



# Metastasectomy could not improve the survival of metastatic urothelial carcinoma: evidence from a meta-analysis

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**Background:** With the advancement of surgical techniques and instruments, surgeries had been increasingly applied to patients with metastatic urothelial carcinoma. However, their survival benefits had not been carefully evaluated.

**Methods:** Eligible articles were conducted by comprehensively searching three online databases (PubMed, EMBASE and Web of Science), published before May 1st, 2019. Overall survival (OS) and cancer-specific survival/progression-free survival (CSS/PFS) were analyzed to clarify their associations.

**Results:** Finally, eight out of 3,581 articles were enrolled in this meta-analysis. In terms of OS, our results indicated that OS was positively associated with the patients underwent radical cystectomy (RC) (pooled HR =0.72, 95% CI, 0.64–0.81, P=0.158,  $I^2=39.4\%$ ), but it was not significantly associated with the patients underwent metastasectomy (MC) (pooled HR =0.78, 95% CI, 0.56–1.08, P=0.093,  $I^2=49.7\%$ ). As for CSS/PFS, our results displayed that patients could benefit from surgery (RC or MC) (pooled HR =0.56, 95% CI, 0.42–0.75, P=0.213,  $I^2=35.3\%$ ).

**Conclusions:** Despite the positive role of the RC in treating metastatic urothelial carcinoma, MC did not suggest a survival benefit in terms of OS. More strictly designed randomized controlled trials (RCTs) were needed to validate our findings.

**Keywords:** Metastasectomy; metastatic urothelial carcinoma; meta-analysis

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## Introduction

Urinary epithelial cancer is the most important pathological type in urinary system tumors, and about 95% of bladder cancers are urothelial cancer. Among male cancer patients in the United States, bladder cancer ranks the eighth highest mortality rate (1). Especially for metastatic urothelial cancer, the 5-year survival rate of patients with metastatic urothelial

carcinoma is only 5% due to the lack of effective treatment. Currently, systemic chemotherapy combining methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or gemcitabine plus cisplatin (GC) is still the standard first-line regimens for treating metastatic urothelial carcinoma patients who cannot be cured by radiotherapy or surgery alone. For those who are not sensitive to cisplatin-based chemotherapy, chemotherapy combining gemcitabine

and carboplatin can also be applied (2). As for metastatic urothelial cancer, the response rate of these patients to platinum-based combined chemotherapy regimens is as high as 40–70%, however their overall 5-year survival rate is less than 15% (3–5). Even if a complete response has been achieved at the beginning of chemotherapy, a progressive disease (PD), partial response (PR) or stable disease (SD) is the inevitable outcome with the advancement of treatment. In addition, systemic chemotherapy has serious heart, liver, and kidney toxic side effects. For patients who cannot tolerate, it is necessary to reconsider treatment options.

Recently, the role of immune checkpoint inhibitors for patients with metastatic urothelial cancer has begun to attract more and more attention. Due to the lack of evidence for clinical practice, whether or not it can be utilized as first-line treatment for metastatic urothelial cancer remains unclear (6). With the advancement of surgical techniques and instruments, surgeries have been increasingly applied to metastatic urothelial carcinoma patients and more clinical practices have been published. Accumulating data had pointed out that survival benefits from metastasectomy/cystectomy could be obtained in proper patients, especially in patients with lung metastases (7,8). However, several researchers also suggested that patients who underwent salvage surgery might gain no significant survival advantage (9,10), comparing with those who accepted other treatment strategies. It still remained controversial whether or not the surgical method could be utilized as a treatment plan to improve the survival benefits of metastatic urothelial cancer. Hence, this study was conducted to clarify the roles of surgeries in metastatic urothelial carcinoma by means of overall survival (OS) or cancer-specific/progression-free survival (CSS/PFS) based on available data. Moreover, our results were anticipated to provide some references for future clinical work.

