

Research Report

Early Bone Metastases are Associated with Worse Outcomes in Metastatic Urothelial Carcinoma

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Abstract.

BACKGROUND: Outcomes of patients with metastatic urothelial carcinoma (mUC) with early bone metastases (eBM) vs no early bone metastases (nBM) have not thoroughly been described in the age of immuno-oncology.

OBJECTIVE: To compare survival and other clinical outcomes in patients with eBM and nBM.

METHODS: We used a multi-institutional database of patients with mUC treated with systemic therapy. Demographic, metastatic site, treatment patterns, and clinical outcomes were recorded. Wilcoxon rank-sum, chi-square tests were performed. Survival was estimated by Kaplan-Meier method; multivariable Cox analysis was performed.

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RESULTS: We identified 270 pts, 67% men, mean age 69 ± 11 years. At metastatic diagnosis, 27% had ≥ 1 eBM and were more likely to have *de novo* vs. recurrent metastases (42% vs 19%, $p < 0.001$). Patients with eBM had shorter overall survival (OS) vs. those with nBM, (6.1 vs 13.7 months, $p < 0.0001$). On multivariable analysis, eBM independently associated with higher risk of death, HR = 2.52 (95% CI: 1.75–3.63, $p < 0.0001$). OS was shorter for patients with eBM who received initial immune checkpoint inhibitor vs platinum-based chemotherapy, (1.6 vs 9.1 months, $p = 0.02$). Patients with eBM received higher opioid analgesic doses compared to patients with nBM and received quantitatively more palliative radiation.

CONCLUSIONS: Patients with mUC and eBM have poorer outcomes, may benefit less from anti-PD-1/PD-L1 therapy and represent an unmet need for novel therapeutic interventions. Dedicated clinical trials, biomarker validation to assist in patient selection, as well as consensus on reporting of non-measurable disease are required.

Keywords: Bladder cancer, urothelial cancer, metastases, bone, immunotherapy, palliative care

INTRODUCTION

Patients with urothelial carcinoma (UC) have substantial morbidity and the five-year overall survival (OS) of patients with UC who have distant metastases is unfortunately very low at approximately 5% [1]. In metastatic urothelial carcinoma (mUC), tissue specific tropism has been recognized, and common sites of metastatic spread include both lymph node, visceral organs and bone [2, 3]. Bone metastases may occur in almost 50% of cases and may confer significant morbidity [3]. Hypercalcemia, bone pain, pathologic fractures, and spinal cord compression are well known complications of bone metastases, and unfortunately many patients with mUC require hospitalization to manage related complications [4]. Visceral metastases have classically been defined for clinical trial data collection, as well as for clinical care, collectively to include liver, lung or bone metastases, the presence of metastases to any of these sites has been considered a negative prognostic clinical biomarker [5–8].

Disparate phenotypic metastatic progression patterns, such as the bone-only phenotype, may correspond with UC molecular subtypes and possibly suggest distinctive responses to systemic chemotherapy [2, 9–12]. For most patients, we continue to rely largely on clinical characteristics reflected in available trial data to inform treatment decision making. An elderly patient with mUC and *de-novo* bone metastases may have preexisting hearing or renal dysfunction and/or poor performance status secondary to bone pain and may not be a candidate for standard first-line cisplatin-based chemotherapy. With the approval of immune checkpoint inhibitors (ICI), there are now additional therapy options available for the non-cisplatin candidates, however little is known about how systemic chemotherapy and immunotherapy agents may differentially impact metastatic sites. Patients with early bone metastases (eBM), which

include those patients with bone metastases identified prior to initial systemic therapy for metastatic disease, have been classically grouped with patients with visceral disease and an absence of early bone metastases (nBM). The optimal care and therapy sequence in patients with and without eBM who cannot tolerate cisplatin has not been definitively clarified in a prospective trial.

