB) in total (UR) patients	Median time to recurrence, mo	Median (range) follow-up, mo
Akkad, 2005 [46]	2 / 85	0 / 85 (0 / 2)	46 / 39 (2 / 0)	Mean 50.5	42 (5−149)
Ali-El-Dein, 2009 [10]	2 / 180	0 / 180 (0 / 2)	180 / 0 (2 / 0)	NR	57 (5-137)
Balci, 2015 [12]	11 / 287	287 / 0 (11 / 0)	141 / 146 (2 / 9)	NR	Mean 28.60 ± 20.88 (8−144)
Boorjian, 2011 [13]	85 / 1,506	1,230 / 276 (78 / 7)	242 / 1243 (5/80)	13.3 (IQR: 6.1−23.2)	43.3 (IQR: 20.5 −90.5)
Bostrm, 2009 [14]	10 / 248	201 / 47 (10 / 0)	96 / 152	18 (10−96)	75 (1−250)
Chen, 2015 [15]	6 / 111	72 / 39	47 / 56 (4/2)	12 − 48	Mean 40.8 (3−155)
Cho, 2009 [16]	13 / 294	294 / 0 (13 / 0)	0 / 294	17 (6−63)	54 (6−227)
Clark. 2004 [17]	47 / 1,054	843 / 211 (47 / 0)	NR	18.5 (2−116)	121
Djaladat, 2013 [11]	2 / 33	33 / 0 (2 / 0)	33 / 0 (2/0)	28.8	57.6 (1.2−252)
Freeman, 1996 [18]	34 / 436	436 / 0 (34 / 0)	174 / 262 (5/29)	19.2 (2.4−105.6)	72 (12−252)
Gakis, 2015 [19]	7 / 297	0 / 297 (0 / 7)	297 / 0 (7/0)	30 (8-64)	64 (25−116)
Giannarini, 2010 [22]	24 / 479	439 / 40	479 / 0 (24 / 0)	10.8 (IQR: 6−20.4)	52
Hassan, 2004 [20]	5 / 390	307 / 83 (5 / 0)	196 / 203 (1 / 4)	NR	Mean 34.4 (0.3−97.3)
Hrbacek, 2014 [33]	12 / 456	0 / 456 (0 / 12)	456 / 0 (12 / 0)	8 (4−55)	64
Huguet, 2008 [21]	34 / 729	729 / 0 (34 / 0)	219 / 510 (5 / 29)	13.9 (7−21)	38 (8−121)
Ichihara, 2013 [23]	2 / 101	101 / 0 (2 / 0)	29 / 72	NR	44 (1.4-175)
Iselin, 1997 [41]	2 / 70	70 / 0 (2 / 0)	70 / 0 (2 / 0)	10.5	35
Kassouf, 2008 [24]	2/ 252	252 / 0 (2 / 0)	252 / 0 (2 / 0)	NR	48 (4−161)
Kates, 2016 [25]	15 / 298	659 / 91	NR	29.1	36.9
Labbate, 2019 [26]	17 / 357	330 / 27	357 / 0 (17 / 0)	NR	27 (IQR 11−53)
Lee, 2020 [27]	7 / 348	348 / 0 (7 / 0)	348 / 0 (7 / 0)	NR	29.8 (5.6−130.0)
Lui. 2020 [28]	30 / 310	310 / 0 (30 / 0)	NR	NR	22 − 60
Mitra. 2014 [42]	55 / 2029	NR	NR	25 (22−28)	144
Nieder, 2004 [29]	8 / 218	218 / 0 (8 / 0)	108 / 110 (1 / 7)	Mean 12.8 (2.6−37.7)	42
Osman, 2012 [30]	15 / 100	100 / 0 (15 / 0)	NR	NR	NR
Perlis, 2013 [31]	18 / 574	397 / 106 (15 / 3)	154 / 420 (6 / 12)	28 (8−96)	45
Reder, 2015 [32]	364	276 / 88	NR	NR	NR
Roth, 2019 [34]	45 / 803	703 / 100	803 / 0 (45 / 0)	13.2−129.6	64 (IQR 21−128
Stein, 2005 [35]	45 / 766	766 / 0 (45 / 0)	397 / 371 (16 / 29)	24 (2.4 − 163.2)	156
Studer, 2006 [43]	25 / 482	442 / 40	482 / 0 (25 / 0)	14 (3−158)	32
Taylor, 2010 [36]	6 / 260	250 / 10 (6 / 0)	260 / 0 (6 / 0)	28.8 (8.4 − 43.2)	54 (0−187)
Varol, 2004 [44]	15 / 371	NR (15 / 0)	371 / 0 (15 / 0)	14 (3−70)	NR
Yamashita, 2003 [37]	10 / 73	58 / 15 (10 / 0)	73 / 0 (10 / 0)	NR	60.5 (2−254)
Yao, 2019 [38]	30 / 310 28 / 137	310 / 0 (30 / 0) 137 / 0 (28 / 0)	0 / 310 (0 / 30) 0 / 137 (0 / 28)	15 (6.5−28.5)	58.0 (30.0−79.3) 52.0 (31.5−77.0)
Yoshida, 2006 [45]	4 / 77	77 / 0 (4 / 0)	77 / 0 (4 / 0)	28 (6−45)	60
Yossepowitch, 2003 [39]	3 / 214	206 / 8 (3 / 0)	214 / 0 (3 / 0)	NR	32.8 (1−153)
Zhou, 2018 [40]	8 / 282	210 / 72 (7 / 1)	282 / 0 (8 / 0)	33 (6−120)	56 (1−174)

