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Does Ureteral Stenting Increase the Risk of Metachronous Upper Tract Urothelial Carcinoma in Patients with Bladder Tumors? A Systematic Review and Meta-analysis

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Abbreviations and Acronyms

BCa = bladder cancer
CT = computerized tomography
OR = odds ratio
RC = radical cystectomy
RCT = randomized controlled trial
TURBT = transurethral resection of bladder tumor
UTUC = upper tract urothelial cancer
UUT = upper urinary tract

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Purpose: Ureteral stenting in patients with bladder cancer may become necessary in order to protect the ureteral orifice during transurethral resection of the tumor or for relief of upper urinary tract obstruction. However, it is believed to increase metachronous upper tract urothelial carcinoma risk.

Materials and Methods: We performed a systematic review and meta-analysis of studies comparing ureteral stenting versus nephrostomy or no drainage with regard to the risk of metachronous upper tract urothelial carcinoma. Records were identified through database searches and sources of grey literature up to October 2020 (PROSPERO: CRD42020178298).

Results: Five studies (3,309 individuals) were included. Overall, 278 ureteral stents were placed and 20 (7.2%) patients developed metachronous upper tract urothelial carcinoma, while 131 patients were treated with nephrostomy and 3 (2.3%) cases of metachronous upper tract urothelial carcinoma occurred. Patients treated with ureteral stents had a higher likelihood of metachronous upper tract urothelial carcinoma compared to no stents (OR: 3.49, 95% CI: 1.43–8.48, I^2=52%) and no upper urinary tract drainage (OR: 3.37, 95% CI: 1.49–7.63, I^2=45%). No difference with regard to metachronous upper tract urothelial carcinoma was observed between stent and nephrostomy (OR: 3.07, 95% CI: 0.41–22.98, I^2=54%). For the same outcomes, no difference was noted for patients with hydronephrosis. The level of evidence for all measures was evaluated as low.

Conclusions: Stenting as a preventive measure after resection of tumors involving the orifice should be avoided, when possible, as it increases the risk of metachronous upper tract urothelial carcinoma. In cases of hydronephrosis, drainage with either nephrostomy or stent is recommended depending on individual patient cases as both interventions do not differ regarding metachronous upper tract urothelial carcinoma risk.

Key Words: urinary bladder neoplasms; carcinoma, transitional cell; stents; hydronephrosis; meta-analysis

UTUC accounts for 5% to 7% of all renal tumors and 5% to 10% of all urothelial tumors of the urinary tract, with an annual incidence of 1 to 2 cases per 100,000 individuals in the U.S.A.[1,2] UTUC and urothelial BCa share the same molecular pathogenetic framework.[3] Therefore, patients with UTUC may have a history of BCa in up to 41% of cases[4] or present with concomitant BCa in approximately 20% of cases,[5] induced by the so-called epigenetic pan-urothelial "field defect".[6] A proportion of patients with BCa present

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with synchronous UTUC (1.8%)[7] or develop metachronous UTUC (0.7% to 4%).[8–11] Following RC, the overall risk of metachronous UTUC ranges from 2% to 7%, with most tumors occurring within the first 2 to 4 years after RC.[11,12]

Drainage of the UUT by retrograde ureteral stenting or percutaneous nephrostomy may become necessary in patients with BCa in order to either treat or prevent UUT obstruction. As a preventive measure, stents are placed during TURBT to avoid ureteric stricture and subsequent obstruction following deep resection-destruction of a ureteral orifice involved by the tumor.[13] As treatment, UUT drainage by means of ureteral stent or nephrostomy is occasionally necessary in muscle invasive BCa in order to maintain or improve renal function before definitive treatment with neoadjuvant chemotherapy and/or cystectomy.[14]

It is believed that ureteral stenting increases the risk of UTUC in patients with BCa and no history of UTUC.[15] The proposed mechanism is that stenting abolishes the anti-reflux mechanism of the intramural ureter and Waldeyer's sheath creating a refluxing system, which enables cancer cell seeding and implantation from the bladder to the UUT.[16,17] Furthermore, manipulation during retrograde stenting may contribute to UUT seeding by actively flushing BCa cells to the UUT.

There is discordance in the current urological practice regarding the optimal management in this clinical scenario. In the absence of specific guideline recommendation against stenting as a risk factor for UTUC,[18–20] management is left to the urologist's judgment with some authorities advocating avoiding stenting after resection of tumors involving the ureteral orifice.[21–23] On the other hand, UUT obstruction is managed with percutaneous nephrostomy, retrograde stenting or conservative treatment depending on the individual case.[24] Still, the clinical decision, in this context, is left to individual clinical judgment.[25,26] Against this background, we generated a systematic review and meta-analysis aiming to identify whether ureteral stenting for either de-obstruction of the UUT or protection of the UUT following resection of the ureteral orifice is a risk factor for metachronous UTUC in patients with BCa.

