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Location of Metastatic Bladder Cancer as a Determinant of In-hospital Mortality After Radical Cystectomy

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Abstract

Background: A recent study of a highly select cohort suggested a survival benefit when local treatment is delivered in patients with metastatic bladder cancer (BCa).
Objective: We examined in-hospital mortality (IHM) rates according to the presence, absence, and location of metastatic disease in a similar highly select cohort of BCa patients treated with radical cystectomy (RC).
Design, setting, and participants: We used data for 25 004 BCa patients included in the National Inpatients Sample (NIS) database between 1998 and 2013.
Intervention: Radical cystectomy.
Outcome measurements and statistical analysis: We tested postoperative IHM rates according to the presence of metastases and the location of metastatic disease (exclusive nodal vs distant metastases). Multivariable logistic regression analyses were adjusted for age, gender, race, comorbidities, length of hospitalization, hospital location, teaching status, hospital surgical volume, and bed size.
Results and limitations: Among 25 004 BCa patients treated with RC, 3830 (14.4%) had nonregional lymph node metastases (NRNM), 693 (2.8%) had distant metastases (DM), and 19 965 (79.8%) had nonmetastatic disease. Virtually all patients with metastatic BCa had a single metastatic focus ($n = 4020$; 93.7%). In multivariable logistic regression analyses, DM (odds ratio [OR] 2.31, 95% confidence interval [CI] 1.57–3.28; $p < 0.001$) but not NRNM (OR 0.88, 95% CI 0.66–1.15; $p = 0.4$) was associated with higher risk of IHM. The absence of information on preoperative chemotherapy and the retrospective study design may limit our findings.
Conclusions: The risk of IHM for highly select individuals with NRNM treated with RC is similar to that for patients with nonmetastatic BCa. Conversely, patients with DM are at higher risk of IHM compared to patients with NRNM.
Patient summary: According to existing data, radical cystectomy in the metastatic bladder cancer setting should be limited to patients with nonregional lymph node metastases, if at all indicated.

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1. Introduction

Patients diagnosed with metastatic bladder cancer (BCa) have poor life expectancy at diagnosis. The standard of care for such patients is chemotherapy. The presence of distant metastases (DM) is considered a contraindication for radical cystectomy (RC) or any other form of definitive local therapy [1], unless delivered in a palliative setting. Despite the general acceptance of these considerations, several studies have proposed RC as a feasible treatment modality with potential for better survival, especially in patients with nonregional lymph node metastases (NRNM) after induction chemotherapy [2,3]. In addition, a recent large-scale, population-based study corroborated better survival after high-intensity local treatment, defined as RC or high-dose pelvic radiation, in patients with NRNM or when compared to no such treatment [4]. These data may be indicative of a paradigm shift in the management of metastatic BCa. Specifically, for the first time consideration might be given to high-intensity local treatment, especially against the backdrop of the unavailability of effective systemic treatment modalities in routine clinical practice.

On the basis of the promising survival benefit of local treatment in patients with metastatic BCa, it is possible that future clinical trials will formally investigate the efficacy of this strategy. In this context, we decided to examine the safety of RC in patients with metastatic BCa, defined as in-hospital mortality (IHM)–free survival. We hypothesized that RC in metastatic BCa might be safest in patients with limited metastases extent in comparison to those with more extensive metastatic disease. Accordingly, we formally tested the hypothesis that patients with NRNM would exhibit lower IHM rates than their counterparts with DM. We relied on patients with nonmetastatic BCa (NMBC) treated with RC as controls.

2. Patients and methods

2.1. Data source and study population

The current study relied on the National Inpatients Sample (NIS) database from the Healthcare Cost and Utilization Project [5]. The NIS database is considered the largest all-payer inpatient care database in the USA and contains data on approximately 20% of all hospital admissions in the USA. Until 2011, data published in the NIS database comprised all discharges from a sample of participating hospitals. From 2012, the NIS data represent a sample of discharges from all participating hospitals rather than a sample of hospitals [6].

