Efficacy of surgery in the primary tumor site for metastatic urothelial cancer: analysis of an international, multicenter, multidisciplinary database

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Running head: local treatment in metastatic urothelial carcinoma
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Abstract

Background: The effect of local treatment on survival in advanced-stage patients has gained interest in several malignancies, however limited data exists regarding urothelial carcinoma (UC).

Objective: To test the impact of surgery of the primary tumor site on cancer specific mortality (CSM) and overall mortality (OM) in patients affected by metastatic UC.

Design, setting and participants: Individual patient-level data from a multicenter collaboration, including metastatic UC treated with first line cisplatin or carboplatin-based chemotherapy administered between January 2006 and January 2011 from hospitals in the USA, Europe, Israel and Canada.

Outcome measurements and statistical analyses: Univariable and multivariable Cox regression analyses were used to assess the effect of surgery on CSM and OM in patients affected by metastatic UC using 3-months landmark analyses. Subgroup analyses included the overall patients population and those patients affected by one metastatic site, or 2 or more metastatic sites.

Results and limitations: Of the 326 patients included in the study, 47 (14%) were treated with surgery of the primary tumor site. Median (IQR) follow-up was 43 (33-45) months. Of the patients treated with surgery, 28 (60%) were affected by a primary BCa and 19 (40%) by a primary upper urinary tract tumor. On multivariable analyses undergoing, surgery was associated with a protective effect on CSM (Hazard Ratio [HR]: 0.59, Confidence Interval [CI]: 0.35-0.98, p=0.04) and OM (HR: 0.45, CI: 0.37-0.99, p=0.04) compared to patients treated with chemotherapy only. Similar results were found in the subgroup of BCa patients only and considering only patients surgically treated before the start of chemotherapy. After stratifying according to the number of metastatic sites, surgery has an effect on survival only in patients with one metastatic site, while no survival benefit was observed in patients with two or more metastatic sites. The study is limited by its retrospective nature.

Conclusion: We found that surgery of the primary tumor site is associated with improved survival in patients with metastatic UC who received standard chemotherapy. This effect disappears in patients affected by two or more metastatic sites. Our results need to be validated in a high-quality prospective trial.

Patient summary: In our multicenter, retrospective series, surgery in metastatic urothelial cancer patients improve survival compared to patients treated with chemotherapy only. This effect was evident in patients with limited disease extent, identified as one metastatic site.

Introduction

Bladder cancer (BCa) is the second most common genitourinary malignancy with 81,190 estimated new diagnosis in the 2018 in the United States only[1]. Approximately, 10% of patients present at diagnosis unresectable or metastatic disease [2]. The current standard treatment for primary or secondary metastatic urothelial cancer (UC) is represented by systemic platinum-based combination chemotherapy, resulting in poor long-term survival of approximately 15% within 5 years[3]. Surgical removal of the primary tumor is an important part of the multimodal treatment of many metastatic urological and non-urological cancers. Several retrospective and population-based investigations reported feasibility and oncological effect of local treatment [4],[5],[6],[7] in other urological cancers. Considering metastatic UC, interest is growing although only limited evidences exist[8]. Seisen et al.[9], using data from National Cancer Data Base reported so far the only existing experience that showed a survival benefit in local treatment (surgery or radiotherapy) for metastatic UC patients compared to those treated with chemotherapy only. Given the current paucity of evidence on this topic, new data are urgently required to validate these findings. We hereby present the first multicenter study testing the effect of surgery in primary tumor site in metastatic UC patients by relying upon the Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC), that is one of the biggest available multicenter collaboration on advanced and metastatic UC.

Materials and methods

RISC is a retrospective study including individual patient-level data from patients with muscle-invasive or advanced UC or non-UC histology who have received systemic therapy in any clinical setting. This contemporary database includes data gathered from January 1, 2006 to January 1, 2011 from hospitals in the USA, Europe, Israel, and Canada. At the end of November 2018, data were extracted to select patients who fulfilled the following characteristics: (1) any tumor primary site (bladder or upper tract urothelial carcinoma [UTUC]), (2) de novo metastatic UC (cT1-4, cN0-3, cM1), (3) complete data regarding local therapy and (4) administration of cisplatin- or carboplatin containing chemotherapy in the first-line metastatic setting. The present study was approved by the ethics committees at each participating institution.