## Methods

### Search strategy

Eligible studies were conducted by comprehensively searching three online databases (PubMed, EMBASE and Web of Science), published before May 1st, 2019. The search strategy was displayed as follows: (“metastatic urothelial carcinoma” or “metastatic bladder cancer” or “locally advanced bladder cancer” or “lymph node positive bladder cancer”) and (“metastasectomy” or “metastasis resection” or “radical cystectomy” or “aborted radical

cystectomy” or “cytoreductive radical cystectomy”). All eligible articles were selected as follows: (I) English articles; (II) metastatic urothelial carcinoma patients; (III) patients underwent metastasectomy/cystectomy; (IV) independent surgical or non-surgical cohort studies; (V) sufficient data for extraction. Meanwhile, the exclusive criteria were detailed as follows: (I) non-English articles; (II) studies not related to metastatic urothelial carcinoma; (III) without surgical or non-surgical cohort studies; (IV) unavailable data for analysis.

### Data extraction

All available data were extracted independently by two investigators and a third investigator would join in to make an appropriate decision when disagreement existed. The extracted variables from included studies were recorded as follows: author’s name, year, median or mean age, ethnicity, study design, survival analysis, months of follow-up, number of patients, treatment, hazard ratio (HR) with 95% confidence interval (CI), source of HR. If HR and its 95% CI could not be obtained from the original studies, data would be extracted from Kaplan-Meier curves by using previously published methods (11,12).

### Quality assessment

All enrolled studies were rated for methodological quality by two investigators independently according to the Newcastle-Ottawa Scale (NOS) ([http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm)) (13). Therein, total scores of quality evaluation ranged from 0 to 9 and if a study got the final score >6, it was regarded as high quality. Detail information of each study was presented in *Table 1*.

### Statistical analysis

Relationships between surgery and metastatic urothelial carcinoma were analyzed by CSS/PFS or OS based on the relevant literature. Heterogeneity assessment was conducted by Chi-square test and I-square test. While Chi-square test  $P < 0.1$  or  $I^2 > 50\%$ , it was considered to be significant heterogeneity. The random-effects model or the fixed-effects model was applied respectively according to the presence or absence of significant heterogeneity. Sensitivity analysis was conducted to examine the stability and reliability of our results in this meta-analysis. Furthermore, Begg’s funnel plot was adopted to check out the potential

**Table 1** Newcastle-Ottawa Quality Assessments Scale

Studies	Year	Quality indicators from Newcastle-Ottawa Scale								Scores
		1	2	3	4	5	6	7	8	
Dong	2017	★	★	–	★	★★	★	★	★	8
Abe	2017	★	★	–	★	★★	–	★	★	7
Galsky	2016	★	–	★	★	★★	★	★	★	8
Necchi	2015	★	★	★	★	★★	–	★	–	7
Bekku	2013	–	★	★	★	★★	–	★	★	7
Fokas	2010	★	–	–	★	★★	★	★	–	6
Als	2007	–	★	★	★	★★	–	–	★	6
Abe	2007	–	–	★	★	★★	–	★	★	6

1, representativeness of the exposed cohort; 2, selection of the non-exposed cohort; 3, ascertainment of exposure; 4, outcome of interest not present at start of study; 5, control for important factor or additional factor; 6, assessment of outcome; 7, follow-up long enough for outcomes to occur; 8, adequacy of follow up of cohorts. ★, each quality choice could be awarded a maximum of one star except for the numbered 5 item which could be granted a maximum of two stars. If the final score >6 stars, we regarded it as high quality.

publication bias. If  $P < 0.05$ , it meant there was publication bias (14). Besides,  $P < 0.05$  was thought to be statistically significant. All above statistical analyses were conducted by Stata 12.0 (StataCorp LP, College Station, TX, USA).

## Results

### Studies characteristics

A total of 3,581 relevant studies were initially identified by a primary search of three online databases and relevant reference lists based on the strategy above. According to our inclusive and exclusive criteria, 3,573 records were excluded and 8 articles were ultimately adopted for a further evaluation in the present meta-analysis accruing from March 2007 to November 2017 (15–22). Detailed literature searching and selecting process was described in *Figure 1*.