IQR = interquartile range; non-ONB = non-orthotopic neobladder; NR = not reported; ONB = orthotopic neobladder; UR = urethral recurrence

funnel plot identified one study over the pseudo-95% CI (Supplementary Fig. 2).

3.1.3. Diversion type in male patients

Five studies provided data on the association between the incidence of UR in patients treated with RC and the type of urinary diversion in male patients [12,18,21,29,35]. The forest plot (Fig. 1C) revealed that ONB diversion in male patients was associated with a decreased probability of UR compared to non-ONB (pooled OR: 0.35, 95% CI: 0.23−0.53, $P < 0.001$). The Cochrane's Q test ($P = 0.56$) and I2 test (I2 = 0%) revealed no significant heterogeneity among trials.

3.2. Risk factors

3.2.1. Stage

Four studies provided data on the association between the urethral RFS in patients treated with RC and BCa stage [13,16,27,28]. The forest plot (Fig. 2A) revealed that tumor stage was not associated with worse urethral RFS (pooled HR: 1.22, 95% CI: 0.56−2.66, $P = 0.63$). The Cochrane's Q test ($P = 0.001$) and I2 test (I2 = 81%)

Table 2
Survival outcomes of patients with urethral recurrence after radical cystectomy

Author, publication year	OS	CSS / DSS
Balci, 2015	NR	No statistically significant relation was found between DSS rates in patients with and without UR ($P = 0.268$).
Boorjian, 2011	NR	The 3- and 5-year CSS after UR was 74% and 63%, respectively. CSS in UR patients did not differ significantly compared to NUR patients ($P = 0.11$). The 5-year CSS after UR diagnosed by cytology was 80% versus 41% for UR patients who presented with symptoms ($P < 0.0001$).
Cho, 2009	NR	The 5-year DSS rates were 52.1% in patients with UR and 71.7% in those without UR ($P = 0.062$).
Gakis, 2015	6 patients (46%) are still alive with no evidence of disease after a median observation time of 6.2 y from RC.	
Huguet, 2008	The median OS after UR diagnosis was 53.9 months (95%CI, 25.9−81.9) with a 5-y OS of 43%.	NR
Perlis, 2013	The 10-y OS was 66 % for patients with UR and 68 % for patients without any recurrences.	NR
Taylor, 2010	Four of six UR patients were alive without disease, one was alive with disease, and one had died from disease.	
Yamashita, 2003	The 5-y OS was 74% and 75% for UR and NUR patients, respectively.	The 5-year CSS was 83% and 79% for UR and NUR patients, respectively. UR did not have a significant effect on CSS ($P = 0.983$).
Yao, 2019	The 5-y OS of 55.5% in the NUR patients and 40.2% in UR patients ($P = 0.616$).	The 5-y CSS of 57.2% in the NUR patients and 46.9% in UR patients ($P = 0.295$).

CSS = cancer-specific survival; DSS = disease-specific survival; NR = not reported; NUR = non-urethral recurrence; OS = overall survival; UR = urethral recurrence

revealed significant heterogeneity among trials. The funnel plot identified one study over the pseudo-95% CI (Supplementary Fig. 3).