The study objective was to test the impact of surgery on survival outcomes in metastatic UC. Separate analyses were performed in the overall population, and according to the number of metastatic sites. For this study purpose, metastatic sites were considered here as follows: for visceral metastases, the number of organs involved was considered, whereas for lymph node metastases we counted any regional lymph node involvement as one anatomic site (typically, retroperitoneal metastases). The following parameters were used as co-variates to adjust for possible confounders: age, gender, Charlson comorbidity index (CCI), smoking habits (never smoker, former smoker, current smoker), primary tumor location (bladder or UTUC), histology (transitional or variant histology), clinical T-stage, clinical lymph node stage, chemotherapy regimen, the number of chemotherapy cycles and the number of

metastatic sites (i.e., 1 versus >1). Primary survival endpoints were cancer specific mortality (CSM) and overall mortality (OM).

Statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and Interquartile Ranges (IQR) were reported for continuously coded variables. The Mann-Whitney test and chi-square test were used to compare the statistical significance of differences in medians and proportions, respectively. The Kaplan-Meier method was used to compare the effect of surgery on CSM, and OM rates. Cox regression analyses (for time-to-event outcomes) were performed to evaluate potential prognostic factors. Complete case analysis was performed, and no imputation was performed for missing data. Multivariable models were based on prespecified factors that were hypothesized to be clinically important. Analyses were performed in the overall population and separately considering primary tumor location and number of metastatic sites involved. Six-month landmark analysis was applied throughout, accounting for OM events. Analyses were repeated considering patients with primary BCa and patients surgically treated before the start of chemotherapy. Statistical significance was considered at $p<0.05$. Statistical analyses were performed using SPSS v.22.0 (IBM Corp., Armonk, NY, USA) and STATA 13 (Stata Corp., College Station, TX, USA).

Results

Baseline Characteristics

Of the 326 individuals included in the study, 47 (14%) were treated with surgery in the primary tumor site. Clinical and pathological characteristic of our cohort stratified by surgical treatment of the primary tumor site are reported in **Table 1**. Patients treated with surgery share similar age, gender, smoking habits, CCI, presence of histological variants, clinical T stage, clinical N stage, metastatic location and number of cycles of chemotherapy (all p value ≥0.1). On the other hand, patients treated with surgery were more likely to have a primary tumor location in the UTUC compared to those who were treated with chemotherapy only (p=0.002), were treated with different chemotherapy schemes and had different metastatic site distributions. The reason why local treatment was indicated cannot be captured from the available information in the RISC Data Base.

Survival estimates

After a median (IQR) follow-up op 43 (33-45) months, 212 cancer specific and 232 overall causes deaths were reported. The 36-months cancer specific survival (CSS) and overall survival (OS) in patients treated versus not treated with surgery were 22% vs 37% (p value=0.02) and 20% vs 35% (p value=0.02) (**Figure 1**). In **Figure 2**, only patients with only one metastatic site were analyzed. The 36-months CSS and OS in patients treated versus not treated with surgery were 25% vs 52% (p value=0.03) and 23% vs 50% (p value=0.03). In **Figure 3**, patients with 2 or more metastatic sites were considered; The 36-months CSS and OS in patients treated vs not treated with surgery

were 22% vs 23% (p value=0.4) and 22% vs 23% (p value=0.3). We evaluated the impact of surgery on survival in metastatic UC in multivariable Cox regression analyses (**Table 2**). Surgery was associated with a protective effect on CSM (Hazard Ratio [HR]: 0.59, Confidence Interval [CI]: 0.35-0.98, p=0.04) and OM (HR: 0.45, CI: 0.37-0.99, p=0.04) compared to patients treated with chemotherapy only. In **Table 3**, only patients with BCa were evaluated. Similarly, surgery was associated with a protective effect on CSM (HR: 0.44, CI: 0.22-0.89, p=0.02) and OM (HR: 0.48, CI: 0.25-0.92, p=0.03) compared to patients treated with chemotherapy only. Finally, analyses were repeated considering only patients who received surgery before the start of chemotherapy (**Table 4**). Surgery was associated with a protective effect on CSM (HR: 0.44, CI: 0.20-0.97, p=0.04) and OM (HR: 0.47, CI: 0.22-0.98, p=0.04) compared to patients treated with chemotherapy only.