Relying on discharge records, we identified the study cohort using International Classification of Diseases, 9th edition (ICD-9-CM) diagnostic and procedure codes from the hospital claims data in the NIS. Specifically, we identified patients diagnosed between 1998 and 2013 with BCa (ICD-9-CM diagnostic codes 188.0–188.9, 233.7, 236.7, and 239.4) and treated with RC (ICD-9-CM codes 57.71 and 57.79). Metastatic disease was defined according to site using specific ICD-9-CM codes (Supplementary Table 1). Only patients aged ≥18 yr were considered. Moreover, we further limited our cohort to include only elective cases. Exclusion criteria consisted of unknown age and/or gender. This resulted in a cohort of 25 004 patients. To evaluate the impact of metastatic BCa on IHM, patients with NMBC were considered as a control group.

2.2. Variable definition

Patient characteristics included age at surgery, gender, and race (Caucasian, African American, other). Comorbidities were assessed in terms of the Charlson Comorbidity Index (CCI) using a previously established method [7]. Patients with metastatic BCa were stratified according to the presence of NRNM in the absence of distant organ involvement versus the presence of DM, regardless of nodal status.

Hospital characteristics were categorized as teaching versus nonteaching status, urban versus rural location, geographical region (Northeast vs Midwest vs South vs West), hospital bed size, and annual hospital surgical volume. Hospital surgical volume was stratified according to tertiles, as previously reported [8].

2.3. Outcomes and statistical analyses

The primary endpoint was IHM after RC according to the presence or absence of metastases and to the location of metastatic disease (NRNM vs DM). Frequency tables were used to describe patient characteristics. We used χ^2 and Kruskal-Wallis tests to evaluate the statistical significance of differences between categorical and continuous variables, respectively. Univariable and multivariable logistic regression analyses were performed to assess the association between metastatic disease and IHM after adjusting for year of surgery, age, gender, race, comorbidities, hospital location, teaching status, hospital surgical volume, and hospital bed size. Internal validation of our findings was performed using 200 bootstrap resamples [9]. Finally, we repeated the survival analyses after exclusion of patients with bowel or peritoneal/retroperitoneal metastases (-$n = 259$), who represented a group with potentially higher IHM owing to the higher severity of recovery and the higher risk of complications in comparison to other patients with DM.

All statistical tests were two-sided, with the level of significance set at $p < 0.05$. Analyses were performed using R software v.3.3.0 (www.r-project.org/).

3. Results

3.1. Baseline characteristics

Overall, a total of 25 004 individuals were identified (Table 1). Specifically, 3596 patients (14.4%) harbored NRNM, 693 (2.8%) harbored DM, and 20 715 (84.7%) had NMBC. Among the 4289 individuals with either NRNM or DM, the most common metastatic sites were lymph nodes

Table 1 – Descriptive characteristics of the study cohort, composed of 25 004 patients diagnosed with bladder and treated with radical cystectomy between 1998 and 2013