3.2.2. CIS

Four studies provided data on the association between the urethral RFS in patients treated with RC and the presence of CIS [13,27,34,38]. The forest plot (Fig. 2B) revealed that CIS was not associated with worse urethral RFS (pooled HR: 1.07, 95% CI: 0.75−1.52, $P = 0.72$). The Cochrane's Q test ($P = 0.44$) and I2 test (I2 = 0%) revealed no significant heterogeneity among trials.

3.2.3. Prostatic urethral involvement

Three studies provided data on the association between the urethral RFS in patients treated with RC and prostatic urethral involvement [13,16,27]. The forest plot (Fig. 2C) revealed that prostatic urethral involvement was associated with worse urethral RFS (pooled HR: 5.44, 95% CI: 3.58−8.26, $P < 0.001$). The Cochrane's Q test ($P = 0.67$) and I2 test (I2 = 0%) revealed no significant heterogeneity among trials.

3.2.4. Prostatic stromal involvement

Two studies provided data on the association between the urethral RFS in patients treated with RC and prostatic stromal involvement [16,27]. The forest plot (Fig. 2D) revealed that prostatic stromal involvement was associated with worse urethral RFS (pooled HR: 5.90, 95% CI: 1.82−19.17, $P = 0.003$). The Cochrane's Q test ($P = 0.92$) and I2 test (I2 = 0%) revealed no significant heterogeneity among trials.

3.2.5. Tumor multifocality

Three studies provided data on the association between the urethral RFS in patients treated with RC and tumor multifocality [13,28,38]. The forest plot (Fig. 2E) revealed that tumor multifocality was associated with worse urethral RFS (pooled HR: 2.97, 95% CI: 2.05−4.29, $P < 0.001$). The Cochrane's Q test ($P = 0.42$) and I2 test (I2 = 0%) revealed no significant heterogeneity among trials.

3.3. Survival outcomes

Nine studies reported on survival outcomes such as overall survival (OS) and cancer-specific survival (CSS) or disease-specific survival (DSS) in patients with UR after RC and urinary diversion [12,13,16,19,21,31,36−38. Five studies did not find a statistically significant difference of CSS or DSS in UR patients compared to non-urethral recurrence (NUR) patients Table 2. Boorjian et al. reported the 3- and 5-year CSS after UR of 74% and 63%, respectively; CSS in UR patients did not differ compared to NUR patients ($P = 0.11$) [13]. Yao et al. reported a 5-year CSS estimate of 57.2% in the NUR patients and 46.9% in UR patients; this difference