Discussion

The role of surgery in metastatic patients affected by urologic malignancies is gaining importance[4],[5],[6],[7]. However, limited information is available regarding the effect of surgery or bladder irradiation in the treatment of metastatic UC. Seisen et al.[9] raised the hypothesis that definitive local treatment (surgery or radiotherapy) provides a therapeutic benefit in metastatic UC patients using the national cancer database. They identified 3753 patients who received multiagent systemic chemotherapy, of them 297 (7.9%) received a concomitant local treatment. They reported an OS benefit for individuals with metastatic UC treated with local treatment compared to those treated with chemotherapy only. At the time, no report evaluated the effect of surgery in metastatic UC patients[8],[10]. The aim of our investigation was to validate these findings using the RISC database, the biggest multicenter collaboration on advanced and metastatic UC.

Our results show that local treatment with standard chemotherapy provide a survival benefit in terms of CSS and OS compared to metastatic UC patients treated with chemotherapy only. Our primary analyses (**Table 2**) included both patients with primary BCa and UTUC. Although several data exist reporting demographics, pathologic and survival differences between these two entities[11], in a recent post hoc analyses similar survival outcomes were reported irrespective of primary tumor location (bladder, renal pelvis or ureter) for patients treated within the EORTC trials 30924,

30986 and 30987 of metastatic UC[12]. However, previously reported analysis of the EORTC 30987[13] and the recent analysis of the ramucirumab trial[14] differences between upper and lower track have been observed. On the other hand, in a sensitivity analyses including only patients affected by BCa we found improved survival outcomes for patients treated with surgery compared to those treated with chemotherapy only (**Table 3**).

We included in the analyses only patients treated with optimal surgical treatment (radical nephroureterectomy or RC) and all the patients who underwent sub-optimal surgery such as partial cystectomy were excluded. In this regard, partial cystectomy is insufficient for the treatment of locally advanced BCa and should not be recommended in the standard management of UC [15]. All patients who received radiotherapy to the primary tumor site were excluded from the final analyses. In this regard, our manuscript tested for the first time the effect of surgery on the primary tumor where previous reports tested the effect of local therapy including radiotherapy and surgery together[9]. The potential effect of cytoreductive surgery in the metastatic setting has not been evaluated in the context of improved local tumor control but evaluating other biologic reason such as the seed and soil theory. According to this theory, the primary tumor produces growth factors that might be able to activate an environment favorable to the dissemination of malignant clones and the formation of metastases. In this regard, the necessity of a radical treatment might have several effects in patients with localized invasive BCa[16],[17],[18]. Analyses were finally repeated considering only patients who received surgery before the start of chemotherapy, reporting again a protective effect of surgery on survival compared to patients treated with chemotherapy only.

Although this effect was proved in the whole population, when stratified according to the number of metastatic sites, we observed that patients affected by low tumor burden were the only ones who benefited from local therapy in terms of CSS and OS (**Figure 1-3**). In this context, although preliminary these data might show a different biological outcome on the basis of metastatic burden as shown for other tumors[6]. Despite the majority of patients presenting with one metastatic site ultimately harbored retroperitoneal lymph node metastases (as in the study by Seisen et al[9]), we could extend the assumption that similar survival benefit may be obtained with local treatment in the remainder presenting with visceral metastatic involvement. Indeed, the granular distribution of small numbers prevented us from applying statistical tests to validate this hypothesis.

In comparison to the only previous study published on this topic [9] our report has several strengths. First, our analyses were based on patients treated with cisplatin- or carboplatin containing chemotherapy as standard first-line treatment in the metastatic setting. In this regard, our population represents the current standard of care. This accurateness in selecting the studied population cannot be achieved considering a population-based analyses. Secondly, our multivariable model was adjusted for the most important confounders regarding UC. For example, smoking history and presence of histological variants play an important role in determining survival outcomes in UC patients and should be taken into consideration in survival models. Third, we included both patients affected by BCa and UTUC. The current trials in the metastatic setting are based on the results of patients with both the primary tumor location and these two subgroups of patients should be considered together. Fourth, we were able to observe

that the beneficial effect of local treatment might be reserved to patients affected by low metastatic tumor burden.