MATERIALS AND METHODS

Search Strategy

The protocol for this systematic review and meta-analysis has been registered in PROSPERO (ID: CRD42020178298) and was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (supplementary Appendix 1, https://www.jurology.com).[27] Two independent reviewers (NP, TK) systematically searched Medline, Scopus and the Cochrane Library from inception up to October 2020. We hand-searched sources of grey literature, including conference proceedings, and perused the reference lists of all eligible studies and relevant reviews. The search strategy is presented in detail in supplementary Appendix 2 (https://www.jurology.com).

Search Eligibility Criteria

We included RCTs and observational studies of patients with nonmuscle invasive or muscle invasive BCa comparing ureteral stenting versus nephrostomy or no UUT drainage. We considered single arm or comparative studies reporting relevant data published in any language. On the contrary, we excluded studies on patients with BCa already treated with RC and urinary diversion, case reports or case series and animal studies.

Data Extraction and Quality Assessment

NP and TK screened all identified records for eligibility. The authors of the included studies were directly contacted with requests for missing data or further clarifications. Information regarding study and patient characteristics, intervention details and outcomes were tabulated in a predefined Microsoft Excel® spreadsheet. Any disagreements were resolved by consensus.

We employed a modified version of the Newcastle-Ottawa Scale for cohort studies to assess independently by 2 authors (PS, NP) the quality of all included records (supplementary Appendix 3, https://www.jurology.com). Based on the Newcastle-Ottawa Scale, each study was judged on 8 items, grouped into 3 categories that included selection of study groups, comparability of groups as well as reported outcomes.[28]

Data Synthesis, Statistical Analysis and Grading of Evidence

We performed a meta-analysis of ORs using an inverse variance random-effects model to determine the risk of metachronous UTUC for patients with BCa and ureteral stent in situ versus 1) no ureteral stent (essentially grouping patients with nephrostomy and patients with no UUT drainage), 2) nephrostomy and 3) no drainage. Accordingly, we explored the overall mortality odds of patients managed with ureteral stent versus 1) no ureteral stent, 2) nephrostomy and 3) no drainage. Moreover, we performed a subgroup analysis estimating the ORs of developing metachronous UTUC for the group of patients presenting with hydronephrosis. Similarly, we undertook another subgroup analysis based on the selection criteria of the included studies (whether they enrolled patients who underwent RC or TURBT).

Heterogeneity was evaluated with the I^2 and its significance was determined with the Cochran's Q test.[29] Values of I^2 over 50% indicate substantial heterogeneity.[29] We did not assess for publication bias due to the small number of included studies.[30] All analyses were performed using the R software (version 3.6.3). Moreover, we reported the overall strength of evidence for the risk of metachronous UTUC in all patient groups using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[31] Two authors (PS, NP) determined risk of bias, inconsistency, indirectness, imprecision and publication bias among included studies.

RESULTS

Study Results and Quality Assessment

The literature search yielded 2,012 potentially relevant records, resulting, after screening titles and abstracts, in 32 eligible articles. Ultimately, 5 retrospective cohort studies were included in the qualitative[32–36] and 4 studies were included in the quantitative synthesis of this systematic review and meta-analysis.[32–35] The step-by-step selection process is illustrated in supplementary Appendix 4 and supplementary figure 1 (https://www.jurology.com). Applying the Newcastle-Ottawa Scale, 3 studies were considered of good[32–34] and 2 of moderate quality[35,36] (supplementary table 1, https://www.jurology.com).

Study Characteristics

A total of 3,309 individuals, mean age of 69.5±8.9 years, were followed for 47.7±20.2 months. Among them, 1,539 patients (46.5%) were diagnosed with nonmuscle invasive BCa. Baseline characteristics of all included trials are depicted in the table.

Hupe et al enrolled 637 individuals from a TURBT cohort.[33] The authors included a highly heterogeneous group of patients who underwent TURBT, of whom 173 were found with muscle invasive BCa following TURBT. Twenty patients were either diagnosed with UTUC before BCa diagnosis or had concomitant BCa and UTUC. Therefore we performed our final analyses with 617 patients. Overall, 78 (12.6%) patients presented with hydronephrosis and 44 of them (56.4%) were managed with ureteral stent, while 34 (43.6%) were managed with percutaneous nephrostomy. In another 35 cases, ureteral stenting was performed during TURBT, not for hydronephrosis per se, but as a measure to prevent UUT obstruction. Within a mean followup of 14.9 months, 8 (1.3%) patients presented with metachronous UTUC and 77 (12%) deaths occurred. UUT recurrence was diagnosed by imaging or biopsy but no information on the followup of patients was provided.[33]