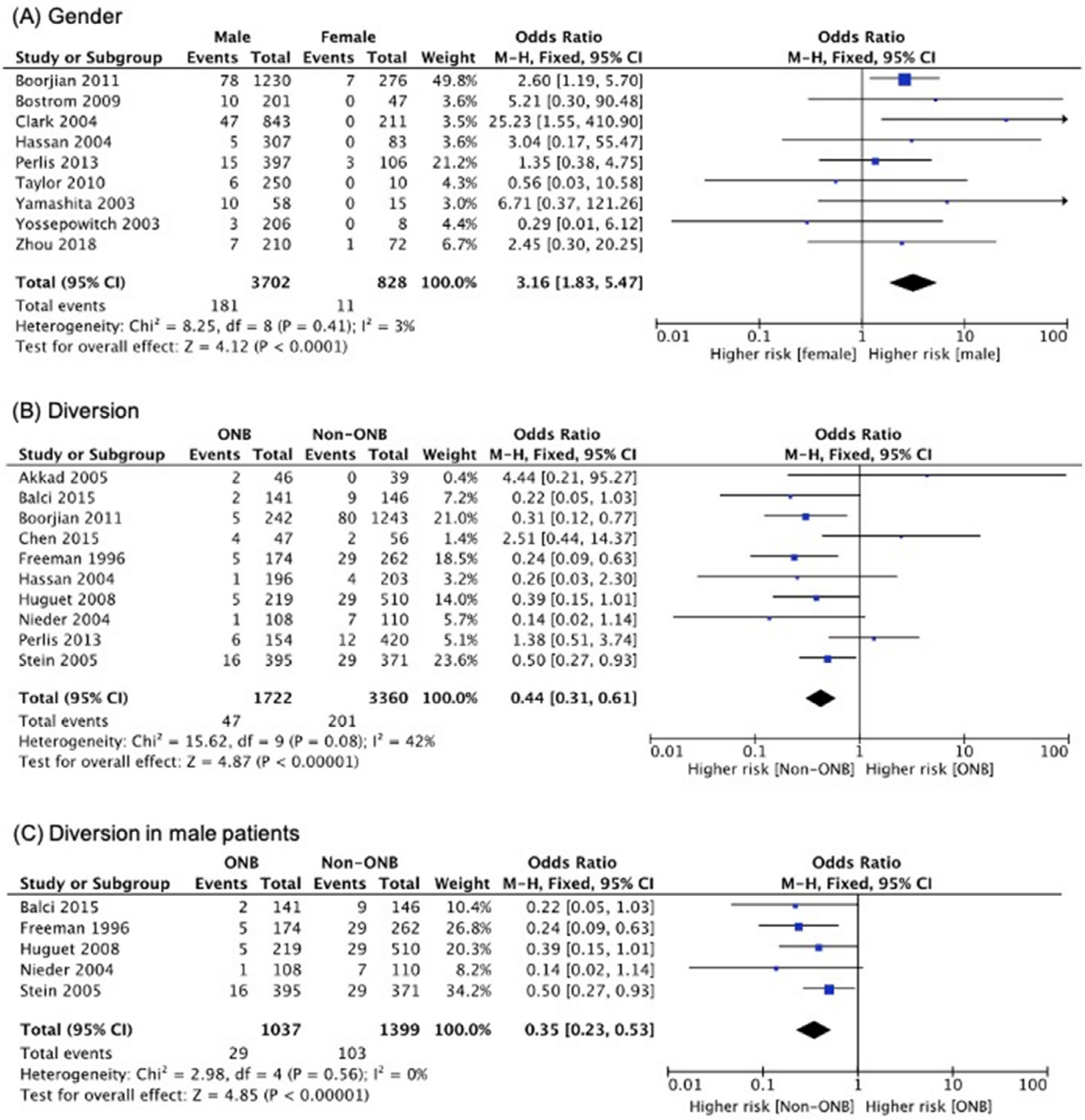

Fig. 1. The forest plot showing the association between incidence of urethral recurrence after radical cystectomy and: (A) gender; (B) type of diversion; (C) type of diversion in male patients.

was, however, not statistically significant ($P = 0.3$) [38]. Similar results were observed in terms of OS. Yao et al. reported a 5-year OS estimate of 55.5% in the NUR patients compared to 40.2% in UR patients ($P = 0.6$) [38]. Similarly, Huguet et al. observed a 5-year OS estimate of 43% in UR patients [21]. Yamashita et al. found higher rates of the 5-year OS estimates with 74% and 75% for both UR and NUR patients, respectively [37]. Summing up, according to currently available literature, in UR patients, the 5-year CSS varies from 47% to 63% and OS - from 40% to 74%; UR does, however, not seem to affect the survival outcomes of patients treated with RC.

4. Discussion

We conducted a systematic review and meta-analysis to assess the incidence and risk factors of UR as well as survival outcomes in patients with UR after RC for BCa. This approach led to several findings.

We found that male patients have a higher risk of UR after RC and urinary diversion. Although, Li et al. reported similar findings with men being at a higher risk for UR (RR 2.49; 95% CI: 1.43, 4.32) [6], Fahmy et al. found no sex-specific difference in UR incidence (OR 2.21; 95% CI: 0.96–5.06) [5]. These controversial results could be

explained with the use of a random effect model in case of no significant heterogeneity among the outcomes. Furthermore, compared to previous meta-analyses, our analysis included more studies with the most recent results. The higher incidence of UR in males might be explained by the anatomical features of the urethra. In contrast, the lower incidence in females could be explained by a predominant squamous cell mucosa of the remnant urethra [47].

Similar to previously published meta-analyses [5,6], we found that patients without ONB are at an increased risk of UR after RC. Our subgroup analysis of studies including only male patients (subgroup analysis for female patients was impossible due to limited number of studies) revealed the higher rates of UR with non-ONB diversion. The detected lower incidence of UR after ONB might be associated with selection bias. Patients with risk factors may be more likely to undergo non-ONB diversion. In addition, the widely common usage of intraoperative urethral frozen section during ONB diversion leads to patient selection. Furthermore, patients receiving an ONB diversion generally undergo a more comprehensive surveillance of their urethra, potentially allowing early diagnosis and management of UR. This would suggest that a stricter surveillance protocol (e.g., cytology and/or urethroscopy instead of a pure clinical follow-up) should be implemented for male treated with RC and non-ONB diversion in order to allow earlier detection and more timely management.