Our study is not devoid of limitations. First, our study was not prospective or randomized, as it was a retrospective chart review, and our findings should be interpreted in this context. However, such retrospective studies are usually the precursor for more extensive prospective investigations. Second, all patients included in our cohort underwent local treatment at a high-volume tertiary referral center. Therefore, findings might represent this specific clinical scenario and not be applicable to other settings. Third, all metastatic UC patients where considered together. RC is potentially morbid surgery [19] and data helping physicians in selecting patients who might benefit more from local treatment are urgently needed. Lastly, information behind the decision for local therapy is not available in the RISC database.

Conclusion

In our multicenter collaboration, 14% of metastatic UC patients were treated with surgery in the primary tumor site as a part of multimodal treatment. We found that surgery improves cancer specific and overall survival even after adjusting for all the available confounders. These results were confirmed in patients with single site metastatic disease, but the effect disappeared analyzing the patients with two or more metastatic sites. Our results need to be validated in a prospective trial who clear selection criteria.

Figure legends

Figure 1- Kaplan-Meier survival analysis of cancer specific mortality (A) and overall mortality (B) in cT1-4cN0-3cM1 patients with or without surgical local treatment

Figure 2- Kaplan-Meier survival analysis of cancer specific mortality (A) and overall mortality (B) in cT1-4cN0-3cM1 patients affected by one metastatic site with or without surgical local treatment

Figure 3- Kaplan-Meier survival analysis of cancer specific mortality (A) and overall mortality (B) in cT1-4cN0-3cM1 patients affected by 2 or more metastatic sites with or without surgical local treatment

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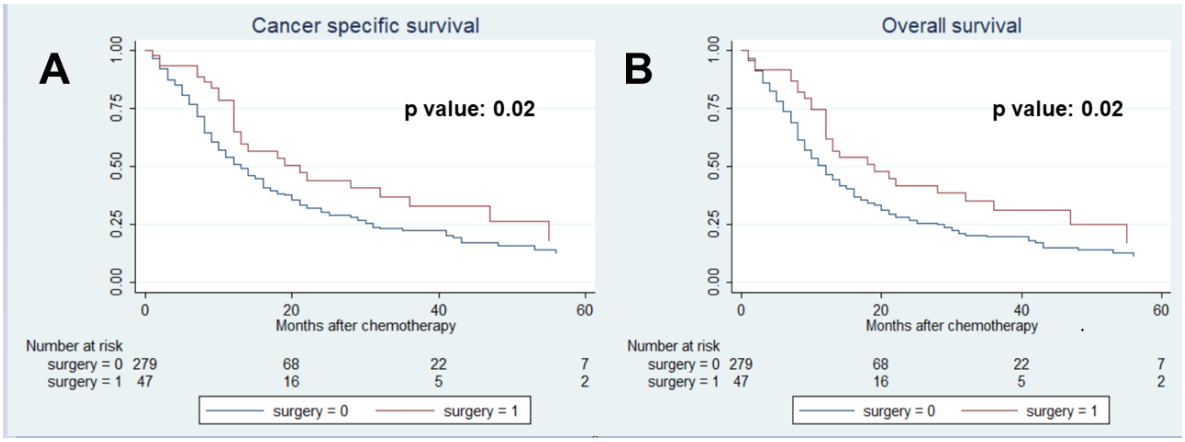