Kiss et al studied a RC cohort of 1005 patients.[34] Overall, 226 (22.4%) patients presented with hydronephrosis, 53 (23.4%) of whom were managed with ureteral stent, 61 (27%) with percutaneous nephrostomy and 112 (49.6%) with no UUT drainage. After a mean followup of 43.5±14.3 months, 31 (3%) patients presented with metachronous UTUC and 628 (62.5%) deaths were observed. Metachronous UTUC occurred within a median followup of 17 months (range: 3–147) from cystectomy. Preoperatively, concomitant UTUC had been excluded by intravenous pyelography or CT-urography. After RC, patients were evaluated at 3, 6 and 12 months during the first year, every 6 months from the second to the fifth year, and then annually as per the guidelines.[37] Monitoring consisted of chest x-ray or chest CT, renal ultrasound, urine cytology, intravenous pyelography or CT of the abdomen and pelvis. In case of suspicious findings, selective cytology from the UUT and/or ureterorenoscopy was performed and all recurrences were confirmed by cytology and/or biopsy.[34]

The study by Miest et al comprised of 1,049 patients, again from a RC cohort. Overall, 262 (25%) patients presented with hydronephrosis, of them 94 (35.9%) were managed with ureteral stent, 36 (13.7%) with percutaneous nephrostomy and 132 (50.4%) received no UUT drainage. At the end of the study followup (54.6±14.4 months), 54 (5.1%) cases of metachronous UTUC and 605 (57.7%) deaths were reported. Preoperative staging included UUT assessment by either CT-urography or magnetic resonance-urography, while the postoperative surveillance scheme was similar to that followed by Kiss et al.[34] Additionally, the authors reported ureteral and infectious complications following RC among study patients. In particular, the number of ureteroenteric anastomotic strictures, anastomotic leaks and pyelonephritis after RC did not differ significantly among patients with no hydronephrosis, hydronephrosis without drainage, nephrostomy and ureteral stent.[32]

Chou et al studied 572 patients from a TURBT cohort of new cases of nonmuscle invasive BCa but provided no information on hydronephrosis.[35] After a mean followup of 80.4±15 months, 22 (3.8%) patients developed UTUC but no information on deaths was provided. Of interest, from 31 (5.4%) of TURBT cases involving the ureteral orifice a ureteral stent was placed in 6 (19.4%) while the remaining 25 patients were managed without UUT drainage. None of the 6 stented patients developed metachronous UTUC, however 4 of the 25 patients without drainage presented with UUT recurrence. All patients were monitored every 3 months during the first year, every 6 months during years 2 to 5, and annually thereafter with cystoscopy and urine cytology.[35]

The study by Jain et al included 46 patients who underwent retrograde stenting due to UUT obstruction and resultant renal function deterioration caused by a bladder tumor.[36] After a mean followup of 28.2±4.6 months, 2 (4.3%) patients developed metachronous UTUC, both within the first year. No information regarding mortality or UUT evaluation before stenting was provided. Patients were evaluated at 3, 6 and 12 months with abdominal ultrasound, cystoscopy, urine cytology and CT or magnetic resonance imaging of the abdomen and pelvis. Since all study patients were treated with ureteral stenting and no comparative arm was present, we excluded this study from quantitative synthesis.[36]

Table. *Characteristics of all included studies*

Included Series	Population	No. Participants	Mean Mos Followup±SD	Age (yrs)	No. Male (%)	Mean kg/m^2 Body Mass Index±SD	No. Smokers (%)	No. BCa Stage (%)	No. Concomitant Carcinoma In Situ (%)	No. Grade (%)	No. Ureteral Orifice Involvement (%)	No. Deaths (%)	No. Metachronous UTUC (%)
Chou 2006[35] Taiwan	Superficial transitional cell carcinoma of bladder	572	80.4±15	Not available	Not available	Not available	Not available	Ta or T1: 572 (100)	Not available	Not available	31 (5.4)	Not available	22 (3.8)
Hupe 2020[33] Germany	Pts with BCa undergoing TURBT	637	14.9	72.5±11.5	506 (79.4)	Not available	Not available	Papillary urothelial neoplasm of low malignant potential: 3 (0.5) pTa: 266 (41.7) pTis: 3 (0.5) pT1: 191 (29.9) pT2: 170 (26.7) pT3: 2 (0.3) pT4: 1 (0.2) Unknown: 1 (0.2)	48 (7.5)	Low: 130 (20.4) High: 477 (74.9) Unknown: 30 (4.7)	Not available	77 (12.1)	8 (1.3)
Jain 2017[36] India	Renal failure management in presence of bladder tumor	46	28.2±4.6	48.2±18.6	43 (93.5)	22.4±4.4	41 (89.1)	pT1: 2 (4.4) pT2: 6 (13) pT3: 38 (82.6)	5 (10.9)	Low: 10 (21.7) High: 36 (78.3)	Not available	Not available	2 (4.3)
Kiss 2017[34] Switzerland	Pts with BCa undergoing RC + urinary diversion	1,005	43.5±14.3	68.7±2.7	714 (71)	25.5±1.1	603 (60)	pTa/pTis: 79 (7.8) pT1: 141 (14) pT2: 303 (30.2) pT3: 374 (37.3) pT4: 108 (10.7) Positive lymph nodes: 277 (27.6)	459 (45.7)	G1/G2: 38 (3.8) G3: 967 (96.2)	Not available	628 (62.5)	31 (3.1)
Miest 2020[32] USA	Pts with BCa undergoing RC + urinary diversion without prior UTUC	1,049	54.6±14.4	69.4	873 (83.2)	Not available	Not available	pTa: 27 (2.6) pTis: 105 (10) pT1: 149 (14.2) pT2: 260 (24.8) pT3: 404 (38.5) pT4: 99 (9.4) Unknown: 5 (0.5) Positive lymph nodes: 259 (24.7)	529 (50.4)	Not available	50 (4.8)	605 (57.7)	54 (5.1)