	No metastases	Nonregional nodal metastases	Distant metastases	*p* value
Patients, *n* (%)	20 715 (84.7)	3596 (14.4)	693 (2.8)	
Median age at surgery, yr (IQR)	70 (62–76)	68 (60–75)	70 (61–76)	<0.001
Gender, *n* (%)				<0.001
Male	17 009 (82.1)	2963 (82.4)	516 (74.5)	
Female	3706 (17.9)	633 (17.6)	177 (25.5)	
Race, *n* (%)				0.02
Caucasian	14 654 (70.7)	2534 (70.5)	464 (67.0)	
African American	745 (3.6)	156 (4.3)	31 (4.5)	
Other	1166 (5.6)	230 (6.4)	47 (6.7)	
Unknown	4150 (20.1)	676 (18.8)	151 (21.8)	
Charlson comorbidity index, *n* (%)				<0.01
0	12 215 (59.0)	2241 (62.4)	426 (61.5)	
1	6146 (29.7)	965 (26.8)	201 (29.0)	
≥2	2354 (11.3)	390 (10.8)	66 (9.5)	
Type of urinary diversion, *n* (%)				<0.01
Neobladder	1630 (7.9)	275 (7.6)	30 (4.3)	
Ileal conduit	15 836 (76.4)	2799 (77.8)	540 (77.9)	
Other	3249 (15.7)	522 (14.6)	123 (17.8)	
Median length of hospitalization, d (IQR)	8 (7–12)	8 (7–11)	10 (7–15)	<0.001
Hospital location, *n* (%)				0.2
Urban	19 659 (94.9)	3430 (95.4)	651 (93.9)	
Rural	1056 (5.1)	166 (4.6)	42 (6.1)	
Hospital teaching status, *n* (%)				0.02
Teaching	14 499 (70.0)	2559 (71.2)	457 (65.9)	
Nonteaching	6216 (30.0)	1037 (28.8)	236 (34.1)	
Hospital US region, *n* (%) [a]				<0.001
Midwest	5302 (25.6)	809 (22.5)	160 (23.1)	
Northeast	4044 (19.5)	721 (20.1)	126 (18.2)	
South	7241 (35.0)	1192 (33.1)	240 (34.6)	
West	4128 (19.9)	874 (24.3)	167 (24.1)	
Hospital surgical volume, *n* (%) [a]				0.1
High	11 507 (55.6)	2063 (57.4)	367 (53.0)	
Moderate	4472 (21.6)	744 (20.7)	150 (21.6)	
Low	4736 (22.8)	789 (21.9)	176 (25.4)	
Hospital bed size, *n* (%) [a]				0.4
Large	14 872 (71.8)	2585 (71.9)	496 (71.6)	
Medium	3774 (18.2)	630 (17.5)	137 (19.8)	
Small	2069 (10.0)	381 (10.6)	60 (8.6)	

IQR = interquartile range.
[a] Proportions are reported by row to better show the rates of patients with nonregional nodal metastases or distant metastases according to hospital characteristics.

(89.2%; $n = 3830$), intestine (5.5%; $n = 235$), and retroperitoneum (4.9%; $n = 209$). Of these 4523 individuals, 93.7% ($n = 4020$) harbored a single BCa metastatic focus (Table 2).

In general, patients with NRNM were younger than those with DM and NMBC (68 vs 70 vs 70 yr; $p < 0.001$). More individuals undergoing RC with CCI of 1 and ≥2 had NMBC (29.7% and 11.4%, respectively) compared to NRNM (26.8% and 10.8%) and DM (29.0% and 9.5%). Conversely, the proportion of patients with CCI of 0 was higher in the NRNM (62.3%) and DM groups (61.5%) than in the NMBC group (59.0%; $p < 0.001$). More female patients underwent RC with DM BCa (25.5%) compared to those with NMBC (17.9%) or NRNM (17.6%; $p < 0.001$). Statistically significant race differences were also recorded between the three groups ($p = 0.02$; Table 1).

Overall, the majority of patients ($n = 19\,175$; 76.7%) underwent ileal conduit urinary diversion; 1935 individuals received a neobladder (7.7%) and 3984 (15.6%) other types of urinary diversion. The proportion of patients treated with neobladder was higher in the NMBC group than in the NRNM and DM groups (7.9% vs 7.6% vs 4.3%; $p < 0.01$). Conversely, the proportion of individuals treated with ileal conduit was lower in the NMBC group (76.4% vs 77.8% vs 77.9%). The median length of hospitalization was 8 d in the NMBC and NRNM groups and 10 d in the DM group ($p < 0.001$).