Fig. 1

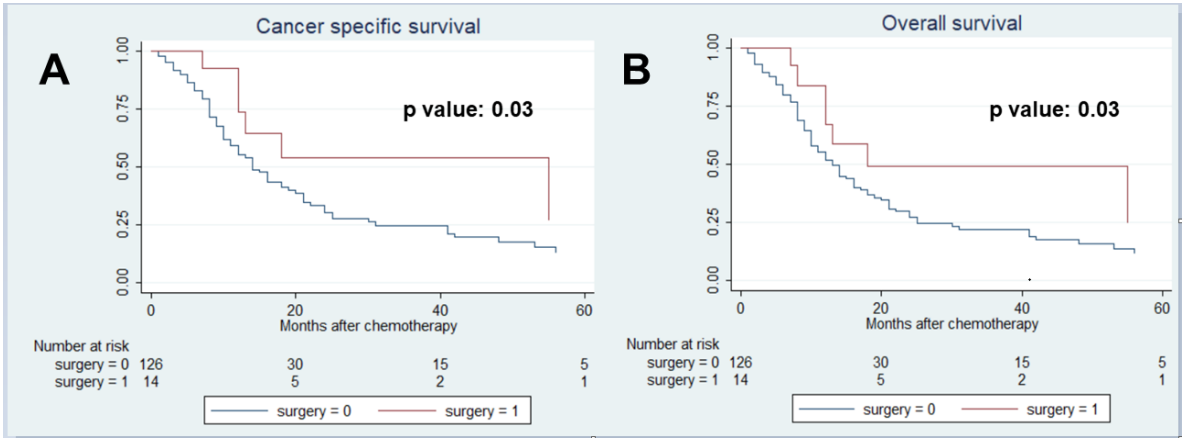

Fig. 2

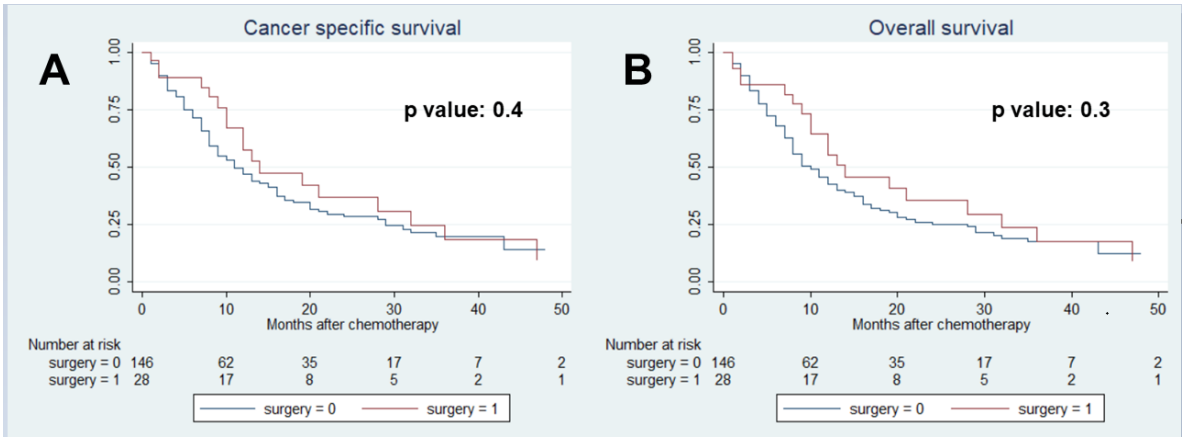

Fig. 3

Table 1- Descriptive statistics of 326 patients treated with surgery in the primary tumor site in metastatic urothelial cancer between January 2006 and 2011.

Variables	Overall (n=326, 100%)	Surgery in the primary site (n=47, 14%)	No surgery (n=279, 86%)	p value
Age, years				
Mean	67	62	67	0.5
Median (IQR)	68 (59-75)	62 (56-69)	69 (60-75)	
Gender				
Male	246 (76%)	37 (79%)	209 (75%)	0.5
Female	80 (24%)	10 (21%)	70 (25%)	
Smoking habits				
Current Smoker	69 (21%)	12 (26%)	57 (20%)	
Former Smoker	120 (37%)	16 (34%)	104 (37%)	0.1
Never-Smoker	72 (22%)	15 (32%)	57 (20%)	
CCI				
0	154 (47%)	25 (54%)	129 (46%)	0.4
1	35 (11%)	3 (6%)	32 (11%)	
≥2	126 (39%)	16 (34%)	110 (39%)	
Primary Tumor				
Bladder	252 (77%)	28 (60%)	224 (80%)	
Renal Pelvis	56 (17%)	16 (34%)	40 (14%)	0.002
Ureter	18 (6%)	3 (6%)	15 (5%)	
Histological				
Transitional	302 (93%)	42 (90%)	260 (93%)	0.3
Variants	19 (6%)	3 (6%)	16 (6%)	
Clinical T stage				
1-2	122 (37%)	22 (47%)	100 (36%)	0.3
3-4	127 (39%)	17 (36%)	110 (39%)	
Clinical N stage				
0	70 (21%)	8 (17%)	62 (22%)	0.4
+	139 (43%)	19 (40%)	120 (43%)	
Chemotherapy type				
Cisplatin based	136 (42%)	14 (30%)	122 (44%)	
Carboplatin based	78 (24%)	9 (19%)	69 (25%)	0.02
Non-platinum	14 (4%)	1 (2%)	13 (5%)	
Others	98 (30%)	23 (49%)	75 (27%)	
Number of cycles of chemotherapy				0.08
Mean	5	6	5	
Median (IQR)	5 (3-6)	5 (3-7)	6 (4-6)	
Metastatic sites				
1	140 (43%)	14 (30%)	126 (45%)	
2 or more	174 (54%)	28 (60%)	146 (52%)	0.007
Metastatic location*				