Among these eligible eight studies (*Table 2*), multivariate Cox regression analysis of prognostic factors influencing OS and CSS was utilized by Dong *et al.*, while Necchi and Bekku *et al.* focused on the OS and PFS. The other five articles only reported the OS of patients underwent surgical consolidation using multivariate or univariable analysis. When taking the treatment regimens into account, Dong and Abe *et al.* divided the surgical cohort into metastasectomy (MC) *vs.* non-surgical therapy (NS) cohort and radical cystectomy (RC) *vs.* NS cohort respectively, while the others concentrated only one cohort. Amongst them, Galsky, Necchi and Als *et al.* discussed RC *vs.* NS

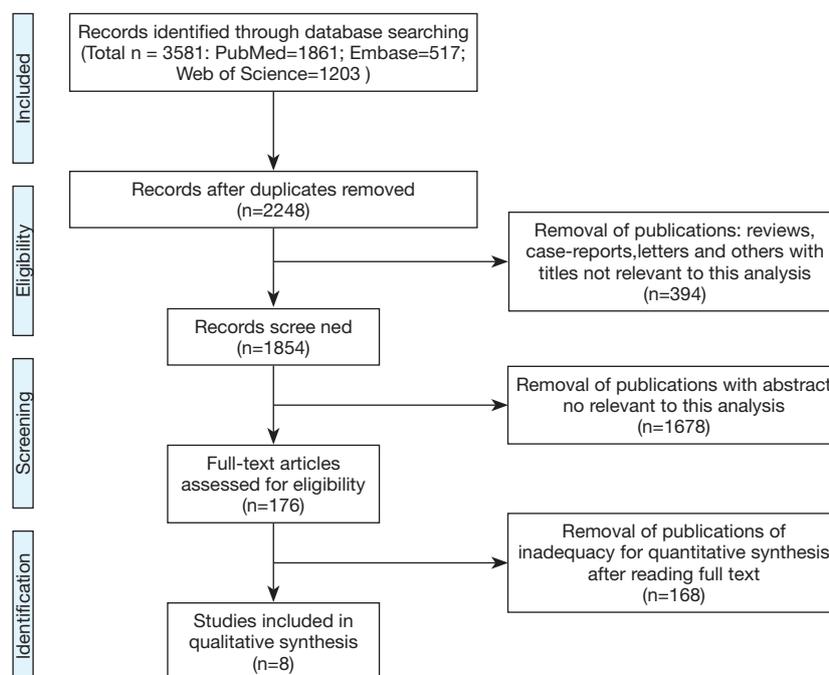
cohort, and Bekku, Fokas and Abe discussed MC *vs.* NS cohort. Four articles provided the data directly. For other articles that did not provide data, we extracted them from Kaplan-Meier curves.

### OS associated with surgery

These enrolled five studies indicated that OS is positively associated with the patients underwent RC by fixed-effects model based on the low heterogeneity ( $P = 0.158$ ,  $I^2 = 39.4\%$ ). This result successfully demonstrated that patients with metastatic urothelial carcinoma could benefit from RC (pooled HR = 0.72, 95% CI, 0.64–0.81) (*Figure 2A*). However, our results didn't predict the significant associations between OS and the patients underwent MC ( $P = 0.093$ ,  $I^2 = 49.7\%$ ), which meant the MC had little impact on prognosis (pooled HR = 0.78, 95% CI, 0.56–1.08) (*Figure 2B*).

### CSS/PFS associated with surgery

Among these included literatures, there were three articles reporting on CSS/PFS, one of which was about CSS and the other two were about PFS. In these studies, Dong and Necchi *et al.* focused on RC *vs.* NS cohort while Bekku focused on MC *vs.* NS cohort. Merging the above data as surgery *vs.* NS cohort, we finally got a significant conclusion that patients could gain survival benefit from the surgery (RC or MC) taking into account CSS/PFS together



**Figure 1** Flow diagram of the whole literature selection process.

( $P=0.213$ ,  $I^2=35.3\%$ , pooled HR =0.56, 95% CI, 0.42–0.75) (Figure 3).

### Sensitivity analysis and publication bias

Sensitivity analysis was conducted to examine the stability and reliability of the results of this meta-analysis. In RC *vs.* NS cohort or MC *vs.* NS cohort on, the sensitivity analysis for the result of salvage surgeries and OS did not alter significantly, demonstrating that no single study could significantly influence the pooled HR or the 95% CI (Figure 4). Overall, our results were stability and reliability.