We sought to evaluate the impact of eBM on OS and other clinical outcomes of patients with mUC treated with systemic therapy at three large academic cancer centers. We hypothesized that eBM would be associated with poorer outcomes vs nBM.

MATERIALS AND METHODS

Patient selection

This retrospective cohort study was conducted at three academic cancer centers in the US, after approval of the institutional review board according to principles by the Declaration of Helsinki (University Hospitals Seidman Cancer Center, #02-14-36; Medical College of Wisconsin, #PRO00035649; University of Washington, #0005690). Patients with mUC diagnosed between March 2005 and August 2019 who received at least one dose of systemic therapy in the metastatic setting were retrospectively identified from the electronic medical record (EMR). All pure urothelial and/or histologic variants were included. Records were reviewed; demographics, clinicopathologic factors, treatment patterns, and OS data were recorded. Imaging studies chosen by the treating physician (CT, bone scan, MRI, or PET) completed prior to initiation of systemic therapy were reviewed, sites of baseline metastatic disease were recorded. The presence of bone lesions on imaging suggestive and/or concerning for metastases as determined by the reading radiologist or those felt to be metastatic by the treating physician

were considered positive for bone metastases. Early bone metastases (eBM) was defined as the identification of ≥ 1 bone metastasis prior to initiation systemic treatment in the metastatic setting; patients who developed bone metastases after the initiation of systemic treatment in the metastatic setting were not included in this definition. Patients with mUC and the absence of early bone metastatic sites were categorized as having nBM. Patients were additionally categorized as having baseline bone only, bone and other non-bone visceral (liver and/or lung), non-bone visceral only, and neither bone nor non-bone visceral metastases. Initial systemic treatment was defined as the first systemic therapy administered in the metastatic setting and recorded and categorized as platinum-based chemotherapy (either cisplatin or carboplatin), ICI, or other (i.e. taxane, gemcitabine, FGFR inhibitor). Patients treated with systemic therapy as part of a clinical trial protocol were included. For patients who received additional lines of systemic therapy, the rationale for changes in treatment were recorded as indicated by the treating physician. Clinical progression was defined as a decline in performance status or development of clinical cancer-related symptoms necessitating a change or hold of systemic treatment. If radiographic progression was identified by the treating physician, the site of progression was recorded as bone, lymph node, lung, liver, CNS or other. Sites of palliative radiation were recorded. Outpatient medication records were reviewed, and maximum prescribed doses of opioid analgesic medications were recorded as morphine milligram equivalents (MME) at the defined oncology visits.

Statistical analysis

Demographic and cancer characteristics were summarized using descriptive statistics and compared between the cohorts using Wilcoxon rank-sum test for continuous and ordinal measures and chi-square tests for categorical outcomes. Patients were followed for OS from the time of the initial systemic treatment in the metastatic setting to death or last follow-up. Follow-up was administratively censored at 36 months due to the small number of patients under follow-up beyond that point. OS curves were estimated using Kaplan-Meier methods, and compared between groups via the log-rank test. Cox regression was used for the multivariable analysis of survival. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

Characteristics of the patient cohorts are listed in Table 1. Overall, 270 patients were identified, 67% men ($n=181$), and mean age was 69 ± 11 years at the start of initial systemic therapy in the metastatic setting. Patients received a median of two lines of systemic treatment. Most patients, 75% ($n=203$) had localized disease at the time of initial cancer diagnosis, and 26% ($n=70$), had received neoadjuvant chemotherapy (NAC). Almost half ($n=139$) of patients received platinum-based chemotherapy (54% cisplatin and 46% carboplatin) and a third ($n=92$) received an ICI as initial systemic treatment in the metastatic setting. Patients who had received prior NAC were more likely to receive an ICI in the initial metastatic setting ($p < 0.001$). A quarter of patients ($n=67$) had *de-novo* metastatic disease and these patients were more likely to be treated with platinum-based chemotherapy ($p < .001$), 61% received cisplatin and 39% received carboplatin.