Upper Urinary Tract Drainage Characteristics

Overall, ureteral stents were placed in 278 individuals. In 237 (85.3%) patients, stenting was necessary for relief of UUT obstruction, and in 41 cases (14.7%) for prevention of ureteral stenosis and subsequent UUT obstruction following TURBT. Only the study by Kiss et al provided information regarding the time of stenting (before, during or after TURBT),[34] while none of the studies provided information regarding prior UUT manipulations. At the end of each study followup (39.2±8.9 months), 20 (7.2%) patients had developed UTUC and 101 (36.3%) had died from any cause. The reported risk factors for UTUC of patients managed with Double-J® stents and the characteristics of patients who developed metachronous UTUC are available in supplementary table 2 (https://www.jurology.com).

Overall, nephrostomies were placed in 131 patients for the management of UUT obstruction. There was no information in any of the studies as to whether percutaneous nephrostomy was placed following unsuccessful attempt at retrograde stenting. Among patients who received a nephrostomy, 3 (2.3%) cases of metachronous UTUC and 93 (71%) deaths were reported after a mean followup of 18.3±8.4 months. Data on patients managed with nephrostomy and the clinical characteristics of patients who developed UUT recurrence are presented in supplementary table 3 (https://www.jurology.com).

The majority of patients (2880) did not receive any UUT drainage; 244 (8.5%) patients, all from RC cohorts, had presented with hydronephrosis but were managed conservatively without UUT drainage. Furthermore, across all studies no information was provided regarding ureteral strictures developing at followup after resection of tumors involving the ureteral orifice. After a mean followup of 50.4±13 months, 94 (3.3%) metachronous UTUC cases and 1,127 (39.1%) deaths were reported. Data concerning cases with no UUT drainage are available in supplementary table 4 (https://www.jurology.com).

Metachronous UTUC

Four records with 3,243 participants provided comparative data on metachronous UTUC at the end of each study followup.[32–35] Comparing ureteral stent versus no ureteral stent (essentially a mixed group of patients treated with percutaneous nephrostomy or no UUT drainage) showed that patients managed with ureteral stent were at a higher risk of metachronous UTUC both in the TURBT and in the RC cohort studies (OR: 3.49, 95% CI: 1.43–8.48, $I^2=52\%$) (fig. 1, *A*). Accordingly, we separated the no ureteral stent group into no UUT drainage and nephrostomy subgroups. Patients undergoing ureteral stenting had a higher likelihood of developing metachronous UTUC compared to patients with no drainage (OR: 3.37, 95% CI: 1.49–7.63, $I^2=45\%$) (fig. 1, *B*). On the other hand, no significant difference in terms of UUT recurrence was observed between Double-J stent and nephrostomy (OR: 3.07, 95% CI: 0.41–22.98, $I^2=54\%$) (fig. 1, *C*).

Metachronous UTUC in Patients with Hydronephrosis

Three records explored the risk of developing metachronous UTUC at the end of each study followup in 566 patients with hydronephrosis.[32–34] Comparing patients who underwent ureteral stenting for relief of UUT obstruction versus no ureteral stenting (essentially nephrostomy and no UUT drainage), no significant difference for the odds of presenting with metachronous UTUC was detected both in the TURBT and in the RC cohort studies (OR: 2.58, 95% CI: 0.79–8.41, $I^2=50\%$) (fig. 2, *A*). This was also observed when assessing ureteral stenting versus no UUT drainage (OR: 1.93, 95% CI: 0.76–4.92, $I^2=28\%$) (fig. 2, *B*) and versus percutaneous nephrostomy (OR: 2.58, 95% CI: 0.79–8.41, $I^2=50\%$) (fig. 2, *C*).

Overall Mortality

Three records with 2,671 participants reported the overall number of deaths at the end of each study followup. Comparing patients with stents and without stents (namely patients receiving nephrostomy or no UUT drainage), no significant difference for the odds of mortality was detected both in the TURBT and in the RC cohort studies (OR: 1.09, 95% CI: 0.61–1.94, $I^2=71\%$) (supplementary fig. 2, *A*, https://www.jurology.com). Patients undergoing ureteral stenting had similar mortality likelihood with individuals receiving no UUT drainage (OR: 1.18, 95% CI: 0.64–2.18, $I^2=74\%$) (supplementary fig. 2, *B*, https://www.jurology.com). On the contrary, patients with stents had better survival than individuals with nephrostomy tubes (OR: 0.33, 95% CI: 0.14–0.75, $I^2=61\%$) (supplementary fig. 2, *C*, https://www.jurology.com).