Extrapelvic nodes	71 (22%)	8 (17%)	63 (23%)	
Lung	28 (9%)	4 (9%)	24 (9%)	0.4
Bone	24 (7%)	1 (2%)	23 (8%)	
Liver	13 (4%)		13 (5%)	
Others	4 (1%)	1 (2%)	3 (1%)	
IQR: interquartile range, CCI: Charlson comorbidity index *refers to patients with the involvement of one metastatic site				

Table 2- Multivariable Cox regression analyses predicting cancer specific and overall mortality in metastatic urothelial cancer patients diagnosed between 2006 and 2011

Variables	Multivariable CSM, 212 events		Multivariable OM, 232 events	
	HR (CI 95%)	p value	HR (CI 95%)	p value
Age, years	1.01 (0.99-1.02)	0.4	1.01 (0.99-1.02)	0.3
Gender (Ref: female)	1.03 (0.72-1.50)	0.8	0.98 (0.69-1.39)	0.9
CCI				
0	Ref	Ref	Ref	Ref
1	1.13 (0.70-1.83)	0.6	1.10 (0.69-1.77)	0.6
≥2	0.78 (0.55-1.10)	0.1	0.82 (0.59-1.13)	0.2
Primary tumor location				
Bladder vs. UTUC	1.04 (0.72-1.51)	0.8	1.00 (0.70-1.43)	0.9
Smoking habits				
Never smoker	Ref	Ref	Ref	Ref
Former Smoker	0.84 (0.52-1.36)	0.3	0.84 (0.56-1.26)	0.4
Current smoker	0.73 (0.45-1.20)	0.5	0.86 (0.54-1.37)	0.5
Histology				
Transitional	Ref	Ref	Ref	Ref
Variants	1.50 (0.79-2.87)	0.2	1.36 (0.72-2.59)	0.3
Clinical T stage				
1-2	Ref	Ref	Ref	Ref
3-4	0.87 (0.61-1.23)	0.4	0.82 (0.59-1.14)	0.2
Clinical node				
0	Ref	Ref	Ref	Ref
+	1.11 (0.75-1.64)	0.6	1.08 (0.75-1.57)	0.7
Chemotherapy type				
Cisplatin based	Ref	Ref	Ref	Ref
Carboplatin based	1.36 (0.93-1.99)	0.1	1.33 (0.92-1.91)	0.1
Non-platinum	1.53 (0.74-3.17)	0.2	1.45 (0.74-2.86)	0.3
Others	1.20 (0.79-1.81)	0.4	1.22 (0.83-1.81)	0.3
Number of chemotherapy cycles	0.91 (0.86-0-98)	0.007	0.91 (0.85-0.97)	0.003
Surgery in primary tumor site	0.59 (0.35-0.98)	0.04	0.45 (0.37-0.99)	0.04

CSM: cancer specific mortality, OM: overall mortality, HR: Hazard ratio, CI: confidence interval, CCI: Charlson comorbidity index, UTUC: upper tract urothelial carcinoma

Table 3- Multivariable Cox regression analyses predicting cancer specific and overall mortality in metastatic bladder cancer patients diagnosed between 2006 and 2011