Patterns of metastatic progression

At the time of metastatic disease diagnosis, 27% ($n=72$) of patients were identified as having eBM. In patients who had non-metastatic disease at initial diagnosis, eBM occurred at similar rates for those who had received NAC vs those who had not (20% vs 21%, $p=0.92$). Patients with eBM were more likely to have *de-novo* metastatic disease, compared to those who progressed from localized to metastatic disease (45% vs 21%, $p < 0.001$) (Table 1). Disease progression after initial systemic therapy in the metastatic setting occurred within the bones in 31% of patients with eBM vs 11% of patients with nBM ($p < 0.001$). Patients with eBM were less likely to have progression within lymph nodes (22% vs 41%, $p=0.005$) and lung (13% vs 26%, $p=0.020$) (Table 2). Patients with eBM were more likely to have a change or stop in initial systemic therapy due to clinical progression (30.6% vs 15.7%, $p=0.006$).

Opioid and palliative radiation outcomes

Patients with eBM were prescribed higher opioid analgesic doses compared to patients with nBM at the time of their first vs last outpatient oncology visit: MME of $60 \text{ mg} \pm 91 \text{ mg}$ vs $28 \text{ mg} \pm 65 \text{ mg}$ ($p=0.004$) and $171 \text{ mg} \pm 214 \text{ mg}$ vs. $94 \text{ mg} \pm 229 \text{ mg}$

Table 1
Demographic, Baseline and Treatment Characteristics

	Total N = 270 (%)	Early Bone Metastases (eBM) N = 72 (%)	No Early Bone Metastases (nBM) N = 198 (%)	P-Value
Sex				
Male	181 (67)	52 (72)	129 (65)	0.274
Female	89 (33)	20 (28)	69 (35)	
Mean Age ± SD	66.8 ± 10.7	68.0 ± 11.0	69.1 ± 10.7	0.432
Smoking History	193 (72)	54 (76)	139 (71)	0.407
Primary Site				
Bladder	211 (78)	60 (83)	151 (76)	0.214
Upper Tract	59 (22)	12 (17)	47 (24)	
Histology				
Urothelial	214 (80)	65 (90)	149 (76)	0.008
Mixed / Variant	55 (20)	7 (10)	48 (24)	
NAC*	69 (34)	14 (33)	55 (34)	0.920
Cisplatin	63 (90)	12 (80)	51 (93)	0.302
Carboplatin	6 (9)	3 (20)	3 (6)	
Adjuvant Chemotherapy	28 (11)	3 (4)	25 (13)	0.040
Definitive Surgery	147 (54)	28 (39)	119 (60)	0.002
Median TTM (range)†	10.6 (1.1 – 91.3)	17.0 (1.1 – 76.3)	10.0 (1.5 – 91.3)	0.459
De-novo metastatic	67 (25)	30 (42)	37 (19)	<0.001
Metastatic Sites‡				
Lymph Node	154 (57)	35 (49)	119 (60)	0.092
Lung	95 (35)	23 (32)	72 (36)	0.501
Liver	59 (22)	19 (26)	40 (20)	0.277
Lymph Node Only	81(30)	16(22)	65(33)	0.093
ECOG PS§				0.057
0	63 (28)	13 (21)	50 (31)	
1	102 (46)	27 (44)	75 (46)	
≥2	58 (26)	21 (34)	37 (23)	
Initial Treatment				0.041
Platinum-based	139 (52)	45 (63)	94 (48)	
Immune Checkpoint Inhibitor	92 (34)	16 (22)	76 (38)	
Other	39 (14)	11 (15)	28 (14)	
Initial Treatment: Platinum				0.532
Cisplatin	75 (54)	26 (58)	49 (52)	
Carboplatin	64 (46)	19 (42)	45 (48)	
Initial Treatment: ICI				0.296
Pembrolizumab	50 (54)	11 (69)	39 (51)	
Atezolizumab	35 (38)	5 (31)	30 (40)	
Nivolumab	7 (8)	0	7 (9)	