We observed statistically significant differences in the proportion of patients in the NMBC, NRNM, and DM groups according to geographical region. Specifically, the proportion of patients treated with RC according to geographical region ranged from 20.1% to 33.1% in the NRNM group, from 18.2% to 34.6% in the DM group, and from 19.5% to 35.0% in the NMBC group ($p < 0.001$). The proportion of patients with NRNM did not significantly differ by hospital surgical volume ($p = 0.1$). Similarly, there was no statistically significant difference according to hospital bed size ($p = 0.4$). Conversely, nonteaching institutions accounted for a higher proportion of patients in the DM group compared to the NRNM and NMBC groups (34.1% vs 28.8% vs 30.0%; $p = 0.02$).

Table 2 – Distribution of metastatic sites in the subgroup of patients with metastatic bladder cancer treated with radical cystectomy between 1998 and 2013

	All patients with metastatic disease (n = 4289)	Patients with distant organ metastases (n = 693)
Metastatic site, n (%)		
Lymph nodes	3,830 (89.2)	234 (33.8)
Large/small intestine	235 (5.5)	235 (33.9)
Peritoneum/retroperitoneum	209 (4.9)	209 (30.1)
Bone/bone marrow	81 (1.9)	81 (11.7)
Kidney	69 (1.6)	69 (10.0)
Respiratory organs	74 (1.7)	74 (10.7)
Liver	55 (1.2)	55 (7.9)
Ovary	29 (0.7) [a]	29 (4.1) [b]
Other metastatic sites	12 (0.2)	12 (1.7)
Number of metastatic sites, n (%)		
1	4,020 (93.7)	424 (61.2)
2	240 (5.6)	240 (34.6)
$\geq$3	29 (0.7)	29 (4.2)

[a] 3.6% if only females with metastatic bladder cancer (n = 935) are considered.
[b] 16.4% if only females with metastatic bladder cancer (n = 935) are considered.

3.2. *Survival analyses*

The IHM rate was 1.6% (n = 59) for the NRNM, 4.9% (n = 34) for the DM, and 2.0% (n = 422) for the NMBC group. The difference in IHM rate between the DM and NMBC groups was statistically significant ($p < 0.001$). Conversely, the NRNM group exhibited lower IHM than the NMBC group, but the difference was not statistically significant ($p = 0.1$).

In multivariable logistic regression analyses predicting IHM (Table 3), DM (odds ratio [OR] 2.31, 95% confidence interval [CI] 1.57–3.28; $p < 0.001$), but not NRNM (OR 0.88, 95% CI 0.66–1.15; $p = 0.4$), was associated with a higher risk of IHM. These relationships remained unchanged after 200 bootstrap resamples, which simulated the testing conditions among 200 cohorts of 25 004 individuals with different baseline characteristics due to resampling. Moreover, when survival analyses were repeated after exclusion of patients with bowel or peritoneal/retroperitoneal metastases, we obtained virtually the same results for the DM (OR 2.70, 95% CI 1.69–4.01; $p < 0.0001$) and NRNM groups (OR 0.90, 95% CI 0.65–1.13; $p = 0.3$).

Relationships between several other variables and IHM were observed. Specifically, IHM risk was proportional to age category. Individuals aged 65–75 yr were at 2.4-fold higher risk of IHM, compared to a 5.2-fold higher risk for patients aged >75 yr, relative to those aged $\leq$64 yr (both $p < 0.001$). In addition, African Americans (OR 1.65, 95% CI 1.05–2.46; $p = 0.02$) and individuals of ethnicity other than Caucasian or African American (OR 1.53, 95% CI 1.06–2.14; $p = 0.02$) and patients with CCI $\geq$2 (OR 1.63, 95% CI 1.26–2.08; $p < 0.001$) had a higher IHM risk. Finally, higher IHM risk was observed for individuals treated at nonteaching institutions (OR 1.29, 95% CI 1.04–1.58; $p = 0.02$). However, no significant IHM relationship was observed for gender, rural location, hospital volume, or hospital bed size (all $p \geq 0.05$; Table 3).