Grading of Evidence

The quality of evidence for the risk of developing metachronous UTUC in patients treated with ureteral stent versus no ureteral stent, nephrostomy or no UUT drainage was downgraded to low. Overall, we detected very serious risk of bias and serious imprecisions that were attributed to the retrospective design of included studies and to the relatively small number of metachronous UTUC cases. Moreover, the included studies did not adequately control for potential confounding factors. The grading of evidence is summarized in supplementary Appendix 5 (https://www.jurology.com).

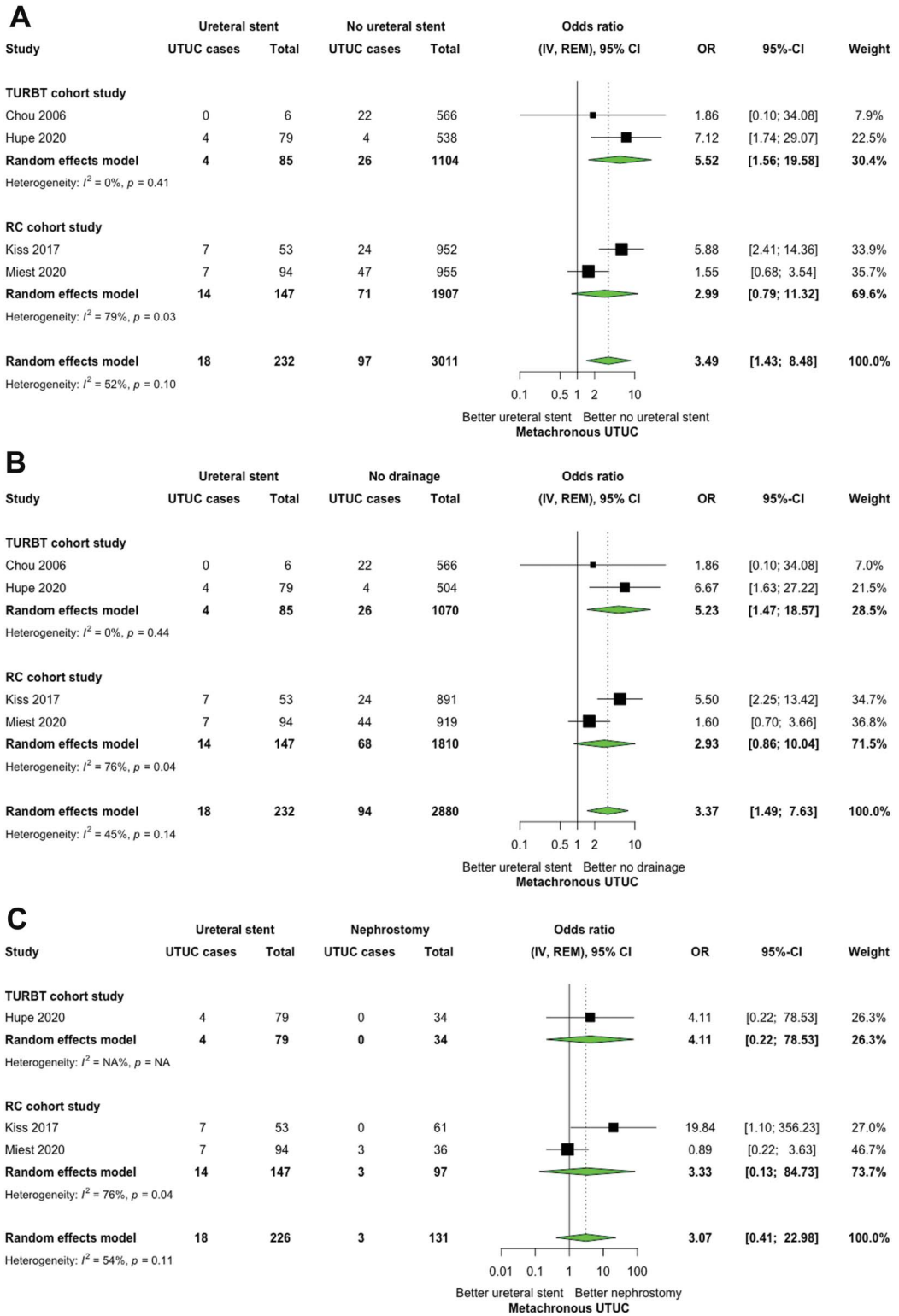

Figure 1. *A*, forest plot comparing ureteral stenting versus no stenting in terms of metachronous UTUC. *B*, forest plot comparing ureteral stenting versus no upper urinary tract drainage in terms of metachronous UTUC. *C*, forest plot comparing ureteral stenting versus percutaneous nephrostomy in terms of metachronous UTUC.

