available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Collaborative Review – Urothelial Cancer

Editorial by Malte W. Vetterlein, Felix K.-H. Chun and Luis A. Kluth on pp. 558–559 of this issue

Systematic Review on the Fate of the Remnant Urothelium after Radical Cystectomy

Georgios Gakis[a,*], *Peter C. Black*[b], *Bernard H. Bochner*[c], *Stephen A. Boorjian*[d], *Arnulf Stenzl*[a], *George N. Thalmann*[e], *Wassim Kassouf*[f]

[a] *Department of Urology, Eberhard-Karls University of Tübingen, Germany;* [b] *Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada;* [c] *Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [d] *Department of Urology, Mayo Clinic, Rochester, MN, USA;* [e] *Department of Urology, Inselspital Bern, University of Bern, Switzerland;* [f] *Division of Urology, McGill University, Montreal, QC, Canada*

Article info

Article history:
Accepted September 22, 2016

Associate Editor:
Giacomo Novara

Keywords:
Bladder cancer
Radical cystectomy
Recurrence
Remnant
Upper urinary tract
Urethra
Urothelium

EU ACME
www.eu-acme.org/europeanurology

Please visit www.eu-acme.org/europeanurology to read and answer questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Context: Urothelial carcinoma is considered a pan-urothelial disease. As such, the remnant urothelium in the upper urinary tract and urethra following radical cystectomy (RC) remains at risk for secondary urothelial tumors (SUTs).
Objective: To describe the incidence, diagnosis, treatment, and outcomes of patients with SUTs after RC.
Evidence acquisition: A systematic search was conducted using PubMed database according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines to identify studies between 1970 and 2016 reporting on malignant diseases of the urothelium after RC for bladder cancer. The search strategy separated between upper and lower tract urothelial tumors.
Evidence synthesis: Of a total of 1069 studies, 57 were considered for evidence synthesis. SUTs occured in approximately 4–10% of patients after RC. Carcinoma in situ of the bladder, a history of nonmuscle invasive bladder cancer, and tumor involvement of the distal ureter are the strongest risk factors for secondary upper tract tumors. Risk factors for secondary urethral tumors represent urothelial malignancy in the prostatic urethra/prostate and bladder neck (in women), nonorthotopic diversions, and positive findings on permanent sections. The majority of patients (84%) with SUTs, presented with urothelial recurrence without evidence of metastasis. Of those, 84.0% were treated with surgery, 10.5% with systemic chemotherapy and/or radiotherapy, and 5.6% with topical chemotherapy and/or immunotherapy. After a median follow-up of 91 mo (range: 26–155), 65.9% of patients died of disease and 21.5% died of other causes. Detection and treatment of SUTs at an asymptomatic stage can reduce the risks of cancer-specfific and overall mortality by 30%. A limitation of the study is that the available data were retrospective.
Conclusions: SUTs are rare oncological events and most patients have an adverse prognosis despite absence of distant disease at diagnosis. Therefore, surveillance of the remnant urothelium should be implemented for patients with histological features of panurothelial disease as it may improve timely detection and treatment.
Patient summary: Secondary tumors of the renal pelvis, ureters, and urethra occur in approximately 4–10% of patients after radical removal of the bladder for bladder cancer. These patients' prognoses are reduced, likely due to delayed diagnosis. Therefore, routine surveillance might be important to detect tumors at an early stage.

* Corresponding author. Department of Urology, University Hospital Tübingen, Eberhard-Karls University of Tübingen, Hoppe-Seyler Strasse 3, Tübingen D-72076, Germany.
Tel. +49-7071-2985092; Fax: +49-7071-295092.
E-mail address: georgios.gakis@med.uni-tuebingen.de (G. Gakis).

http://dx.doi.org/10.1016/j.eururo.2016.09.035
0302-2838/

CrossMark

1. Introduction

Radical cystectomy (RC) is the mainstay of treatment for muscle-invasive bladder cancer (BC) [1]. The main goal of RC is to completely remove the tumor-bearing bladder with negative surgical margins in order to provide optimal cancer control. Urothelial carcinoma (UC) is considered a pan-urothelial disease [2]. Therefore, the remnant urothelium in the upper tracts and urethra remains at life-long risk for recurrence after RC.

In this regard, the carcinogenesis of multifocal lesions in UC is still controversial. According to the oligoclonal theory or field cancerization, multifocal UC is a result of different genomic events at different time points in the urothelium, whereas the clonal theory considers that multifocal urothelial tumours arise by tumor spread or implantation in the urothelial layer and are genetically identical [2].

A better understanding of the cancerogenic potential of the remnant urothelium after RC is prerequisite for any individualized and evidence-based follow-up strategy of patients at risk of secondary urothelial tumors (SUTs). The present analysis aims to synthesize the available evidence on the incidence, diagnosis, treatment, and outcomes of patients with SUTs after RC in order to address the issue as to whether it is possible to identify patients who are likely to develop SUTs and profit from early detection and treatment.

2. Evidence acquisition

A systematic literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [3] to identify studies reporting on malignant diseases of the remnant urothelium after RC between 1970 and 2016. The PubMed database was searched along with a free-text hand search using one or several combinations of the following items: BC, remnant, radical cystectomy, upper urinary tract, upper tract urothelial carcinoma, urethral carcinoma, upper tract recurrence, urethral recurrence, and urothelium. A total of 1069 studies were initially identified. The selection process was conducted in three stages. The first stage was performed via initial screening of the title to identify eligible publications including a search of respective publications in journals not listed in PubMed to avoid missing any eligible study. In the second stage, publications were screened for eligibility according to the abstracts. The third stage was performed via full-text reading of the respective publications. For this systematic review, we excluded: (1) non-English articles, (2) review articles (without systematic review or meta-analysis), (3) editorial reports and case reports, and (4) repeated publications to avoid publication bias. We decided to exclude review articles as the interpretation of published results without systematic assessment or meta-analysis of data does not offer significant novel insights into the issue of diagnosis and treatment of secondary urothelial tumors.

A total of 57 papers were finally considered for evidence synthesis (Tables 1 and 2). Notably, these studies are retrospective which inevitably inherit the risk of selection bias for which this review cannot control. A Consolidated Standards of Reporting Trials diagram [4] is provided in Figure 1.

3. Evidence Synthesis

3.1. Incidence and clinicopathological risk factors for secondary urothelial recurrences

3.1.1. Risk factors for secondary upper tract urothelial carcinoma

Generally, secondary tumors of the upper tract are considered as late oncological events, occurring after a median of 24–36 mo after RC [1,5]. For this reason, it is important to evaluate clinical and pathological risk factors which may help to assess the intensity of follow-up. In 2012, a meta-analysis was published [6] which aimed to address risk factors for upper tract urothelial carcinoma (UTUC) after RC. The study cohort consisted of 13 185 patients (included from 22 retrospective studies) treated with RC for BC between 1970 and 2010. The follow-up interval ranged between 0.4 mo and 349 mo and the rates of UTUC between 0.8% and 6.4% (Table 1). A significantly higher risk for secondary UTUC was reported for the following subgroups: nonmuscle invasive tumor stages and carcinoma in situ (CIS) at RC, histologically confirmed negative lymph nodes (pN0), tumor multifocality and history of multifocal BC, a prior history of UTUC prior to RC, a positive ureteral or urethral margin at RC, and the presence of low-grade tumors (G1) [6]. The latter finding seems to be contraintuitive from a biological standpoint. However, in the context of patients treated with RC for BC those who are at low risk of cancer-related death (ie, those with nonmuscle invasive disease) or exhibit histological features of pan-urothelial disese (ie, CIS) are the ones at particular risk for subsequent upper tract tumors during the long-term follow-up compared with those who present with advanced disease at surgery and are more likely to die from metastatic disease which usually occurs in the 1st 2 yr after RC [1]. Recently, urethral margin status on permanent section was also found to be an independent prognosticator for metachronous UTUC [7], whereas frozen section analysis (FSA) of the distal ureteral margin was only associated with recurrence in univariable but not multivariable analysis [8]. Similarly, in another large retrospective study on 1420 RC patients, CIS of the bladder, a history of recurrent BC, nonmuscle invasive bladder cancer stage, and tumor involvement of the distal ureter were reported to be independently associated with the risk for secondary UTUC. Indeed, while for the total cohort the overall rate of UTUC was very low (0.8%), its prevalence increased to 13.5% for patients with three to four risk factors [9].