4. Discussion

Metastatic disease spread usually heralds a lack of benefit from local treatment. In such circumstances, chemotherapy becomes the pivotal treatment modality. Indeed, chemotherapy occupies a pivotal role in metastatic BCa [1]. Nonetheless, evidence supports treatment of the primary tumor despite the presence of metastatic disease in several urological malignancies, including testicular [10], renal [11,12], and prostate cancers [13–15]. Similarly, evidence supporting better survival after treatment of the primary tumor is mounting for metastatic BCa, at least among select patients [4,16]. For example, de Vries et al [2] observed a better survival rate among 14 patients who underwent RC for NRNM after primary chemotherapy (24% 5-yr survival). Previously, Dodd et al [3] found better survival among patients with metastatic urothelial carcinoma who underwent local surgical treatment after complete response to primary chemotherapy (33% 5-yr survival). Similarly, another recent population-based analysis [4] revealed that high-intensity local treatment improved overall survival (median survival 10 vs 15 mo; $p < 0.001$). All these studies were performed in highly select cohorts, in which all the patients were potential chemotherapy candidates. Despite their selection biases, these studies provide a proof of concept suggesting and corroborating a potential survival benefit from RC, despite metastatic disease spread, which ideally has to be validated in randomized prospective designs using the concepts derived from such retrospective studies. However, such a trial cannot be formally started without safety data for RC when performed in the metastatic setting. For example, in the study by Seisen et al [4] the omission of patients who died between local treatment and chemotherapy, or vice versa, when the intention was to perform both treatments must be considered. It is well established that perioperative mortality after RC is not zero. Immortal time bias due to exclusion of patients who died in either scenario might have falsely improved the survival benefit of high-intensity local treatment relative to conservative treatment.

For these reasons, we decided to verify the safety, defined as IHM-free survival, for RC performed in patients with metastatic BCa. Information derived from the current study could potentially help with better design of such a

Table 3 – Univariable and multivariable logistic regression models assessing in-hospital mortality risk

	Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Metastatic burden				
No metastases	Reference		Reference	
Nonregional node metastases	0.80 (0.60–1.05)	0.1	0.88 (0.66–1.15)	0.4
Distant metastases	2.48 (1.70–3.49)	<0.001	2.31 (1.57–3.28)	<0.001
Age group				
<65 yr	Reference		Reference	
65–75 yr	2.67 (2.00–3.62)	<0.001	2.42 (1.81–3.29)	<0.001
>75 yr	5.88 (4.45–7.89)	<0.001	5.16 (3.89–6.94)	<0.001
Gender				
Male	Reference		Reference	
Female	1.11 (0.89–1.37)	0.4	0.94 (0.74–1.17)	0.6
Race				
Caucasian	Reference		Reference	
African American	1.38 (0.89–2.04)	0.1	1.65 (1.05–2.46)	0.02
Other	1.35 (0.95–1.87)	0.08	1.53 (1.06–2.14)	0.02
Unknown	1.09 (0.87–1.35)	0.4	1.23 (0.96–1.54)	0.09
Charlson comorbidity index				
0	Reference		Reference	
1	1.35 (1.10–1.64)	<0.01	1.22 (0.99–1.48)	0.055
≥2	1.86 (1.45–2.37)	<0.001	1.63 (1.26–2.08)	<0.001
Length of hospitalization				
≤ median (8 d)	Reference		Reference	
> median (8 d)	2.85 (2.35–3.48)	<0.001	2.38 (1.95–2.91)	<0.001
Hospital surgical volume				
High	Reference		Reference	
Moderate	0.89 (0.71–1.12)	0.3	0.95 (0.75–1.20)	0.7
Low	1.05 (0.85–1.20)	0.6	0.92 (0.73–1.14)	0.5
Hospital location				
Urban	Reference		Reference	
Rural	1.78 (1.28–2.41)	<0.001	1.37 (0.95–1.92)	0.08
Hospital teaching status				
Teaching	Reference		Reference	
Nonteaching	1.54 (1.28–1.84)	<0.001	1.29 (1.04–1.58)	0.02
US region				
Midwest	Reference		Reference	
Northeast	1.49 (1.44–1.95)	<0.01	1.56 (1.17–2.07)	<0.01
South	1.35 (1.07–1.73)	0.01	1.43 (1.11–1.85)	<0.01
West	1.19 (0.90–1.57)	0.2	1.12 (0.84–1.49)	0.5
Hospital bed size				
Large	Reference		Reference	
Medium	1.30 (1.05–1.60)	0.02	1.25 (0.99–1.55)	0.05
Small	0.97 (0.71–1.31)	0.9	1.05 (0.76–1.42)	0.8