DISCUSSION

In this systematic review and meta-analysis, we demonstrated that BCa patients who were stented in order to de-obstruct the UUT or prevent impending obstruction had more than 3 times higher likelihood of metachronous UTUC compared to patients not treated with ureteral stents. This was also evident when comparing stenting versus no UUT drainage.

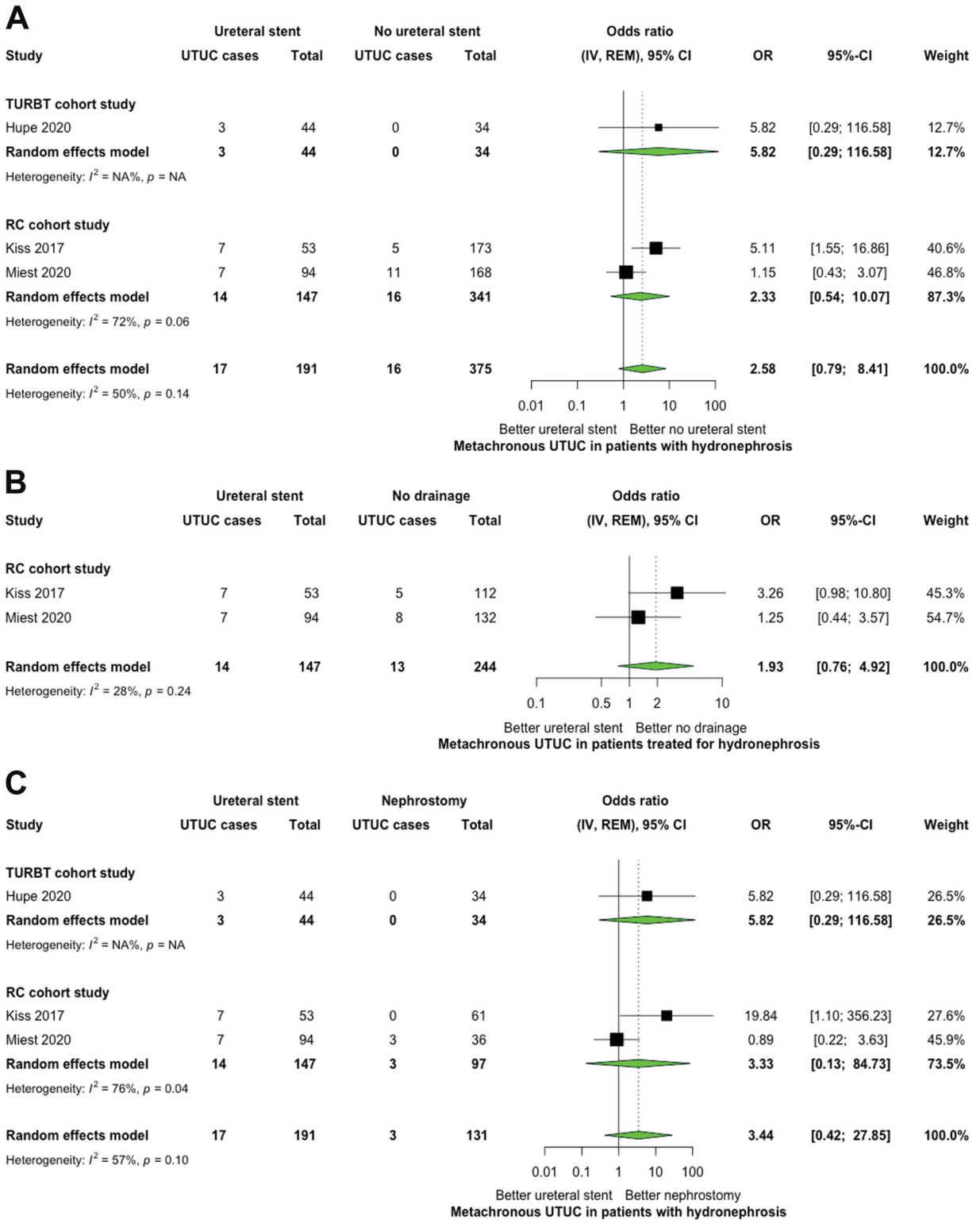

Figure 2. *A,* forest plot of patients with hydronephrosis comparing ureteral stenting versus no stenting in terms of metachronous UTUC. *B,* forest plot of patients with hydronephrosis comparing ureteral stenting versus no upper urinary tract drainage in terms of metachronous UTUC. *C,* forest plot of patients with hydronephrosis comparing ureteral stenting versus percutaneous nephrostomy in terms of metachronous UTUC.