3.1.2. Risk factors for secondary urethral tumors

As for SUTs of the upper tract, the median time to secondary urethral tumors has been reported to range between 13 mo and 28 mo in men [10–12] and 30 months in women [13]. Secondary urethral tumors after RC are relatively rare (incidence: 0.8–6.1%; Table 2) and associated with a trend towards lower 5-yr cancer-specific survival compared with patients without urethral tumors (63% vs 71%; $p = 0.11$)

Table 1 – Overview of 40 of the 57 publications selected for this systematic review addressing mainly patient characteristics, treatment, and outcomes of patients with secondary upper tract recurrences or secondary upper tract and urethral recurrences

Study (author, yr)	Total sample size/*N* (pat) with SUT (%)	Type of diversion OBS/non-OBS; (% of pat. with OBS	Location studied UUT vs URE	Sex (m/w) for patients with SUT	Median (or range) time to recurrence (mo)	Recurrence pattern	Incidence of urothelial recurrence with OBS vs non-OBS	Treatment for SUT	Outcome after treatment of SUT	Median (mean) follow-up (or range) for total cohort (mo)
Akkad, 2006 [33]	85/4 (4.7)	46/39 (54.1)	UUT+UTE	0/4	36–76	U: 4	3/1	Ux: 2; NUX:1; CTx+S: 1	DOC: 2; alive: 1; DOD: 1	42
Boorjian, 2011 [48]	1599/154 (9.6)	n.r.	UUT+URE	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Caraway, 2007 [55]	83/7 (8.4)	n.r.	UUT	n.r.	n.r.	U+P: 1; U+D: 1; U: 4	n.r.	n.r.	DOD: 1; AWD: 4; UKN: 2	6–37
Chen, 2016 [52]	111/11 (9.9)	47/64 (42.3)	UUT+URE	10/1	35	U: 11	7/4	n.r.	n.r.	41 (3–155)
Fernandez, 2012 [53]	271/10 (3.7)	n.r.	UUT	n.r.	23	n.r.	3/7	n.r.	n.r.	31 (2–202)
Furukawa, 2007 [56]	583/12 (2.1)	247/336 (42.4)	UUT	12/0	29.5	U only 7; U+D: 5	8/4	CTx only: 5; CTx+NUX: 1; BCG: 1; NUX: 5	DOD: 8; AWD: 2; ANED: 2	42
Gakis, 2011 [23]	218/5 (2.3)	n.r.	UUT	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	24 (1–116)
Giannarini, 2010 [46]	479/38 (7.9)	n.r.	UUT+URE	n.r.	n.r.	U only: 34; U+D: 4	n.r.	CTx:2; S:10; TUR+BCG: 13	alive: 6; rest unknown	52
Giannarini, 2014 [43]	110/57 (high-risk NMIBC after BCG; 51.8%)	n.a.	UUT+URE	51/6 (86 sites of recurrence)	42	U: 57	n.a.	(According to sites) BCG: 38; NUX: 11, Partial UTx: 4; UX: 2; ENDO: 12; None: 2; Incidental detection at RC w/o further treatment: 17	alive: 34; DOD: 11; DOC: 12	109
Gordetsky, 2014 [37]	822/n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Hoang, 2014 [25]	660/n.r.	n.r.	UUT	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	32
Johnson, 1989 [27]	403/0	n.r.	UUT	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	72
Kim, 2014 [57]	311/11 (3.5)	168/143 (54.0)	UUT	n.r.	26	U: 3; 6 local concomitant pelvic and 2 concomitant urethral recurrence 2	7/4	NUX+adj.CTx: 7; NUX: 4	DOD: 6; LWD: 5	53 (13–207)
Kim, 2015 [20]	402/11 (2.7)	n.r.	UUT	n.r.	26	U: 11	n.r.	NUX: 10; partial UTX: 1	DOD: 4; DOC: 1	n.r.
Linder, 2014 [5]	2091/167 (8.0)	n.r.	UUT+URE	146/21	n.r.	n.r.	19/148	n.r.	n.r.	199
Loeser, 2014 [24]	243/2 (0.8)	n.r.	UUT	n.r.	25/53	U: 2	n.r.	Partial resection: 1; BCG+NUX+adj. CTx: 1	Dead: 1; alive:1	26 (1–72)
Mazzucchelli, 2009 [38]	248/n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Mitra, 2014 [58]	2029/80 (3.9)	n.r.	UUT+URE	n.r.	26-58	n.r.	44/36	NUX: 24; UX:49; Intraurethral chemo: 2; observation: 1; UKN: 4	DOD (UUT): 11; DOD (URE): 28	144
Nelles, 2008 [44]	2401/n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.-	n.r.	n.r.	29
Osman, 2007 [21]	100/n.r.	58/42 (58)	UUT	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Perlis, 2013 [12]	574/39 (6.8)	154/420 (26.8)	UUT+URE	27/12	28	n.r.	11/28	n.r.	n.r.	45
Picozzi, 2012 [6]	13185/218 (1.6) outcome reported in 201	n.r.	UUT	n.r.	2.4–164	n.r.	n.r.	S: 175; inoperable: 38; refused therapy: 5	Alive: 74; dead: 127	n.r.
Raj, 2006 [22]	1330/82 (6.2)	n.r.	UUT	n.r.	n.r.	U: 82	n.r.	n.r.	n.r.	46

Table 1 (*Continued*)

Study (author, yr)	Total sample size/*N* (pat) with SUT (%)	Type of diversion OBS/non-OBS; (% of pat. with OBS	Location studied UUT vs URE	Sex (m/w) for patients with SUT	Median (or range) time to recurrence (mo)	Recurrence pattern	Incidence of urothelial recurrence with OBS vs non-OBS	Treatment for SUT	Outcome after treatment of SUT	Median (mean) follow-up (or range) for total cohort (mo)
Rundstedt von, 2015 [39]	101/n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Rink, 2012 [59]	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	44
Sanderson, 2007 [60]	1069/27 (2.5)	n.r.	UUT	19/8	40	U: 27	24/3	NUX: 24; ENDO: 1; CTx: 1; UKN: 1	DOD: 18; alive: 9	124
Satkunasivam, 2015 [8]	2047/28 (1.4)	1245/79 (61.1)	UUT	n.r.	37	U: 28	n.r.	NUX: 27; partial UTx: 1	n.r.	149
Schumacher, 2006 [30]	805/31 (3.9)	n.r.	UUT	n.r.	30	n.r.	n.r.	n.r.	DOD: 20; alive: 11	n.r.
Stein, 1995 [36]	67/n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Stewart-Merrill, 2016 [50]	n.r	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Sureka, 2015 [35]	151/2 (0.9)	151/0	UUT	2/0	24/72	U: 2	2/0	n.r.	n.r.	46
Takayanagi, 2012 [7]	362/11 (3.0)	n.r.	UUT	n.r.	48.4	U: 6; U+D:5	9/2	S: 6; CTx: 4, None: 1	DOD: 8; NED: 2; AWD: 1	48
Tollefson, 2010 [28]	1397/69 (4.9)	n.r.	UUT	n.r.	37	n.r.	n.r.	NUX: 46; ENDO: 14; CTx: 6, topical BCG/CTx: 3	DOD: 42, n.r.: 27	71
Tran, 2008 [61]	1329/80 (6.0)	n.r.	UUT	n.r.	25	n.r.	n.r.	n.r.	n.r.	37
Umbreit, 2010 [62]	1388/67 (4.8)	n.r.	UUT	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Volkmer, 2009 [9]	1420/25 (1.8)	n.r.	UUT	n.r.	39	n.r.	n.r.	S: 25	DOD: 16; n.r.: 9	58
Westerman, 2016 [29]	2523/38 (1.5) only stricture associated recurrences	38/183	UUT	32/6	32.4	U: 28 U+D: 10	5/31 (missing: 2)	open S: 22; ENDO: 6	26/32 evaluable pat. died	126
Yafi, 2012 [54]	2287/n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Yoshimine, 2010 [51]	125/8 (6.4)	19/106	UUT	8/0	63.3	U: 8	1/7	NUX: 6; CTx: 1; BCG: 2	NED: 4; DOD: 3; DOC: 1	64
Yossepowitch, 2003 [26]	214/13 (6.1)	214/0	UUT+URE	n.r.	n.r.	U: 13	13/0	UKN: 6; TUR: 2; S: 1; NUX: 4	NED: 6; DOD: 7	44

adj. = adjuvant; ANED = alive with no evidence of disease; AWD = alive with disease; BCG = Bacille-Calmette Guerin; CTx = systemic chemotherapy; D = distant recurrence; DOC = death of other cause; DOD = death of disease; ENDO = endoscopic management; LWD = living with disease; m = men; *N* = number; n.a. = not applicable; non-OBS = non orthotopic bladder substitute; n.r. = not reported; NED = no evidence of disease; NUX = nephroureterectomy; OBS = orthotopic bladder substitute; P = pelvic recurrence; pat. = patients; S = surgery; SUT = secondary urothelial tumor; TUR = transurethral resection; w = women; w/o = without; U = urothelial recurrence; UKN = unknown; URE = urethra; UUT = upper urinary tract; UTx = partial ureterectomy; Ux = urethrectomy.