According to our analyses, prostatic urethral involvement, prostatic stromal involvement, and tumor multifocality, among previously described risk factors, were associated with a higher risk of UR. In contrast, tumor stage and CIS were not associated with a higher risk of UR. The clinical tumor stage is notoriously inaccurate, and CIS is often missed in standard white light cystoscopy [48,49]. Previous meta-analyses reported controversial results in terms of risk factors. Fahmy et al. reported that muscle invasion, CIS, and prostatic stromal, or urethral involvement at the time of RC had no significant effect on UR [5]. While Li et al. found that patients with concomitant CIS, superficial or intravesical bladder cancer, prostatic involvement, bladder neck involvement, positive urethral margins or multifocal bladder cancer were at a higher risk of UR [6]. This difference in the results may be due to the use of different statistical approaches: a pooled analysis of the examined factors based on extracted hazard or risk ratios. Finally, our results are in agreement with the AUA guidelines regarding tumor multiplicity, prostatic urethral involvement, and prostatic stromal invasion. However, due to lack of data for pooled analysis, we were unable to assess papillary pattern and bladder neck involvement as risk factors [4]. Nevertheless, we believe that increased awareness of UR and the need for dedicated follow-up is warranted in patients with risk factors such as prostatic urethral or stromal involvement and tumor multifocality.

We did not observe difference in survival outcomes between patients who had an UR and those who had not. The 5-year CSS estimates were 47% to 63% and OS estimates were 40% to 74% in UR patients. Various UR management approaches, including early urethrectomy, transurethral resection, intraurethral BCG, local radiotherapy or systemic chemotherapy might explain the fact that UR does not seem to affect the survival outcomes of patients treated with RC. Diagnostic and follow-up approaches were highly heterogenous and poorly reported. Some of the studies reported the clinical follow-up (based on presence of symptoms) where other ones reported urethroscopy, urethral washing or urine cytology (when appropriated). It should be highlighted that, according to Boorjian et al., the 5-year CSS after UR can be improved when the UR is diagnosed early by cytology 80% versus 41% for UR patients who presented with symptoms ($P < 0.001$) [13]. Therefore, although the role of routine cytology and its impact compared to symptoms screening remains unclear [2,50,51], using regular cytology during the surveillance of the urethral remnant stamp may be useful in patients at risk for UR. Regarding the best timing and the frequency of urethral follow-up, there were not enough data to provide relevant evidence-based recommendations. Nevertheless, it seems reasonable to propose a cytology and/or urethroscopy to high-risk patients at the same frequency than CT-scan for at least the first five years.

The main strength of the present systematic review and meta-analysis is that, to our knowledge, these the most updated analyses with the highest number of patients assessing the incidence and risk factors of UR as well as survival outcomes in patients who experienced UR. There are several potential limitations in this study. Among the main limitations of the present study there are the retrospective design, small sample size, and heterogeneous patients' populations across the included studies. Additionally, most of the included studies did not report the impact of variant histology as well as the influence of positive surgical margins on UR; although that might be questionable, we were unable to perform analyses in that regard. The second limitation is the significant heterogeneity across the studies in the analysis of the association between the incidence of UR and stage, thus limiting the value of these findings. Although the random effects model was used to address heterogeneity among studies, our conclusions should still be interpreted with caution. The third limitation is the significant heterogeneity across the studies in terms of definitions of survival outcomes (endpoints). Hence, calculating pooled results of survival outcomes was not possible. Well-designed large-scale trials are required to validate our findings.