As displayed in Figure 5, the P value of Begg's test was 0.462 and the P value of Egger's test was 0.200 in the pooled analysis of RC *vs.* NS cohort based on OS. In the pooled analysis of MC *vs.* NS cohort based on OS, the P value of Begg's test and Egger's test was 0.806 and 0.509 respectively. P values were all above 0.05, indicating no evidence of significant publication bias in this article.

### Discussion

Although the first-line combination chemotherapy scheme has been continuously improved, the treatment of metastatic urothelial cancer has not achieved great progress over

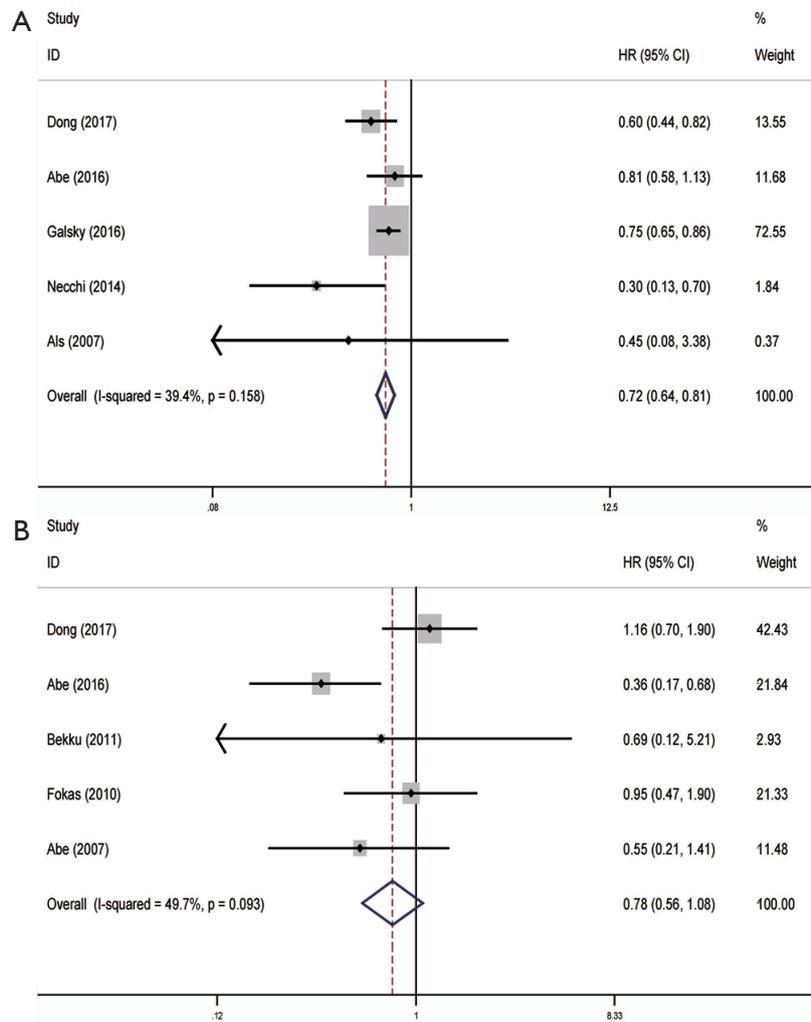
several decades (3). Despite the arrival of immunotherapy with checkpoint inhibitors (23), as the terminal stage of bladder cancer, metastatic urothelial carcinoma has rather lower survival rates after its diagnosis. Traditionally, surgery remains the treatment for the patients with malignancy in an appropriate condition such as early stage of tumor without metastasis. It was still elusive whether or not patients suffering from metastatic urothelial carcinoma could benefit from surgeries aiming to excise the primary or metastatic lesion. Moreover, clinical researchers are also paying more attention to the roles of surgical treatment in metastatic urothelial carcinoma.