Table 2 – Overview of selected publications addressing specifically patient characteristics, treatment, and outcomes of secondary urethral recurrence

Study (author, yr)	Total sample size/*N* (pat) with SUT (%)	Type of diversion OBS/non-OBS; (% of pat. with OBS	Sex (m/w) for patients with SUT	Median (or range) time to recurrence (mo)	Recurrence pattern	Incidence of urothelial recurrence with OBS vs non-OBS	Treatment for SUT	Outcome after treatment of SUT	Median (mean) follow-up (or range) for total cohort (mo)
Balci, 2015 [15]	287/11 (3.8)	141/146 (49.1)	11/0	n.r.	n.r.	2/9	TUR+BCG: 1; CTx: 4; Ux: 2; RTx: 4	n.r.	29
Boorjian, 2011 [10]	1506/85 (5.6)	242/124 (19.5)	78/7	13.3	n.r.	5/80	UX: 73; CTx/RTx: 6; No therapy: 6	DOD: 35; DOC: 38; n.r.: 12	155
Cho, 2009 [14]	412/13 (3.2)	n.r.	n.r.	17	n.r.	n.r.	S only: 5; S+CTx: 6; S+RTx: 1; CTx only: 1	Alive: 6; Dead: 7	54 (6–227)
Clark, 2004 [49]	1054/47 (4.5)	n.r.	n.r.	18.5 (2–116)	n.r.	14/33	Partial or total Ux: 41; CTx: 2; CTx+RTx: 1; Topical 5-FU +/- ENDO: 3	Alive: 10; DOD: 25; DOC: 11	121
Djaladat, 2013 [16]	33/2 (6.1)	33/0 (100)	2/0	14/44	U: 2	2/0	n.r.	n.r.	58
Gakis, 2015 [31]	297/7 (2.4)	297/0 (100)	0/7	30	U: 7	7/0	n.r.	n.r.	64
Gaya, 2014 [40]	234/3 (1.3)	68/166 (29.1)	n.r.	26	U: 3	n.r.	S: 3	n.r.	31
Hrbacek, 2015 [63]	456/12 (2.6)	456/0 (100)	0/12	8	U: 3; U+D:4, U+P+D: 2; U+P: 3	12/0	S alone: 5; RTx: 2; CTx: 3; BCG: 2	Dead: 9; Alive: 3	64
Huguet, 2008 [11]	729/34 (4.7)	219/510 (30.0)	34/0	14	n.r.	5/29	TUR: 2; BCG: 1; Ux: 31	DOD: 16; DOC: 3; NED: 15	38
Ichihara, 2013 [64]	101/2 (2.0)	29/72 (26.1)	2/0	7/24	U: 2	0/2	S: 2	DOD: 2	44
Jentzmik, 2012 [65]	121/1 (0.8)	121/0 (100)	1/0	n.r.	n.r.	1/0	n.r.	n.r.	56
Kassouf, 2008 [41]	252/2 (0.8)	252/0 (100)	2/0	n.r.	n.r.	2/0	n.r.	n.r.	48
Lebret, 1998 [32]	118/0	n.a.	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Osman, 2012 [34]	100/4 (4.0)	n.r.	n.r.	n.r.	U+D: 3, U+P: 1	n.r.	n.r	n.r.	n.r.
Stein, 2005 [17]	768/45 (5.9)	397/371 (51.7)	n.a.	24	n.a.	n.a.	n.a.	n.a.	156
Taylor, 2010 [66]	260/6 (2.3)	260/0 (100)	n.r.	29	U: 6	6/0	CTx: 1; Ux: 2; UKN: 1; CTx+Ux: 1; TUR: 1	AWD: 1; NED: 4; DOD: 1	61
Varol, 2004 [47]	371/15 (4.0)	371/0 (100)	15/0	14 (3–70)	U: 11; U+D: 4	15/0	BCG: 8; BCG+Ux: 3; CTx: 2; No local therapy: 2	DOD: 7; DOC: 3; Alive: 5	n.r.

AWD = alive with disease; BCG = Bacille-Calmette Guerin; CTx = systemic chemotherapy; D = distant recurrence; DOC = death of other cause; DOD = death of disease; ENDO = endoscopic management; 5-FU = 5-fluorouracil; m = men; *N* = number; n.a. = not applicable; non-OBS = non orthotopic bladder substitute; n.r. = not reported; NED = no evidence of disease; OBS = orthotopic bladder substitute; P = pelvic recurrence; pat. = patients; RTx = radiotherapy; S = surgery; SUT = secondary urethral tumor; TUR = transurethral resection; w = women; w/o = without; U = urothelial recurrence; UKN = unknown; Ux = urethrectomy.

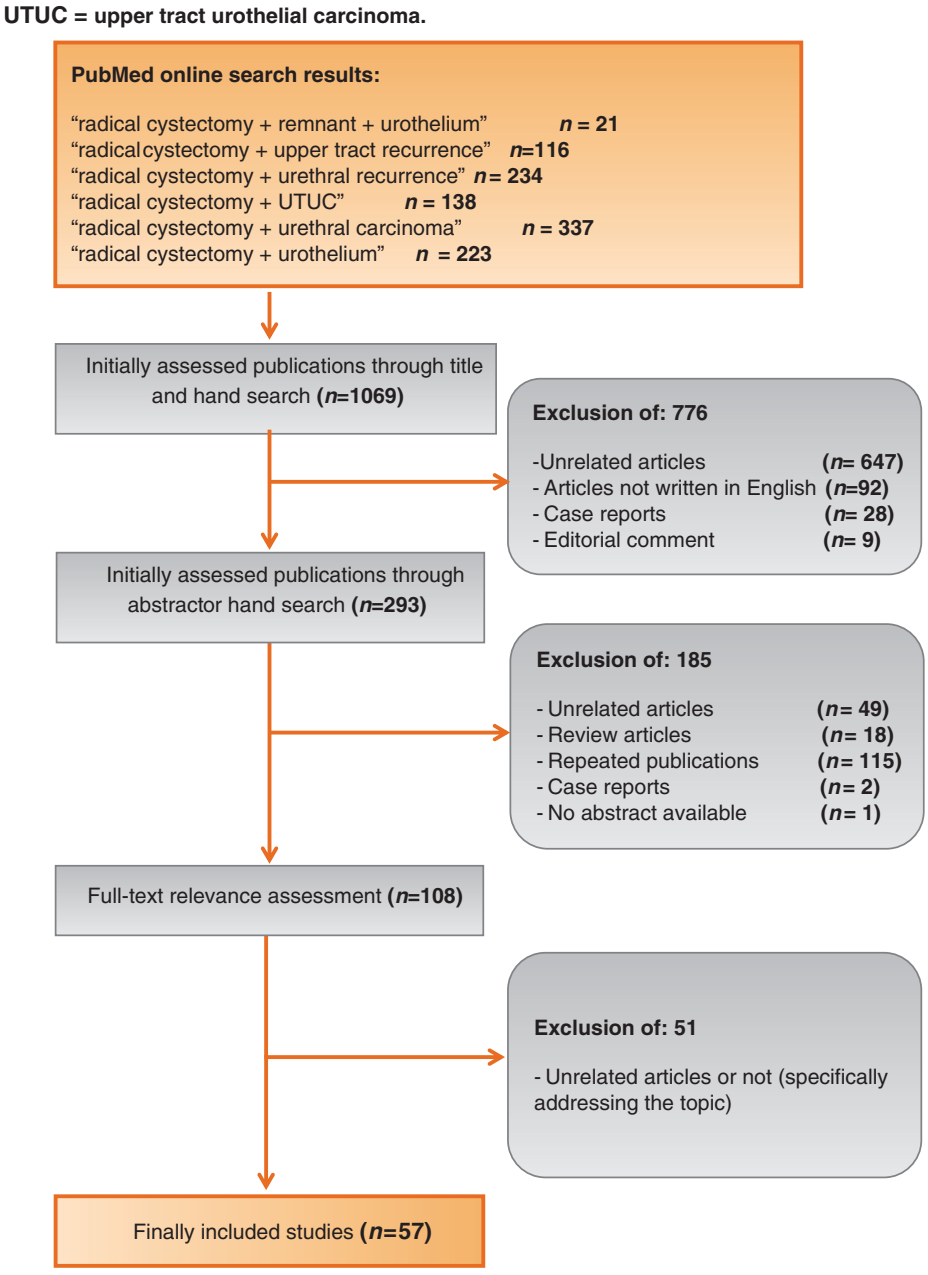

Fig. 1 – This Consolidated Standards of Reporting Trials diagram outlines the selection process of the included studies. UTUC = upper tract urothelial carcinoma.