OR = odds ratio; CI = confidence interval.

randomized controlled trial (RCT), and might also be useful for medical decision-making with respect to RC in patients with metastatic BCa.

It is of interest that in our study 17% of RC patients harbored either NRNM or DM. Moreover, of these 4523 individuals, the majority had NRNM (n = 3596). This implies that the majority of patients with metastatic BCa who undergo RC may have relatively limited disease extent in the form of NRNM. Although more detailed localization of NRNM was not available in the database, 15.3% of all patients with metastatic BCa harbored distant organ metastases other than lymph node metastases. This proportion should be noted and investigated in other analyses assessing this topic. Of note, the distribution of metastatic sites is not reflective of all patients with metastatic BCa but instead depicts the pattern in patients with metastatic BCa who are treated with RC (Table 2). Specifically, in our study, fewer than 2% of patients with metastatic BCa harbored bone, liver or lung metastases. Conversely, in a previous investigation using the NIS database by Bianchi et al [17], bone, liver, and lung metastases were identified in 24.7%, 18.1% and 19.4% of cases, respectively. This implies that a bias in surgical selection might have been in effect, as individuals with bone and especially liver or lung metastases might have been considered very poor surgical candidates. This consideration is of pivotal importance, as no previous study stratified between NRNM and DM. Thus, the volume and distribution of metastatic disease sites may vary between studies and may affect the endpoints examined. For example, Seisen et al [4] did not specify the proportion of patients with NRNM versus DM. Lack of such detail renders comparison with other studies, such as ours, impossible, and limits the degree of interpretation or generalization.

In the current study, we showed that IHM risk was significantly higher in the DM compared to the NMBC group (OR 2.31, 95% CI 1.58-3.28; $p < 0.001$). There was no significant difference in IHM risk between the NRNM and NMBC groups ($p = 0.4$). Several important observations are noteworthy. Patients with bowel or peritoneal/retroperitoneal metastases might represent a very different patient population compared to other patients with metastatic BCa in terms of the severity of recovery and the risk of complications. Therefore, inclusion of these patients might have artificially increased the mortality rate in the DM subgroup. To remove this potential selection bias, we repeated the analysis after exclusion of these patients. Even after exclusion of patients with peritoneal/retroperitoneal or bowel metastases, we obtained virtually the same results. Specifically, we found that patients with DM had a 2.7-fold higher risk of IHM compared to patients with NMBC. Thus, IHM was higher in the DM group regardless of the inclusion of patients with a higher risk of in-hospital complications such as those with peritoneal/retroperitoneal or bowel metastases. These results corroborate the validity of our primary results.

Despite not showing higher IHM risk for patients with NRNM, these individuals exhibited lower absolute IHM rates than their counterparts without metastatic disease, although the difference was not significant ($p = 0.1$). This might imply a surgical selection bias towards individuals at lower risk of IHM when RC is contemplated in the context of NRNM. Conversely, the mortality rate was significantly higher in the DM compared to the NMBC group (4.9% vs 2.0%; $p < 0.001$). This observation is particularly noteworthy for future RCT designs, in which RC should potentially be avoided in patients with DM on the basis of safety considerations. The higher mortality rate in the DM group compared to the NMBC and NRNM groups validates the definition of DM in our cohort. This characteristic indeed independently predisposed to higher mortality risk, after holding all other patient and institution characteristics constant (Table 3).