Since the early 1980s, postchemotherapy surgery with curative intent had been tried (24). In 2001, Herr and colleagues indicated that RC and pelvic lymph node dissection could be a consolidative intervention in patients experiencing complete or significant response to induction systemic CHT (25). Many other studies had also evaluated the roles of surgical resection of metastatic deposits as a part of a multidisciplinary approach (26-31). However, most researches were based on small sample sizes or single-institutional studies or in the absence of stable and reliable conclusions. Therefore, meta-analysis, as a powerful tool in providing favorable suggestions was carried out to clarify the merits of surgeries for metastatic

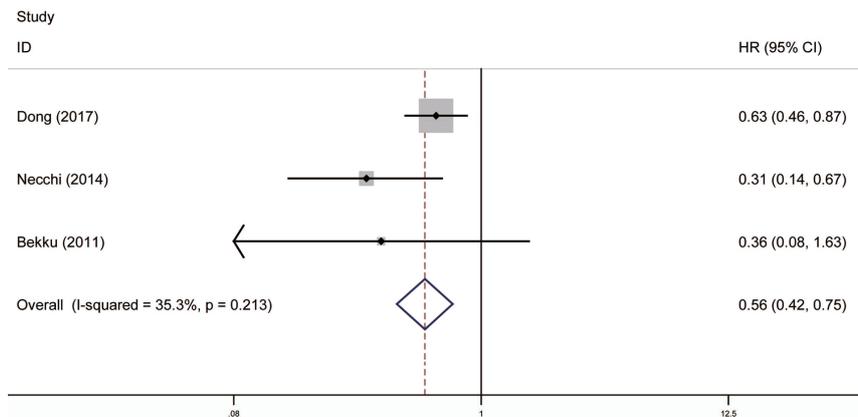
**Table 2** Main characteristics of individual studies included in the meta-analysis

First author	Publish year	Median or mean age	Dominant ethnicity	Study design	Survival analysis	Months of follow-up	Number of patients	Treatment	HR (95% CI)	Source of HR
Dong <sup>1,3</sup>	2017	70	White, Black, others	R	OS <sup>M</sup>	0–59	1,862	RC/NS	0.6 (0.44–0.818)	Reported
Dong <sup>1,4</sup>	2017	70	White, Black, others	R	CSS <sup>M</sup>	0–59	1,862	RC/NS	0.632 (0.462–0.865)	Reported
Dong <sup>2,3</sup>	2017	70	White, Black, others	R	OS <sup>M</sup>	0–59	1,862	MC/NS	1.157 (0.705–1.898)	Reported
Dong <sup>2,4</sup>	2017	70	White, Black, others	R	CSS <sup>M</sup>	0–59	1,862	MC/NS	1.184 (0.712–1.969)	Reported
Abe <sup>1</sup>	2017	67	NA	R	OS <sup>M</sup>	>60	228	RC/NS	0.81 (0.58–1.131)	Reported
Abe <sup>2</sup>	2017	67	NA	R	OS <sup>M</sup>	>60	228	MC/NS	0.364 (0.171–0.68)	Reported
Galsky	2016	NA	White, Black, others	R	OS <sup>M</sup>	0–60	1,376	RC/NS	0.752 (0.654–0.855)	Reported
Necchi <sup>3</sup>	2015	59	NA	R	OS <sup>M</sup>	>60	59	RC/NS	0.30 (0.13–0.70)	Reported
Necchi <sup>5</sup>	2015	59	NA	R	PFS <sup>M</sup>	>60	59	RC/NS	0.31 (0.14–0.67)	Reported
Bekku <sup>3</sup>	2013	64	NA	R	OS <sup>U</sup>	4.5–66	27	MC/NS	0.69 (0.12–5.21)	SC
Bekku <sup>5</sup>	2013	64	NA	R	PFS <sup>U</sup>	4.5–66	27	MC/NS	0.36 (0.08–1.63)	SC
Fokas	2010	NA	NA	R	OS <sup>U</sup>	>60	62	MC/NS	0.95 (0.47–1.9)	SC
Als	2007	NA	NA	R	OS <sup>U</sup>	>60	20	RC/NS	0.45 (0.08–3.38)	SC
Abe	2007	66	NA	R	OS <sup>M</sup>	>60	48	MC/NS	0.55 (0.21–1.41)	SC