[10]. It is important to identify patients at highest risk of urethral malignant disease. A number of studies have tried to address this issue in recent years. In these series, prostatic urethral [10,12] and stromal [14] involvement, tumor multifocality [10], pathological T-stage [15], especially nonmuscle invasive tumor stage (Ta, Tis, T1) [11], performance of nonorthotopic diversions [10], and a positive final urethral margin at RC [14] have been independently associated with secondary urethral carcinoma. In this regard, the rate of secondary urethral tumors in men with stage T4a disease treated with RC and orthotopic bladder substitution (OBS) was found to be only 6%. This occured after a median of approximately 2 yr after RC and suggests the prognostic value of nonorgan confined disease at the time of RC [16,17]. For women, bladder neck involvement has been shown to be a strong predictor for the presence of concomitant urethral as well as secondary urethral tumors [18].

Interestingly, large studies have reported that patients with OBS are at a significantly lower risk for secondary urethral malignancy compared to those with nonorthotopic diversions [10,15]. Of the 224 patients with urethral recurrence (Table 1), 71 (31.7%) were found in patients with orthotopic bladder substitutes compared with

153 (68.3%) in patients with nonorthotopic bladder substitutes. From a clinical perspective, this finding is likely a selection bias as patients with advanced tumor stage, prostatic urethral disease, or extensive CIS were more likely to receive incontinent diversions. However, one may also hypothesize that connecting urothelial and intestinal tissue induces immune reactions resulting in an enhancement of the local immune response to carcinogenic antigens. A recent study immunohistochemically investigated urethral tissues obtained from seven neobladder patients and nine healthy controls [19]. In neobladder patients, there was a nonsignificant trend towards a higher relative fraction of B-cells, especially CD138 positive plasma cells, and a lower relative fraction of T-cells [19]. Yet, whether this immunological finding may be causative for the apparently lower risk of secondary urethral tumors in neobladder patients is unclear. This study lacked a comparative group of patients undergoing cystectomy with ileal conduit. As studies evaluating risk factors for secondary upper tract malignancies did not find OBS to be associated with a reduced risk of metachronous UTUC [6], connecting urethral and intestinal tissue may not per se induce immunological changes. Instead, the constant flow of neobladder urine through the retained urethra may lead to immuno-inductive processes. Another possible explanation is the potential for earlier diagnosis of recurrence in patients with orthotopic diversion due to their voiding through the urethra. It is more likely that conduit patients who develop urethral recurrence may also present with advanced disease due to a large local recurrence. These considerations suggest that follow-up for patients with ileal conduit should include urethral inspection or cytology obtained with brushing.

3.2. *Accuracy and prognostic significance of frozen section analysis of urothelial margins at RC*

3.2.1. *Ureteral frozen section analysis*

In contemporary RC series, the rate of positive ureteral margins on permanent sections ranges between 6.8% and 14.0% (Table 3) [20–23]. Tumor multifocality [23], a positive FSA of the distal ureter [21,23], male sex [21], and the presence of bladder CIS [22,24] were found to independently predict malignancy at the distal ureteral margin on permanent section. For ureteral FSA, the majority of studies have reported sensitivity and specificity rates around 75–80% and 95–99%, respectively [20,22,23,25]. A large study on 2047 patients treated with RC over a time period of 40 yr investigated the accuracy of intraoperative FSA of the ureteral margins. The sensitivity of FSA for correctly predicting the final ureteral margin status was only 59% and showed only a moderate increase to 69% for CIS [8]. The rate of secondary UTUC was noticeably low at 1.4% ($N = 28$) and no recurrences were observed at the ureteroileal anastomosis. A positive FSA was associated with metachronous UTUC only in univariable analysis. In addition, authors reported that 15 of the 28 patients (54%) with subsequent UTUC had negative results for FSA of the ureteral margins. While these data question the utility of routine FSA for the intraoperative assessment of the distal ureters, some consideration needs to be given to the interpretation of these results. Although the sample size is large, it covers a period of almost 40 yr which may have implications on histopathologic assessment during the study period. The reported sensitivity for the detection of malignancy at the margin was considerably less than in other series and the rate of metachronous UTUC after a median follow-up of more than 12 yr was exceptionally low.

Malignant ureteral margins on permanent section show CIS or severe dysplasia in more than 75% of the cases [25]. Various series have demonstrated that the presence of CIS at the ureteral margin on permanent section after RC carries an increased risk of metachronous UTUC [22,23]. Moreover, prior studies have suggested that patients with SUTs at the ureteroileal anastomosis have a higher risk for cancer-specific death compared with patients with proximal tumors [26,27]. Thus, one may hypothesize that converting a positive margin into a negative one by means of reresection(s) impacts favorably on prognosis. However, the presence of *skip* lesions, or pagetoid spread, particularly for CIS, limits the therapeutic value of obtaining a negative FSA for preventing metachronous UTUC. A recent study investigated the presence of *skip* lesions in patients who had at least two resections of the same ureter at RC [25]. *Skip* lesions were found in ~5% of the patients, with CIS being the most prevalent histological malignant entity. *Skip* lesions were associated with lymphovascular invasion and non-muscle invasive disease at RC and were also associated with a lower overall survival. These findings suggest that *skip*

Table 3 – Assessment of urothelial malignancy at radical cystectomy with different methods

Study	Site	Method	*N* total	*N* (malig.)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
Satkunasivam [8]	Ureter	FSA	2047	178 (8.6)	59	93	n.r.	n.r.	n.r.
Kim [20]	Ureter	FSA	402	46 (11.2)	75	96	n.r.	n.r.	95
Osman [21]	Ureter	FSA	100	14 (14.0)	45	98	81	91	n.r.
Raj [22]	Ureter	FSA	1330	171 (12.9)	75	99	n.r.	n.r.	n.r.
Gakis [23]	Ureter	FSA	218	15 (6.8)	74	100	94	99	98
Osman [34]	Urethra	FSA	100	6 (6.0)	33	99	83	89	89
von Rundstedt [39]	Urethra	TUPBx	272	101 (37.1)	71	100	100	86	89
Gaya [40]	Urethra	TUPBx	234	81 (34.6)	81	82	62	92	n.r.
Ichihara [63]	Urethra	TUPBx	101	25 (24.8)	86	91	72	96	n.r.

FSA = frozen section analysis; malig. = malignant; *N* = number of patients; NPV = negative predictive value; n.r. not reported; PPV = positive predictive value; TUPBx = transurethral prostatic urethral biopsy.

lesions likely represent the degree to which an individual patient's disease is of pan-urothelial character. Despite this limitation, the strategy of performing sequential resections of the distal ureter during RC with the objective of converting a positive into negative margin was found to be successful in ~40–82% of the patients [23,28] and has been also reported to result in lower rates of secondary UTUC [25,28].

Taken together, as secondary UTUC occurs infrequently and relatively late after RC, studies with a limited sample size and short follow-up are unsuitable to demonstrate or disprove the beneficial prognostic effect of sequentially resecting the distal ureters in case of positive FSA. This is because in smaller studies, the denominator (absolute number of patients without recurrence) decreases more significantly with prolonged follow-up compared with the absolute number of patients (numerator) who live long enough to develop UTUC [20,22]. Nonetheless, in the absence of robust data, a positive ureteral margin on FSA should influence surgeons to consider reresection(s) of the given ureter as this simple procedure may render a considerable subset (40–82%) of patients cancer-free at the margin [23,28]. With regard to the indication for FSA, some centers have utilized a risk-adapted approach for the usage of FSA during RC to ensure negative margins based on the existence and number of risk factors for ureteral malignancy [29]. As an alternative technique, cutting the ureters at the crossing with the common iliac arteries, results in a low rate of positive ureteral margins at RC (1.2%) [30]. This practice may obviate the need of sequential resection but necessitates a longer segment of ileum for neobladder reconstruction [31].