However, when assessing only patients with hydronephrosis, no significant difference between ureteral stenting versus no ureteral stenting, percutaneous nephrostomy or no UUT drainage was observed. Accordingly, no significant difference in terms of overall mortality between ureteral stenting and no

ureteral stenting occurred. Still, the robustness of our results was considered low for all outcomes, as available evidence derived from retrospective observational studies that enrolled different populations and did not adequately control for potential confounding factors.

There is discordance and hence variation in the clinical management of the UUT in cases of BCa. The treatment plan after a wide transurethral resection of bladder tumors involving the ureteric orifice includes either no drainage or retrograde stenting as a preventive measure to avoid ureteral orifice stricture and subsequent obstruction. In cases of UUT obstruction the treatment options include no UUT drainage when RC is shortly planned, retrograde stenting or percutaneous nephrostomy. Although concerns about UUT seeding of tumor cells leading to increased risk of UUT recurrence in cases of stenting had been raised this issue has never been prospectively assessed by RCTs. In the absence of such level of evidence we provide, to our knowledge, the first systematic review and meta-analysis evaluating whether ureteral stenting in patients with BCa increases the risk of metachronous UTUC. In this scope, our results raise concern about the role of stenting as a potential independent risk factor for metachronous UTUC.

It should be stressed that the findings of the present study should be interpreted within the context of certain limitations relevant to the nonprospective design, the relatively short and different followup across patient groups, the nonblinded nature and the small number of the included studies. Not having access to patient-level data, we were not able to address UUT recurrence and mortality in a time-to-event manner by performing a meta-analysis of hazard ratios. Accordingly, we could not adjust for specific risk factors and comorbidities, which might have affected certain outcomes. In particular, data about cancer characteristics and prior management were not available. Similarly, tumor multifocality, involvement of the ureteral orifice, previous UUT manipulations in the course of the disease and a history of UUT tumor remained underreported in most of the included studies.[23] Therefore, it should be highlighted that the nonrandomized, retrospective and observational nature of the included studies limits the generalizability of our results due to potential selection bias.

Bladder tumors involving the ureteral orifice area occur in 5% to 35% of all BCa cases, are treated with wide excision of the tumor and the ureteral orifice during TURBT and are related to an increased risk of UTUC.[21,22] In some cases, UUT obstruction may already exist as a result of ureteral orifice infiltration by a muscle invasive bladder tumor or by enlarged retroperitoneal lymph nodes.[38] In other cases, UUT obstruction might follow TURBT due to stricture formation from wide deep resection of the orifice. In this scenario, some urologists advocate prophylactic placement of a ureteral stent to keep the orifice open and prevent obliteration and subsequent UUT obstruction. Our findings suggest that this choice may, however, further increase the risk for developing metachronous UTUC as a result of destruction of the anti-reflux mechanism and UUT tumor seeding. The risk of UTUC recurrence should be weighed against the possibility of UUT obstruction, therefore close monitoring is mandatory with nephrostomy placement in case of late UUT obstruction.

There are certainly quality of life issues related to both management options. Ureteral stents cause more lower urinary tract symptoms compared to percutaneous nephrostomy.[39] Bladder irritation, dysuria and urgency are the more common and lead to reduced quality of life in most patients.[40] On the other hand, percutaneous nephrostomy causes local pain and discomfort, and is associated with poor personal hygiene and self-care difficulties, but contrary to ureteral stent, these local symptoms improve shortly after the procedure.[41] Still, percutaneous nephrostomy is more invasive and is associated with more major periprocedural complications.[42]

In the scenario of patients with BCa presenting with UUT obstruction, considering that hydronephrosis is an independent risk factor for worse survival and poor oncologic outcomes after RC,[43] UUT drainage with percutaneous nephrostomy or ureteral stenting is recommended. The AUA (American Urological Association) guidelines for muscle invasive BCa propose ureteral stenting for treating preoperative hydronephrosis, not considering the potential increased risk of metachronous UTUC.[20] Even though nephrostomy under those circumstances technically has higher success rates and provides more durable UUT drainage, it is often sought for decompression after failure at attempted stenting.[25,44] Our results suggest that ureteral stenting is related to better survival than nephrostomy. However, it is not clear if this effect is due to other factors such as more advanced disease stage of patients receiving nephrostomy and need for treatment with neo-adjuvant or adjuvant chemotherapy following RC. Accordingly, ureteral stenting and nephrostomy present similar outcomes in terms of developing metachronous UTUC. Therefore, in those cases clinical judgment based on individual patient profile should prevail.

It should be stressed that multiple factors have been associated with UUT recurrence in patients with BCa. Studies have shown that higher BCa stage or grade, larger tumor diameter, frequency of tumor recurrence, multifocality, concomitant carcinoma in situ, ureteral orifice involvement, previous UUT

manipulations, stent indwelling time, prostatic urethra or lymphovascular invasion, treatment with intravesical bacillus Calmette-Guérin, hydronephrosis, aging, smoking and vesicoureteral reflux are associated with a higher risk of developing metachronous UTUC after BCa diagnosis.[43,45–50] Since many of these parameters were not reported in the included studies, RCTs or well-designed observational studies could theoretically adjust for these potential confounders.