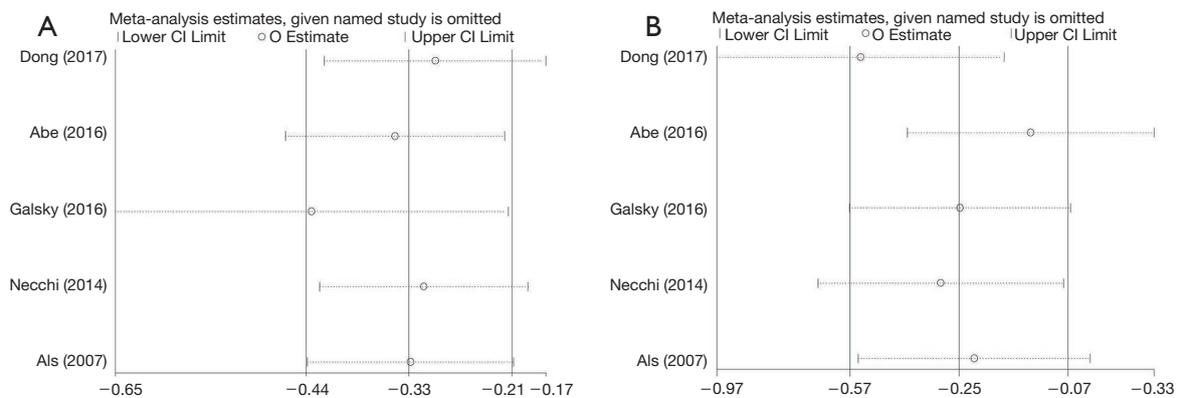
<sup>1</sup>, the treatment group of RC vs. NS. <sup>2</sup>, the treatment group of MC vs. NS. <sup>3</sup>, the survival analysis of OS. <sup>4</sup>, the analysis of CSS. <sup>5</sup>, the analysis of PFS. NA, not available; R, retrospective study; OS, overall survival; CSS, cancer specific survival; PFS, progression free survival; <sup>U</sup>, univariate analysis; <sup>M</sup>, multivariate analysis; RC, radical cystectomy; MC, metastasectomy; NS, non-surgery; SC, survival curves.



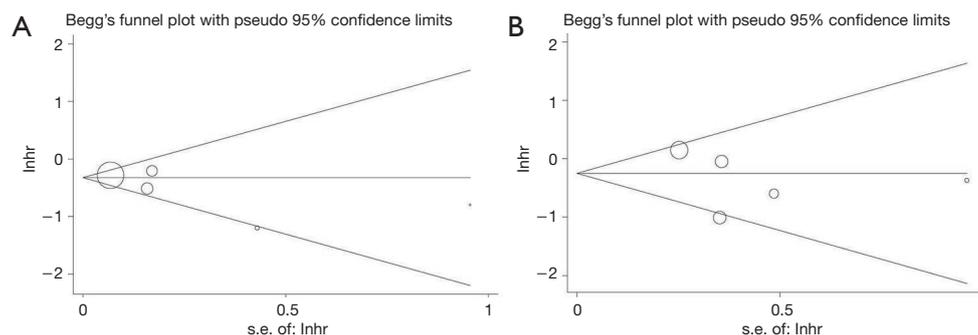
**Figure 2** Forest plots of overall survival (OS) in association with surgery for metastatic urothelial carcinoma. (A) Radical cystectomy vs. non-surgical therapy for metastatic urothelial carcinoma based on OS; (B) metastasectomy vs. non-surgical therapy for metastatic urothelial carcinoma based on OS.



**Figure 3** Forest plots of cancer-specific survival (CSS)/progression-free survival (PFS) in association with surgery (metastasectomy/radical cystectomy vs. non-surgical therapy) for metastatic urothelial carcinoma.



**Figure 4** Sensitivity analysis of each included study. (A) Radical cystectomy *vs.* non-surgical therapy for metastatic urothelial carcinoma based on OS; (B) metastasectomy *vs.* non-surgical therapy for metastatic urothelial carcinoma based on OS. OS, overall survival.