3.2.2. *Urethral frozen section analysis*

Even if a prostatic urethral biopsy is positive prior to RC, it has been shown that a negative urethral frozen section at the time of RC results in a tumor-free urethra after a follow-up period of 10 yr [32]. Therefore in patients scheduled for OBS, intraoperative exclusion of malignant disease at the level of urethral dissection should be performed before urethrointestinal anastomosis. This also holds true for patients with nonorthotopic or incontinent diversions and a retained (afunctional) urethra, particularly if prostatic urothelial maligancy was detected prior to RC [10]. Intraoperative FSA of the urethral margin may be helpful for the decision-making with regards to immediate urethrectomy. However, in contrast to ureteral FSA, there is only scarce data on the accuracy of urethral FSA at RC. In women, a study on 85 patients reported on a 100% sensitivity and specificity of FSA for the accurate prediction of the final urethral margin status at RC [33]. By contrast, a small series of 100 men treated with RC for BC reported on a low sensitivity (33%) but high specificity (~99%) for urethral FSA [34].

3.3. *Can urethral FSA be replaced by bladder neck and prostatic urethral biopsy?*

3.3.1. *Bladder neck biopsy in women*

For women, some urologists consider a bladder neck biopsy to be oncologically equivalent to urethral FSA [35]. To evaluate this further, a retrospective study analyzed outcomes of 297 women who underwent RC with OBS for BC in four centers between 1994 and 2011 [13]. None of them exhibited bladder neck involvement on preoperative assessment. After a median follow-up of 64 mo (interquartile range: 25–116), 81 women developed recurrent disease (27%) with a corresponding 15-yr recurrence-free survival rate of 66%. Two (0.6%) women experienced secondary malignancies in the urethra only, four (1.2%) concomitantly in the urethra and in distant organs, and in one (0.3%) in the urethra and in the local surgical bed. The median time to secondary urethral malignancy was 30 mo (total range: 8–64). Although primary tumors were located at the trigone in 27 women (9%), none of these developed secondary tumors. FSA was negative in six of the seven women with urethral recurrence and only one of them had a positive urethral margin on permanent section. A positive permanent urethral margin status was found in seven and was significantly associated with secondary urethral malignancy ($p < 0.001$). No significant associations were reported for CIS, pathologic tumor and nodal stage, and involvement of the bladder trigone.

While these data suggest that careful preoperative assessment of the bladder neck may obviate the need for intraoperative FSA of urethral margins, the clinically more important question is whether women with tumor involvement of the bladder neck who still desire an OBS should be excluded from OBS a priori. As anatomical studies have shown that malignancy at the bladder neck is associated with a positive final urethral margin status in only 40% of the patients [36], a carefully obtained full-thickness biopsy for intraoperative FSA of the distal urethral margin may be a better method to exclude malignancy at the level of dissection, particularly given the very low observed recurrence rate in women selected using intraoperative FSA. Nonetheless, there is currently no data comparing the accuracy of bladder neck biopsy and FSA of the urethra in a head-to-head manner for predicting the final urethral margin status as well as its impact on clinical decision-making for concurrent urethrectomy. Therefore, it should be emphasized that in cases of equivocal histological findings on intraoperative FSA—denudation or atypia—obtaining additional biopsies should be considered to lower the risk of a positive final urethral margin on permanent section [37].

3.3.2. *Prostatic urethral biopsy*

Analyses of whole-mounted prostate sections have demonstrated that prostatic urothelial malignancy is present in up to 38% of cystectomy specimens [38]. Analogous to the role of preoperative bladder neck assessment in women, it can be hypothesized that a prostatic urethral biopsy predicts urethral involvement at RC. In this regard, the value of transurethral prostatic biopsy was assessed in a recent series of 272 patients scheduled for RC [39]. Transurethral resection biopsies of the prostatic urethra were performed at the 5 o'clock position and 7 o'clock position adjacent to the verum montanum. Malignancy in the prostatic urethra was identified in 101 patients (~37%). The sensitivity and specificity of transurethral prostatic biopsy for predicting

prostatic urethral involvement in the RC specimen was 71% and 100%, respectively, with an overall accuracy of 89%. However, this study did not compare biopsy results with frozen or permanent section analysis of the distal urethral margin, which is the key clinical question. Futhermore, prostatic urethral biopsy failed to detect prostatic stromal invasion of the urothelial carcinoma in 11 of 15 patients (~73%). Apart from this study, it should be emphasized that a prostatic cold cup urethral biopsy results in lower accuracy rates compared with a transurethral loop biopsy for the detection of prostatic urothelial malignancy [40].

Given the high rates of concomitant prostatic urethral malignancy (37–38%) and low rates of distal urethral malignancy (~6–9%) at the level of urethral transection [8,34], the routine use of preoperative prostatic urethral biopsy is likely to unnecessarily exclude a considerable number of patients who desire OBS as their preferred type of diversion. Furthermore, as there is a relatively low positive predictive value of prostatic urethral biopsy for predicting disease at the urethral margin at RC, collective data suggest that a FSA of the urethral margin should be performed for men scheduled for OBS [41]. Therefore, in the authors' opinion a positive transurethral biopsy before cystectomy is not a reason to exclude a patient a priori from undergoing an orthotopic diversion.

3.4. What are treatment options and outcomes of secondary urothelial tumors after RC?

3.4.1. Treatment of secondary upper tract tumors

Table 1 provides a comprehensive overview on the available data on treatment and outcomes of secondary upper recurrences. Thirteen studies reported explicitly on the location of recurrences (urothelial and/or local [retroperitoneum/pelvic] and/or distant) during staging of 238 patients with secondary upper tract recurrence. Of these, 210 (88.2%) patients had urothelial recurrence without evidence of local/pelvic or distant disease at the time of diagnosis. Concomitant urothelial and distant recurrence was present in 21 (8.8%) patients and concomitant urothelial and pelvic recurrence in seven (2.9%).

Modality of treatment of upper tract recurrence was reported in 14 studies in a total of 263 patients. Of these patients, 160 (60.4%) were treated with radical nephroureterectomy, which was done with preoperative or postoperative systemic chemotherapy in nine cases (3.4%). Three (1.1%) patients were treated with segmental ureterectomy, while endoscopic surgery was utilized in 21 (7.9%) patients. Systemic chemotherapy alone was administered in 17 (6.4%) patients and topical chemotherapy or immunotherapy with Bacille Calmette-Guerin (BCG) in nine (3.4%). In 53 (33.1%) patients some kind of surgical treatment was performed but not further defined in the respective publications.

Survival outcomes after treatment of secondary upper tract recurrence were reported in 13 studies including a total of 464 patients. Survival data with regard to duration of follow-up was available in nine studies with a median follow-up of 88 mo (range: 26–126). Overall survival status with information on disease status was reported in 363 patients. Of these, 259 (55.2%) died of disease and 58 (12.4%) died of other causes. Thirty-three (7.0%) patients were living without evidence of disease and 13 were alive with disease (2.8%). Overall survival status without information on disease status was additionally reported in 101 patients. Of these, 58 (12.4%) were reported to be alive and 43 (9.2%) to have died.

Altogether, these findings suggest that although most recurrences were detected in nonmetastatic stages, outcomes were poor possibly due to the presence of micrometastatic disease at the time of surgery. These data reinforce our suggestion for a risk-adapted approach to identify recurrences at the earliest possible to stage in order to treat in a curative intent. However, there is some evidence supporting renal-sparing approaches for the treatment of upper tract recurrences with low-grade, low-volume disease [42]. These include endoscopic ablation of tumor or open kidney-sparing surgery with reconstruction of the upper tract [1]. Similar to patients with urethral CIS, those with CIS of the upper tract can be managed effectively with antegrade instillation of BCG via a percutaneous nephrostomy [43].

3.4.2. Treatment of urethral recurrences

Table 2 provides a comprehensive overview of the available data on recurrence patterns, treatment, and outcomes of patients with secondary urethral recurrences. Eight studies reported on recurrence patterns in 51 patients with secondary urethral recurrences after RC. Urothelial recurrence was identified in the urethra only in 34 (66.7%) of the patients. Urethral plus distant recurrences were present in 11 (21.6%). Concomitant urethral and pelvic recurrences were noted in four (7.8%) patients and concomitant urethral, pelvic, and distant recurrences in two (3.9%).

The modality of treatment of urethral recurrence was reported in 10 studies including 223 patients. Of these patients, 153 (66.2%) were treated with partial or complete urethrectomy. Systemic chemotherapy and/or radiotherapy were utilized in 34 (14.7%) patients, of whom eight underwent also surgery. Topical chemotherapy or immunotherapy with BCG was administered in 18 (7.8%) patients. Transurethral resection was conducted alone in three patients (1.3%). In 15 (6.5%) patients some kind of surgery was performed but not further defined in the respective publications.