Variables	Multivariable CSM, 163 events		Multivariable OM, 180 events	
	HR (CI 95%)	p value	HR (CI 95%)	p value
Age, years	1.01 (0.99-1.03)	0.4	1.01 (0.99-1.03)	0.3
Gender (Ref: female)	1.08 (0.71-1.64)	0.7	1.01 (0.68-1.51)	0.9
CCI				
0	Ref	Ref	Ref	Ref
1	1.47 (0.81-2.69)	0.2	1.40 (0.79-2.49)	0.2
≥2	0.78 (0.53-1.16)	0.2	0.82 (0.57-1.18)	0.3
Smoking habits				
Never smoker	Ref	Ref	Ref	Ref
Former Smoker	0.76 (0.47-1.23)	0.3	0.81 (0.51-1.29)	0.4
Current smoker	0.95 (0.55-1.65)	0.8	0.91 (0.54-1.55)	0.7
Histology				
Transitional	Ref	Ref	Ref	Ref
Variants	1.23 (0.60-2.51)	0.5	1.09 (0.54-2.20)	0.8
Clinical T stage				
1-2	Ref	Ref	Ref	Ref
3-4	0.99 (0.66-1.48)	0.9	0.92 (0.63-1.34)	0.6
Clinical node				
0	Ref	Ref	Ref	Ref
+	1.03 (0.65-1.62)	0.9	1.03 (0.68-1.58)	0.8
Chemotherapy type				
Cisplatin based	Ref	Ref	Ref	Ref
Carboplatin based	1.48 (0.93-2.34)	0.1	1.43 (0.93-2.22)	0.1
Non-platinum	1.33 (0.52-3.41)	0.5	1.18 (0.49-2.82)	0.7
Others	1.29 (0.82-2.06)	0.3	1.33 (0.86-2.05)	0.2
Number of chemotherapy cycles	0.92 (0.85-0.99)	0.03	0.91 (0.84-0.98)	0.01
Surgery in primary tumor site	0.44 (0.22-0.89)	0.02	0.48 (0.25-0.92)	0.03

CSM: cancer specific mortality, OM: overall mortality, HR: Hazard ratio, CI: confidence interval, CCI: Charlson comorbidity index

Table 4- Multivariable Cox regression analyses predicting cancer specific and overall mortality in metastatic bladder cancer patients diagnosed between 2006 and 2011 with available date of surgery.

Variables	Multivariable CSM, 161 events		Multivariable OM, 177 events	
	HR (CI 95%)	p value	HR (CI 95%)	p value
Age, years	1.01 (0.99-1.03)	0.5	1.01 (0.99-1.03)	0.4
Gender (Ref: female)	1.04 (0.68-1.59)	0.8	0.98 (0.66-1.47)	0.9
CCI				
0	Ref	Ref	Ref	Ref
1	1.52 (0.83-2.78)	0.2	1.37 (0.76-2.49)	0.3
≥2	0.85 (0.57-1.25)	0.4	0.87 (0.61-1.26)	0.5
Smoking habits				
Never smoker	Ref	Ref	Ref	Ref
Former Smoker	0.92 (0.52-1.61)	0.7	0.80 (0.50-1.27)	0.4
Current smoker	0.73 (0.41-1.28)	0.2	0.88 (0.51-1.51)	0.6
Histology				
Transitional	Ref	Ref	Ref	Ref
Variants	1.20 (0.59-2.45)	0.6	1.06 (0.52-2.16)	0.8
Clinical T stage				
1-2	Ref	Ref	Ref	Ref
3-4	0.94 (0.63-1.41)	0.7	0.88 (0.60-1.29)	0.5
Clinical node				
0	Ref	Ref	Ref	Ref
+	1.03 (0.65-1.62)	0.8	1.05 (0.68-1.62)	0.8
Chemotherapy type				
Cisplatin based	Ref	Ref	Ref	Ref
Carboplatin based	1.48 (0.93-2.35)	0.1	1.45 (0.94-2.25)	0.1
Non-platinum	1.33 (0.52-3.41)	0.5	1.19 (0.49-2.87)	0.7
Others	1.35 (0.85-2.15)	0.2	1.40 (0.90-2.17)	0.1
Number of chemotherapy cycles	0.92 (0.85-0.99)	0.03	0.91 (0.85-0.95)	0.02
Surgery in primary tumor site before chemotherapy	0.44 (0.20-0.97)	0.04	0.47 (0.22-0.98)	0.04

CSM: cancer specific mortality, OM: overall mortality, HR: Hazard ratio, CI: confidence interval, CCI: Charlson comorbidity index