Of note, previous reports that relied on the NIS database examined IHM rates in patients treated with RC. Konety et al [8] reported an overall IHM rate of 2.9% for a cohort of 13 964 RC patients treated between 1988 and 1999. More recently, Kim et al [18] evaluated 10 285 individuals who underwent RC for BCa between 2001 and 2008 and reported an overall IHM rate of 2.1%. Despite their thorough analyses, Konety et al [8] and Kim et al [18] did not stratify their study cohort according to the extent or type of metastatic disease. In this regard, our study provides better insight regarding IHM among patients treated with RC for metastatic BCa, as well as patients with NMBC.

Taken together, these findings suggest the use of stricter selection criteria among patients with NRNM and DM when RC is contemplated. However, further studies are needed to quantify the trade-off between higher IHM and the potential survival benefit of RC in metastatic BCa.

Interestingly, we observed significant differences in race distribution between the NRNM and DM groups. Established treatment barriers according to race have previously been recorded [19]. Thus, our observation suggests that racial differences might have influenced the decision to perform RC in NRNM and DM settings. In addition, African Americans exhibited a higher mortality risk in multivariable Cox regression analyses, as previously described [20].

Several important observations regarding hospital characteristics are also noteworthy. Specifically, we did not observe differences in DM rates for RC performed at hospitals with a high surgical volume. However, we observed lower rates of teaching institutions among individuals with DM, compared to non-metastatic patients (Table 1). It is possible that differences in staging might have been in effect between teaching and nonteaching institutions. For example, it is possible that a certain proportion of RC procedures might have been performed without prior knowledge of NRNM or DM. However, this confounding variable would not influence the results from our analysis. In addition, we observed differences in RC rates for NRNM and DM disease according to geographical location. This variability should ideally be reduced or eliminated, and uniformly distributed rates of RC should be reached regardless of geographical location.

Our study is not devoid of limitations. First, as noted, individuals undergoing RC in the context of NRNM or DM represent highly select subgroups. However, prospective randomized data are not and will not be available owing to the lack of ongoing trials evaluating IHM after RC in patients with metastatic BCa. Therefore, our study represents the largest and most contemporary source of evidence comparing IHM in these patient subgroups. Second, the extent of metastatic disease was quantified using ICD-9-CM codes. However, use of these codes provides only a partial description of the extent of metastatic disease and does not allow us to establish the metastatic disease burden. As a consequence, a more detailed definition of metastatic disease, such as that within an RCT, was not possible. Third, the NIS does not specify whether identification of metastatic disease was known before or after the surgery. Therefore, the intent for the surgical procedure (curative vs palliative) represents another piece of missing information. Similarly, the NIS database does not include several variables for the primary tumor such as clinical or pathological stage, and longitudinal data, such as 90-d mortality, were also unavailable. Highly importantly, the absence of information about preoperative chemotherapy must also be considered. These unmeasured confounders could have contributed to potentially interesting observations, as previously described [4].

5. Conclusions

In summary, RC performed in patients with DM predisposes to higher risk of IHM. Conversely, RC performed in patients with NRNM does not increase IHM risk. This observation might be of value for safety considerations in the design of future RCTs testing a potential survival benefit of RC according to the presence and extent of metastases. The current data originate from highly select patient subgroups with NRNM or DM BCa and should be interpreted with caution.

Author contributions: Marco Bandini 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: Zaffuto, Bandini, Karakiewicz.
Acquisition of data: Leyh-Bannurah.
Analysis and interpretation of data: Moschini.
Drafting of the manuscript: Zaffuto, Bandini, Karakiewicz.
Critical revision of the manuscript for important intellectual content: Gallina, Shariat, Briganti, Montorsi, Saad.
Statistical analysis: Zaffuto, Bandini.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.euo.2018.02.001.

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