**Figure 5** Begg's funnel plots of the publication bias. (A) Radical cystectomy *vs.* non-surgical therapy for metastatic urothelial carcinoma based on OS; (B) metastasectomy *vs.* non-surgical therapy for metastatic urothelial carcinoma based on OS. OS, overall survival.

urothelial carcinoma. The present study was the first to shed light on the relationships between surgical treatment and metastatic urothelial carcinoma in terms of OS or CSS/PFS. Subsequently sensitivity analysis and publication bias manifested robustness of this study.

As for muscle-invasive urothelial carcinoma or high-risk non-muscle invasive disease refractory to instillation therapy, RC associated with pelvic lymph node dissection was the gold standard treatment. For patients with metastatic urothelial carcinoma, RC was considered to be cytoreductive surgery (32). In the other urologic tumor, metastatic prostate cancer patients with oligometastatic sites could also benefit from radical prostatectomy (33). Similarly, in metastatic urothelial carcinoma, researchers indicated that surgery might contribute to long-term disease-free survival in selected patients (25,34). Moreover, our study successfully demonstrated the feasibility of RC surgery and the survival benefit of improving OS. For its

advantages of prognosis, cytoreductive RC had also been recognized by other researchers (5,35). Our findings on RC were consistent with previous studies. For instance, Seisen *et al.* (36) shed light on that OS was better when local treatment was performed after systemic CHT by using the National Cancer Database.

Since the primary lesion cannot be removed, whether or not metastasectomy could benefit metastatic urothelial carcinoma patients remained a debate. Matsuguma *et al.* (7) emphasized that pulmonary metastasectomy could have a curative role in metastatic cases. Another study carried out by Lehmann *et al.* (34) thought that survival benefits could be achieved in patients following surgical removal of metastases including retroperitoneal lymph nodes, distant lymph, lung, bone, adrenal gland, brain, small intestine and subcutaneous. The forest map of a newly published systematic review also pointed out that improved OS was shown in patients treated with metastasectomy compared

with nonsurgical treatment of metastatic lesions (18). However, our results concluded that no improving OS was observed for patients treated with metastasectomy (HR =0.78, 95% CI, 0.56–1.08). This might attribute to two aspects of reasons: on the one hand, surgical cohort were divided into RC *vs.* NS cohort and MC *vs.* NS cohort in the present study and analysis of stratified data was performed respectively, while the former meta-analysis merely mixed two different surgical regimens into one; on the other hand, our study recruited recently published studies revealing more comprehensive data of individual patient with different metastatic lesions.

Although our results indicated that MC could not improve the survival benefits of metastatic urothelial carcinoma, is there any difference among different metastatic sites? The different effect of metastatic sites on patients' prognosis had been discussed in several previous studies (37,38). Without specifying which kind of metastases played roles, Taguchi *et al.* (39) pointed out that patients with visceral metastasis might have prognostic values for outcomes. Abe *et al.* (16) conducted a multivariate analysis on pretreatment prognostic characteristics and identified that single organ metastasis was associated with prolonged OS. As for distant metastatic sites, Dong *et al.* (15) revealed that bone and lung metastases could be independent prognostic factors, whereas distant lymph node metastases or multi-site metastases were not an independent prognostic indicator for both OS and bladder cancer specific survival.

To the best of our knowledge, it was the first for us to shed light on the relationships between surgical treatment and metastatic urothelial carcinoma in terms of OS or CSS/PFS. Before fully understanding this article, some assignable limitations should not be ignored. On the one hand, more literature with sufficient data should be involved in the study to disclose the independent prognostic factor of metastatic urothelial carcinoma and CSS/PSF of patients underwent different surgeries. On the other hand, upcoming prospective randomized controlled trials (RCTs) were warranted to provide more available data to elaborate the efficacy.

## Conclusions

Although our results shed light on the positive roles of RC in the treatment of metastatic urothelial carcinoma, MC surgery displayed no effect on the OS. This was contrary to usual clinical work, indicating that metastatic urothelial carcinoma patients could not gain survival benefits

from MC. Our results were anticipated to provide some references for further clinical work. Subsequent prospective RCTs were also required to provide more evidence to elaborate the efficacy.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.01.42>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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