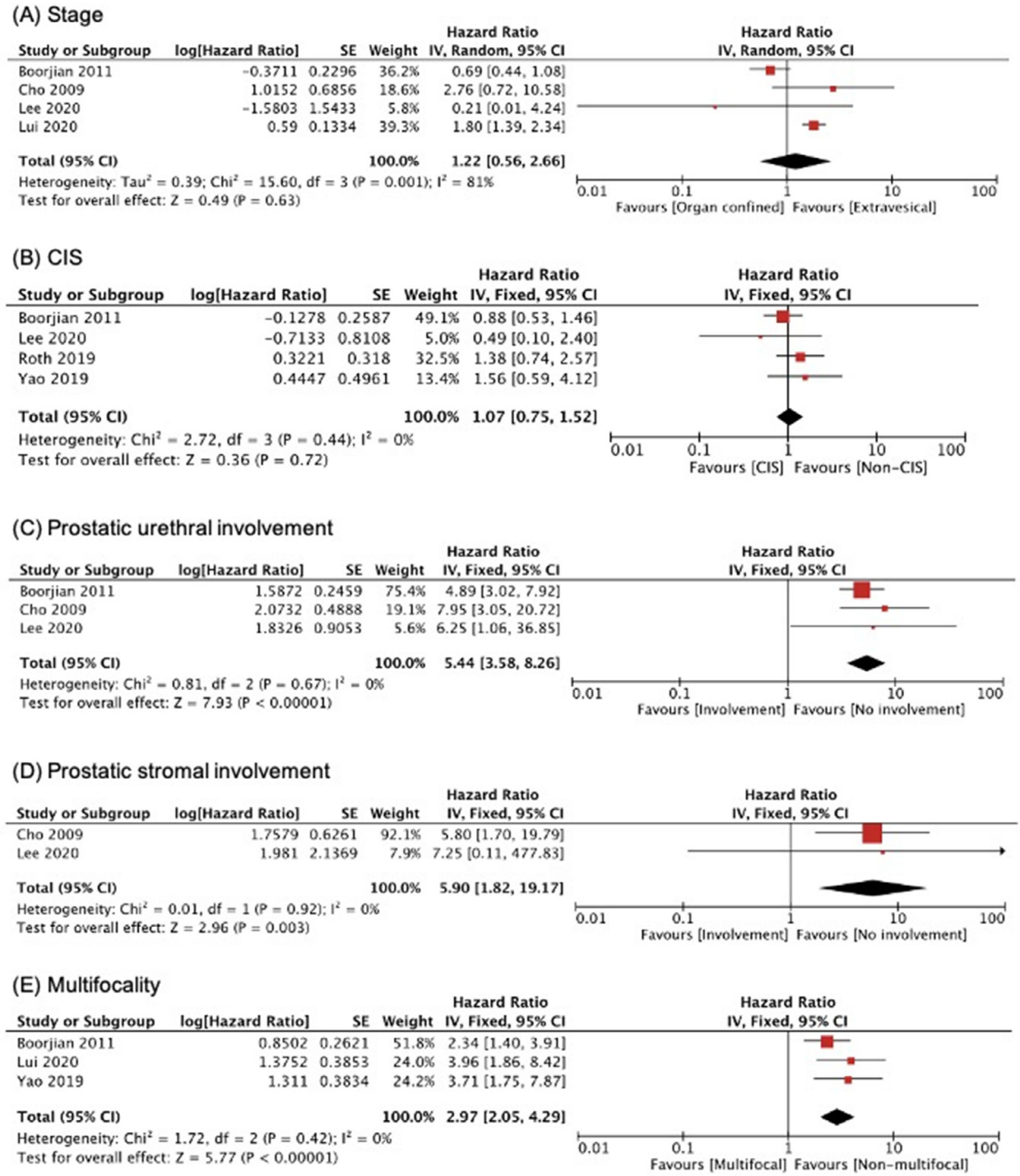

Fig. 2. The forest plot showing the association between urethral recurrence-free survival after radical cystectomy and: (A) tumor stage; (B) CIS presence; (C) prostatic urethral involvement; (D) prostatic stromal involvement; (E) tumor multifocality.

5. Conclusions

Male patients treated with non-ONB diversion as well as those with prostatic urethral involvement, prostatic stromal involvement, or tumor multifocality seem to be at a significantly increased risk of UR after RC. At the same time, patients with UR did not demonstrate significantly worse survival outcomes compared to NUR patients. Nevertheless, increased awareness of UR and the need for dedicated follow-up is warranted. Standardized risk-adjusted surveillance protocols should be developed and implemented into clinical practice to facilitate early UR detection in those who may benefit from it.

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Supplementary material

Supplementary Fig. 1. Flow diagram of the study selection procedure for the systematic review and meta-analysis.

Supplementary Fig. 2. Funnel plots of association between incidence of urethral recurrence after radical cystectomy and: (A) gender; (B) type of diversion; (C) type of diversion in male patients.

Supplementary Fig. 3. Funnel plots of association between urethral recurrence-free survival after radical cystectomy and: (A) tumor stage; (B) CIS presence; (C) prostatic urethral involvement; (D) prostatic stromal involvement; (E) tumor multifocality.

Conflict of interest

All authors state that they have no conflict of interest that might bias this work.

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Supplementary materials

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