These proposed parameters may serve as a guide for the design of future protocols, aiming to elucidate whether ureteral stenting is an independent risk factor for metachronous UTUC based on individual patient characteristics. Moreover, given the scarcity of available data, well-conducted studies are needed to assess the safety and efficacy of ureteral stenting in patients with BCa. RCTs comparing ureteral stenting versus no stenting after resection of tumors located in the ureteral orifice and RCTs comparing internal versus external UUT drainage in patients with BCa with obstruction would theoretically overcome the selection bias of observational studies. However, it should be noted that UUT recurrence is rare and RCTs exploring the risk of developing metachronous UTUC would be difficult to conduct, as they would require an enormous sample size to adjust for confounders. Furthermore, data on the incidence of ureteric strictures after resection of tumors that involve the ureteral orifice as well as UUT drainage-related complications are scarce and should be sought in adequately designed studies. Overall, due to the paucity of available data, this meta-analysis may serve as a guide to patient management and also encourage colleagues to review and publish their institutional TURBT and RC registries or to design relevant RCTs in an attempt to provide results with a higher level of evidence.

CONCLUSION

Our findings suggest that patients with bladder cancer treated with ureteral stenting, either to protect the ureteral orifice and prevent obstruction or to decompress established upper urinary tract obstruction, may be associated with a higher risk of developing metachronous upper tract urothelial carcinoma compared to no stenting. Given this risk, it is recommended that prophylactic stenting after resection of tumors involving the orifice should be avoided. On the other hand, as a therapeutic option in cases of hydronephrosis, drainage is imperative and should be performed with either ureteral stenting or percutaneous nephrostomy, considering the similar impact of both on the risk of metachronous upper tract urothelial carcinoma.

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EDITORIAL COMMENT

The impact of preoperative renal decompression in patients affected by BCa on the development of upper tract urothelial carcinoma (UTUC) is still an object of discussion.

In 2017 Kiss et al suggested that preoperative ureteral stenting for hydronephrosis prior to RC was an independent predictor of UTUC incidence and that patients with hydronephrosis prior to RC

should be drained by percutaneous drainage rather than ureteral stenting (reference 34 in article).

In disagreement with the latter study, Miest et al (2) investigated 1,049 patients who underwent RC (reference 32 in article).

Five-year post-RC UTUC incidence ranged from 6.6% to 18.7% and nephrostomy tube drainage and preoperative ureteral stenting were both associated with UTUC after RC. Nevertheless, ureteral stenting did not have a significantly higher association with UTUC than nephrostomy tube drainage.

In the present systematic review, Sountoulides et al analyzed 5 retrospective cohort studies including 3,309 individuals and compared ureteral stenting versus nephrostomy or no drainage with regard to the risk of metachronous UTUC.

Applying the Newcastle-Ottawa Scale, 3 studies were considered of good and 2 of moderate quality. Patients treated with ureteral stenting were associated with a higher risk of developing metachronous UTUC compared to no stenting.

The first important recommendation we learn from this study is to avoid prophylactic stenting after resection of tumors involving the orifice. Moreover, this study highlights the similar impact of ureteral stenting or percutaneous nephrostomy on the risk of metachronous upper tract urothelial carcinoma.

Future randomized studies comparing ureteral stenting or percutaneous nephrostomy as a therapeutic option in cases of hydronephrosis in patients planned for RC are mandatory in order to evaluate the best approach, which could improve preoperative renal function without significantly worsening oncologic outcomes.

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REPLY BY AUTHORS

The impact of drainage on the development of metachronous upper tract urothelial cancer in patients with bladder cancer remains a matter of discussion. The study by Kiss et al on a radical cystectomy cohort suggesting that ureteral stenting before RC is an independent risk factor for metachronous UTUC was criticized for not taking into account known risk factors of UUT such as multiplicity of resections, multifocality of bladder lesions, direct tumor involvement of the ureteric orifice or the indications for RC (reference 23 in article).

The present meta-analysis has demonstrated that routine prophylactic stenting after transurethral resection of tumors involving the orifice should be avoided as it increases the risk of UTUC. The decision should still be weighed against the risk of ureteral stenosis with higher tumor stage and size tumor (>1.5 cm) being independent predictive factors for distal ureteral stenosis.[1]

In cases where drainage is judged as imperative, the present meta-analysis showed no difference with regard to metachronous UTUC risk between stent and nephrostomy even for patients with hydronephrosis.

It should be highlighted that the level of evidence is mitigated by the retrospective design, the different eligibility criteria and the small number of included studies. However since conducting a RCT to compare internal to external upper tract drainage on the risk of metachronous UTUC would require an enormous sample size due to necessary adjustments for multiple variables and risk factors (ie indwelling stent time, previous upper tract manipulations), our results may serve as a clinical guide in this highly debated issue.

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