Survival outcomes after treatment of urethral recurrence were reported in nine studies including a total of 202 patients with a median follow-up of 97 mo (range: 29–155). Overall survival status with information on disease status was reported in 162 patients. Of these, 87 (43.1%) patients died of disease and 55 (27.2%) died of other causes. Nineteen (9.4%) patients were living without evidence of disease and one was alive with disease (0.5%). Twenty-four (11.9%) patients were reported to be alive and 16 (7.9%) to have died with no further information on disease status at the time of analysis.

As for secondary upper tract recurrences, outcomes after treatment of urethral recurrence are poor despite use of

extirpative surgery. Therefore, the question arises whether prophylactic urethrectomy may provide a prognostic benefit in those at high risk of urethral recurrence.

At RC, urethrectomy is typically a part of the procedure in women when OBS is not planned, whereas in men there is no conclusive evidence to support the use of prophylactic urethrectomy routinely at the time of RC. In men, the use of prophylactic urethrectomy at RC was investigated in a Surveillance, Epidemiology, and End Results analysis including 2401 men treated with RC for BC [44]. Of these, a total of 195 men (8.1%) underwent urethrectomy for urethral recurrences or a malignant urethral margin as detected by permanent histological analysis. Patients were subdivided into two groups: immediate (within 6 wk after RC) or delayed urethrectomy (6 wk after RC or later). As expected, patients who underwent immediate urethrectomy had a higher rate of stage T4 disease compared with those who underwent delayed urethrectomy (33% vs 16%, $p < 0.001$). Performance of immediate urethrectomy did not confer a statistically significant survival benefit compared with delayed urethrectomy (hazard ratio = 0.775, 95% confidence interval: 0.59–1.01, $p = 0.063$). Nonetheless, in our opinion, as urethrectomy is technically easy and less time-consuming in women, those who do not receive an OBS should undergo concurrent urethrectomy at RC to eliminate the risk of malignant transformation of the remnant urethral urothelium. For patients diagnosed with urethral CIS after OBS, while urethrectomy with conversion to a conduit diversion remains an option, a urethra-preserving strategy with transurethral resection followed by adjuvant BCG instillation therapy has been reported as well [1,43,45,46]. In one series, intraurethral application of BCG in six patients with CIS resulted in complete response in five but was ineffective in patients with papillary or invasive tumors [47]. There is a lack of data differentiating between treatment options in low- and high-grade urethral recurrences after OBS. While high-grade invasive recurrences in the urethra often necessitate radical surgery [1], it is the authors' opinion that patients with low-grade or Ta recurrences can be managed initially with resection and intraurethral instillation therapy.

3.5. Is there a rationale for implementing surveillance regimens for secondary urothelial tumors?

Generally, patients with SUTs after RC have only a beneficial long-term prognosis if tumors are detected in noninvasive or early invasive stages [23]. In line with these findings, a growing body of evidence supports the assumption that detection of SUTs at an asymptomatic stage is associated with prolonged survival [46,48], which also translates into significantly improved cancer-specific survival [46]. Therefore, in order to improve outcomes, it is essential to firstly understand the impact of follow-up investigations on the detection of SUTs. In a meta-analysis of 22 retrospective studies, it was reported that secondary UTUCs after RC were diagnosed by routine follow-up investigations in a total of ~37% of the patients [6]. Among these patients, tumors were detected as a result of suspicious upper tract imaging in ~30% and positive urinary cytology in ~7%. For patients who were followed-up with cytological examinations only, the rate was 1.8/1000 compared with 7.6/1000 for those who also had upper urinary tract imaging during follow-up. Thus, the incidence of secondary UTUC depends on the modality of surveillance.

Risk factors for secondary UTUC and urethral carcinoma are similar and reflect the propensity of the remnant urothelium for pan-urothelial disease, for example, positive urothelial (ureteral or urethral [including prostatic urethra]) disease, CIS of the bladder, and multifocal nonmuscle invasive disease prior to RC. As only a minority (10–20%) of cystectomized patients exhibits (one or several of) these risk factors it is reasonable to implement a surveillance regimen for SUTs for this specific group of patients where the yield of detecting SUT is increased.

3.6. How should we survey the upper tract and urethra after radical cystectomy?

Surveillance of the upper tract and urethra after RC aims to monitor for oncological and functional abnormalities in order to detect them at the earliest possible stage and confer a therapeutic benefit. The majority of patients treated for secondary urethral malignancy after RC presents initially with symptoms (~57%) and only one-third due to a positive urinary cytology, while a minority (~10%) undergo prophylactic urethrectomy [49]. In this regard, it has been demonstrated that the detection of asymptomatic urothelial recurrences is associated with an approximately 30% reduction in the risk of mortality (hazard ratio = 0.69, 95% confidence interval: 0.59–0.79) [50].

For oncological surveillance, the intensity of follow-up regimens should depend primarily on the time since RC and the presence of risk factors for recurrence. Secondary urothelial tumors develop mainly in patients with histological features of panurothelial disease at RC. Given the rarity but clinical relevance of SUTs after RC, all patients with histologic features of panurothelial disease should be considered for routine surveillance irrespective of number of risk factors. Yet, as the number of risk factors has shown to impact on the incidence of secondary urothelial tumors [9] the intensity of surveillance should be based on a risk-adapted strategy [9]. We submit that the presence of risk factors should be an impetus to consider a more intense follow-up regimen for the upper tract and urethra: (1) bladder neck (in women) and prostatic urethral involvement, (2) multifocality, (3) history of nonmuscle-invasive BC, and (4) positive ureteral and/or urethral disease on permament sections.

Follow-up investigations should be based on history, physical examination, urinary cytology with urethral washings in case of a retained urethra, cross-sectional imaging of the upper tract, and when indicated, urethroscopy. Of note, by contrast to prior series [51], recent studies report on high sensitivity and specificity rates of 80–82% and 85–97%, respectively, of urinary cytology for the detection of recurrences in the remnant urothelium after RC while urine analyses by fluorescence in situ hybridization do not result

in higher accuracy rates [52,53]. A recent report by Yafi et al [54] investigated patterns of recurrence among 1890 patients treated with RC for bladder cancer. Annual urinary cytology was recommended as optional in all cystectomized patients irrespective of stage every 12 mo postoperatively until completion of the 5th postoperative year. In our opinion, as voided urinary cytology (or urethral washings) is a simple, cheap, and easily performable diagnostic procedure, it should be conducted at least annually in patients with risk factors for pan-urothelial disease for the 1st 5 yr after RC. In case of positive findings a diagnostic urethroscopy and cross-sectional imaging of the upper tract should be performed along with biopsy assessment of the urethra and upper tract in case of suspicious findings.

In addition, combined cytological evaluation and quantitative digital cytometry has shown to improve the detection of malignant cells in urine samples after diversion [55]. Yet, it has to be stated that the exact frequency and duration of surveillance of the remnant urothelium after RC remain to be determined. Admittedly, prospective trials are needed to demonstrate whether an intense surveillance regimen is prognostically superior to a less-intense or symptom-oriented strategy for patients who show several histological features of panurothelial disease at RC.

4. Conclusions

Secondary urothelial tumors occur in approximately 4–10% of patients following RC and are often associated with adverse prognosis, in part due to delayed diagnosis. Indeed, nephrouretectomy and urethrectomy can be curative in noninvasive and early invasive disease stages. There is a need for early diagnosis and treatment of urethral recurrences as they are often detected at late stages with worse outcomes. As such, follow-up based on a risk-adapted strategy should be adopted for patients with histological features of panurothelial disease to facilitate early detection in those at high risk of recurrence and avoid overtesting patients at low risk for subsequent metachronous urothelial tumor development.

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

Study concept and design: Gakis, Kassouf.
Acquisition of data: Gakis.
Analysis and interpretation of data: Gakis, Black, Bochner, Stenzl, Thalmann, Kassouf.
Drafting of the manuscript: Gakis.
Critical revision of the manuscript for important intellectual content: Gakis, Black, Bochner, Stenzl, Thalmann, Kassouf.
Statistical analysis: Gakis.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Kassouf.
Other: None.

Financial disclosures: Georgios Gakis certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

References

[1] Gakis G, Efstathiou J, Lerner SP, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2013;63:45–57. http://dx.doi.org/10.1016/j.eururo.2012.08.009.

[2] Denzinger S, Mohren K, Knuechel R, et al. Improved clonality analysis of multifocal bladder tumors by combination of histopathologic organ mapping, loss of heterozygosity, fluorescence in situ hybridization, and p53 analyses. Hum Pathol 2006;37:143–51. http://dx.doi.org/10.1016/j.humpath.2005.10.014.

[3] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1. http://dx.doi.org/10.1186/2046-4053-4-1.

[4] Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. PLoS Med 2010;7:e1000251. http://dx.doi.org/10.1371/journal.pmed.1000251.

[5] Linder BJ, Boorjian SA, Hudolin T, et al. Late recurrence after radical cystectomy: patterns, risk factors and outcomes. J Urol 2014;191:1256–61. http://dx.doi.org/10.1016/j.juro.2013.11.103.

[6] Picozzi S, Ricci C, Gaeta M, et al. Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13 185 patients. J Urol 2012;188:2046–54. http://dx.doi.org/10.1016/j.juro.2012.08.017.

[7] Takayanagi A, Masumori N, Takahashi A, Takagi Y, Tsukamoto T. Upper urinary tract recurrence after radical cystectomy for bladder cancer: incidence and risk factors. Int J Urol 2012;19:229–33. http://dx.doi.org/10.1111/j.1442-2042.2011.02916.x.

[8] Satkunasivam R, Hu B, Metcalfe C, et al. Utility and significance of ureteric frozen section analysis during radical cystectomy. BJU Int 2016;117:463–8. http://dx.doi.org/10.1111/bju.13081.

[9] Volkmer BG, Schnoeller T, Kuefer R, Gust K, Finter F, Hautmann RE. Upper urinary tract recurrence after radical cystectomy for bladder cancer—who is at risk? J Urol 2009;182:2632–7. http://dx.doi.org/10.1016/j.juro.2009.08.046.

[10] Boorjian SA, Kim SP, Weight CJ, Cheville JC, Thapa P, Frank I. Risk factors and outcomes of urethral recurrence following radical cystectomy. Eur Urol 2011;60:1266–72. http://dx.doi.org/10.1016/j.eururo.2011.08.030.

[11] Huguet J, Monllau V, Sabate S, et al. Diagnosis, risk factors, and outcome of urethral recurrences following radical cystectomy for bladder cancer in 729 male patients. European urology 2008;53:785–92. http://dx.doi.org/10.1016/j.eururo.2007.06.045.

[12] Perlis N, Turker P, Bostrom PJ, et al. Upper urinary tract and urethral recurrences following radical cystectomy: review of risk factors and outcomes between centres with different follow-up protocols. World J Urol 2013;31:161–7. http://dx.doi.org/10.1007/s00345-012-0905-2.

[13] Gakis G, Stenzl A. Considerations for orthotopic diversions in women. Curr Opin Urol 2015;25:550–4. http://dx.doi.org/10.1097/MOU. 0000000000000224.

[14] Cho KS, Seo JW, Park SJ, et al. The risk factor for urethral recurrence after radical cystectomy in patients with transitional cell carcinoma of the bladder. Urol Int 2009;82:306–11. http://dx.doi.org/10.1159/000209363.

[15] Balci U, Dogantekin E, Ozer K, Gorgel SN, Girgin C, Dincel C. Patterns, risks and outcomes of urethral recurrence after radical cystectomy for urothelial cancer; over 20 year single center experience. Int J Surg 2015;13:148–51. http://dx.doi.org/10.1016/j.ijsu.2014.12.006.

[16] Djaladat H, Mitra AP, Miranda G, Skinner EC, Daneshmand S. Radical cystectomy and orthotopic urinary diversion in male patients with pT4a urothelial bladder carcinoma: oncological outcomes. Int J Urol 2013;20:1229–33. http://dx.doi.org/10.1111/iju.12133.

[17] Stein JP, Clark P, Miranda G, Cai J, Groshen S, Skinner DG. Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. J Urol 2005;173:1163–8. http://dx.doi.org/10.1097/01.ju.0000149679.56884.0f.

[18] Stein JP, Penson DF, Wu SD, Skinner DG. Pathological guidelines for orthotopic urinary diversion in women with bladder cancer: a review of the literature. The Journal of urology 2007;178:756–60. http://dx.doi.org/10.1016/j.juro.2007.05.013.

[19] Niegisch G, Hulsbergen van de Kaa C, Ploeg M, Hendricksen K, Witjes J. Do orthotopic ileal diversions induce immunological changes in retained urethral tissue? Bladder Cancer 2015;1:97–103. http://dx.doi.org/10.3233/BLC-140001.

[20] Kim HS, Moon KC, Jeong CW, Kwak C, Kim HH, Ku JH. The clinical significance of intraoperative ureteral frozen section analysis at radical cystectomy for urothelial carcinoma of the bladder. World J Urol 2015;33:359–65. http://dx.doi.org/10.1007/s00345-014-1306-5.

[21] Osman Y, El-Tabey N, Abdel-Latif M, Mosbah A, Moustafa N, Shaaban A. The value of frozen-section analysis of ureteric margins on surgical decision-making in patients undergoing radical cystectomy for bladder cancer. BJU Int 2007;99:81–4. http://dx.doi.org/10.1111/j.1464-410X.2006.06567.x.

[22] Raj GV, Tal R, Vickers A, et al. Significance of intraoperative ureteral evaluation at radical cystectomy for urothelial cancer. Cancer 2006;107:2167–72. http://dx.doi.org/10.1002/cncr.22238.

[23] Gakis G, Schilling D, Perner S, Schwentner C, Sievert KD, Stenzl A. Sequential resection of malignant ureteral margins at radical cystectomy: a critical assessment of the value of frozen section analysis. World J Urol 2011;29:451–6. http://dx.doi.org/10.1007/s00345-010-0581-z.

[24] Loeser A, Katzenberger T, Vergho DC, Kocot A, Burger M, Riedmiller H. Frozen section analysis of ureteral margins in patients undergoing radical cystectomy for bladder cancer: differential impact of carcinoma in situ in the bladder on reliability and impact on tumour recurrence in the upper urinary tract. Urol Int 2014;92:50–4. http://dx.doi.org/10.1159/000353230.

[25] Hoang AN, Agarwal PK, Walton-Diaz A, et al. Clinical significance of ureteric 'ip lesions' at the time of radical cystectomy: the M.D. Anderson experience and literature review BJU international 2014;113:E28–33. http://dx.doi.org/10.1111/bju.12344.

[26] Yossepowitch O, Dalbagni G, Golijanin D, et al. Orthotopic urinary diversion after cystectomy for bladder cancer: implications for cancer control and patterns of disease recurrence. J Urol 2003;169:177–81. http://dx.doi.org/10.1097/01.ju.0000041411.03266.14.

[27] Johnson DE, Wishnow KI, Tenney D. Are frozen-section examinations of ureteral margins required for all patients undergoing radical cystectomy for bladder cancer? Urology 1989;33:451–4.

[28] Tollefson MK, Blute ML, Farmer SA, Frank I. Significance of distal ureteral margin at radical cystectomy for urothelial carcinoma. J Urol 2010;183:81–6. http://dx.doi.org/10.1016/j.juro.2009.08.158.

[29] Westerman ME, Parker WP, Viers BR, et al. Malignant ureteroenteric anastomotic stricture following radical cystectomy with urinary diversion: patterns, risk factors, and outcomes. Urol Oncol 2016;34:485.e1–485.e6. http://dx.doi.org/10.1016/j.urolonc.2016.06.008.

[30] Schumacher MC, Scholz M, Weise ES, Fleischmann A, Thalmann GN, Studer UE. Is there an indication for frozen section examination of the ureteral margins during cystectomy for transitional cell carcinoma of the bladder? J Urol 2006;176:2409–13. http://dx.doi.org/10.1016/j.juro.2006.07.162.

[31] Gakis G, Ali-El-Dein B, Babjuk M, et al. Urethral recurrence in women with orthotopic bladder substitutes: A multi-institutional study. Urol Oncol 2015;33:204.e217–23. http://dx.doi.org/10.1016/j.urolonc.2015.01.020.

[32] Lebret T, Herve JM, Barre P, et al. Urethral recurrence of transitional cell carcinoma of the bladder. Predictive value of preoperative latero-montanal biopsies and urethral frozen sections during prostatocystectomy. Eur Urol 1998;33:170–4.

[33] Akkad T, Gozzi C, Deibl M, et al. Tumor recurrence in the remnant urothelium of females undergoing radical cystectomy for transitional cell carcinoma of the bladder: long-term results from a single center. J Urol 2006;175:1268–71. http://dx.doi.org/10.1016/S0022-5347(05)00643-9.

[34] Osman Y, Mansour A, El-Tabey N, et al. Value of routine frozen section analysis of urethral margin in male patients undergoing radical cystectomy in predicting prostatic involvement. Int Urol Nephrol 2012;44:1721–5. http://dx.doi.org/10.1007/s11255-012-0276-z.

[35] Sureka SK, Yadav A, Arora S, Kapoor R, Mandhani A. Is frozen section analysis of the urethra at the time of radical cystectomy and orthotopic neobladder urinary diversion mandatory? Indian J Urol 2015;31:349–53. http://dx.doi.org/10.4103/0970-1591.163309.

[36] Stein JP, Cote RJ, Freeman JA, et al. Indications for lower urinary tract reconstruction in women after cystectomy for bladder cancer: a pathological review of female cystectomy specimens. J Urol 1995;154:1329–33.

[37] Gordetsky J, Bivalacqua T, Schoenberg M, Epstein JI. Ureteral and urethral frozen sections during radical cystectomy or cystoprostatectomy: an analysis of denudation and atypia. Urology 2014;84:619–23. http://dx.doi.org/10.1016/j.urology.2014.05.037.

[38] Mazzucchelli R, Barbisan F, Santinelli A, et al. Prediction of prostatic involvement by urothelial carcinoma in radical cystoprostatectomy for bladder cancer. Urology 2009;74:385–90. http://dx.doi.org/10.1016/j.urology.2009.03.010.

[39] von Rundstedt FC, Lerner SP, Godoy G, et al. Usefulness of transurethral biopsy for staging the prostatic urethra before radical cystectomy. J Urol 2015;193:58–63. http://dx.doi.org/10.1016/j.juro.2014.07.114.

[40] Gaya JM, Matulay J, Badalato GM, Holder DD, Hruby G, McKiernan J. The role of preoperative prostatic urethral biopsy in clinical decision-making at the time of radical cystectomy. Can J Urol 2014;21:7228–33.

[41] Kassouf W, Spiess PE, Brown GA, et al. Prostatic urethral biopsy has limited usefulness in counseling patients regarding final urethral margin status during orthotopic neobladder reconstruction. J Urol 2008;180:164–7. http://dx.doi.org/10.1016/j.juro.2008.03.037.

[42] Gakis G, Schubert T, Alemozaffar M, et al. Update of the ICUD-SIU consultation on upper tract urothelial carcinoma 2016: treatment of localized high-risk disease. World J Urol. In press. http://dx.doi.org/10.1007/s00345-016-1819-1

[43] Giannarini G, Birkhauser FD, Recker F, Thalmann GN, Studer UE. Bacillus Calmette-Guerin failure in patients with non-muscle-invasive urothelial carcinoma of the bladder may be due to the urologist's failure to detect urothelial carcinoma of the upper

urinary tract and urethra. Eur Urol 2014;65:825–31. http://dx.doi.org/10.1016/j.eururo.2013.09.049.

[44] Nelles JL, Konety BR, Saigal C, Pace J, Lai J. Urologic Diseases in America Project Urethrectomy following cystectomy for bladder cancer in men: practice patterns and impact on survival. J Urol 2008;180:1933–6. http://dx.doi.org/10.1016/j.juro.2008.07.039.

[45] Gakis G, Witjes JA, Comperat E, et al. EAU guidelines on primary urethral carcinoma. Eur Urol 2013;64:823–30. http://dx.doi.org/10.1016/j.eururo.2013.03.044.

[46] Giannarini G, Kessler TM, Thoeny HC, Nguyen DP, Meissner C, Studer UE. Do patients benefit from routine follow-up to detect recurrences after radical cystectomy and ileal orthotopic bladder substitution? Eur Urol 2010;58:486–94. http://dx.doi.org/10.1016/j.eururo.2010.05.041.

[47] Varol C, Thalmann GN, Burkhard FC, Studer UE. Treatment of urethral recurrence following radical cystectomy and ileal bladder substitution. J Urol 2004;172:937–42. http://dx.doi.org/10.1097/01.ju.0000135626.9158.7.c8.

[48] Boorjian SA, Tollefson MK, Cheville JC, Costello BA, Thapa P, Frank I. Detection of asymptomatic recurrence during routine oncological followup after radical cystectomy is associated with improved patient survival. J Urol 2011;186:1796–802. http://dx.doi.org/10.1016/j.juro.2011.07.005.

[49] Clark PE, Stein JP, Groshen SG, et al. The management of urethral transitional cell carcinoma after radical cystectomy for invasive bladder cancer. J Urol 2004;172:1342–7.

[50] Stewart-Merrill SB, Alahdab F, Benkhadra K, et al. Oncologic surveillance in bladder cancer following radical cystectomy: A systematic review and meta-analysis. Urol Oncol 2016;34:. http://dx.doi.org/10.1016/j.urolonc.2015.11.025, 236.e213–21.

[51] Yoshimine S, Kikuchi E, Matsumoto K, et al. The clinical significance of urine cytology after a radical cystectomy for urothelial cancer. Int J Urol 2010;17:527–32. http://dx.doi.org/10.1111/j.1442-2042.2010.02516.x.

[52] Chen H, Liu L, Pambuccian SE, Barkan GA, Quek ML, Wojcik EM. Urine cytology in monitoring recurrence in urothelial carcinoma after radical cystectomy and urinary diversion. Cancer Cytopathol 2016;124:273–8. http://dx.doi.org/10.1002/cncy.21650.

[53] Fernandez MI, Parikh S, Grossman HB, et al. The role of FISH and cytology in upper urinary tract surveillance after radical cystectomy for bladder cancer. Urol Oncol 2012;30:821–4. http://dx.doi.org/10.1016/j.urolonc.2010.08.006.

[54] Yafi FA, Aprikian AG, Fradet Y, et al. Surveillance guidelines based on recurrence patterns after radical cystectomy for bladder cancer: the Canadian Bladder Cancer Network experience. BJU Int 2012;110:1317–23. http://dx.doi.org/10.1111/j.1464-410X.2012.11133.x.

[55] Caraway NP, Khanna A, Payne L, Kamat AM, Katz RL. Combination of cytologic evaluation and quantitative digital cytometry is reliable in detecting recurrent disease in patients with urinary diversions. Cancer 2007;111:323–9. http://dx.doi.org/10.1002/cncr.22950.

[56] Furukawa J, Miyake H, Hara I, Takenaka A, Fujisawa M. Upper urinary tract recurrence following radical cystectomy for bladder cancer. Int J Urol 2007;14:496–9.

[57] Kim SH, Yang HK, Lee JH, Lee ES. A retrospective analysis of incidence and its associated risk factors of upper urinary tract recurrence following radical cystectomy for bladder cancer with transitional cell carcinoma: the significance of local pelvic recurrence and positive lymph node. PloS one 2014;9:e96467.

[58] Mitra AP, Alemozaffar M, Harris BN, Schuckman AK, Skinner EC, Daneshmand S. Outcomes after urothelial recurrence in bladder cancer patients undergoing radical cystectomy. Urology 2014;84:1420–6.

[59] Rink M, Ehdaie B, Cha EK, et al. Stage-specific impact of tumor location on oncologic outcomes in patients with upper and lower tract urothelial carcinoma following radical surgery. Eur Urol 2012;62:677–84.

[60] Sanderson KM, Cai J, Miranda G, Skinner DG, Stein JP. Upper tract urothelial recurrence following radical cystectomy for transitional cell carcinoma of the bladder: an analysis of 1,069 patients with 10-year followup. J Urol 2007;177:2088–94.

[61] Tran W, Serio AM, Raj GV, et al. Longitudinal risk of upper tract recurrence following radical cystectomy for urothelial cancer and the potential implications for long-term surveillance. J Urol 2008;179:96–100.

[62] Umbreit EC, Crispen PL, Shimko MS, Farmer SA, Blute ML, Frank I. Multifactorial, site-specific recurrence model after radical cystectomy for urothelial carcinoma. Cancer 2010;116:3399–407.

[63] Ichihara K, Kitamura H, Masumori N, Fukuta F, Tsukamoto T. Transurethral prostate biopsy before radical cystectomy remains clinically relevant for decision-making on urethrectomy in patients with bladder cancer. Int J Clin Oncol 2013;18:75–80.

[64] Jentzmik F, Schrader AJ, de Petriconi R, et al. The ileal neobladder in female patients with bladder cancer: long-term clinical, functional, and oncological outcome. World J Urol 2012;30:733–9.

[65] Taylor JM, Spiess PE, Kassouf W, et al. Management of urethral recurrence after orthotopic urinary diversion. BJU Int 2010;106:56–61.