*NAC=Neoadjuvant Chemotherapy; †TTM= Time from definitive surgery to metastases development in months; ‡Metastatic disease may have been identified in more than one site with exception of lymph node only; §ECOG Performance Status at start of initial treatment, missing 17% of data

Table 2
Patterns of Disease Progression

Reason for change in Initial Treatment*	Total N = 270 (%)	Early Bone Metastases (eBM) N = 72 (%)	No Early Bone Metastases (nBM) N = 198 (%)	P-Value
Bone Progression	43(16)	22(31)	21(11)	<0.001
Liver Progression	56(21)	14(19)	42(21)	0.751
Lung Progression	60(22)	9(12.5)	51(26)	0.020
Nodal Progression	97(36)	16(22)	81(41)	0.005
Clinical Progression	53(20)	22(31)	31(16)	0.006

*Progressive disease may have been identified in more than one site

($p < 0.001$). There was no difference in the mean increase in MME usage between the two groups ($p = 0.151$).

Sixty-three percent ($n = 45$) of patients with eBM received palliative radiation to any site compared to 34% ($n = 66$) of patients with nBM ($p < 0.001$); those

with bone metastases received palliative radiation to quantitatively more sites ($p < 0.001$). Fifty-eight percent ($n = 42$) of patients with eBM received radiation to bone vs 11.6% ($n = 23$) of patients with nBM ($p < 0.001$).

Overall survival (OS)

The median OS from the start of initial systemic therapy in the metastatic setting was 11.5 months (95% CI: 9.3–12.9) for the entire cohort, median length of follow up was 18.4 months (0.5 – 36). Patients with eBM had significantly shorter OS than those with nBM (median 6.1 vs 13.7 months, $p < 0.0001$) (Fig. 1B). Comparison of OS between subgroups with different metastatic patterns demonstrated patients with metastatic disease at sites other than bone had longer OS compared to those with only bone metastases or both bone and visceral metastases ($p < 0.0001$) (Fig. 1C).

Multivariate analysis controlling for age, sex, smoking history, site of primary tumor, histology, presence of *de-novo* metastases, presence of liver and lung metastases, lymph node only metastases, ECOG PS, and initial systemic therapy, demonstrated a 2.5 fold increase in the risk of death for patients with eBM at the time of metastatic diagnosis, HR = 2.52 (95% CI: 1.75–3.63, $p < 0.0001$) (Table 3). The presence of liver metastases was also associated with increased risk of death, but not as much as that of eBM, HR = 1.47 (95% CI: 1.01–2.12, $p = 0.04$). Interestingly, lung metastases were not significantly associated with increased risk of death, HR = 0.91 (95% CI: 0.64–1.30, $p = 0.61$). Primary site of upper tract was also associated with longer OS when compared to bladder primary, HR = 0.66 (95% CI: 0.45–0.95, $p = 0.03$), as was treatment with initial platinum-based chemotherapy in the metastatic setting, HR of 0.60 versus ICI (95% CI: 0.54–0.85, $p = 0.004$). Neither variant histology, nor the presence of *de-novo* metastatic disease significantly impacted OS, HR = 0.76 (95% CI: 0.53–1.10, $p = 0.15$) and HR = 0.94 (95% CI: 0.65–1.36, $p = 0.74$) respectively.

OS comparisons between initial systemic therapy regimens for metastatic disease in patients with eBM demonstrated shorter OS for those who received ICI ($n = 14$) compared to patients who received platinum-based chemotherapy regimens ($n = 43$), median OS of 1.6 vs 9.1 months ($p = 0.02$) (Fig. 2A). Pairwise comparison of OS with stratified log-rank test of ICI versus platinum-based chemotherapy supported this finding ($p = 0.02$). In patients with nBM who

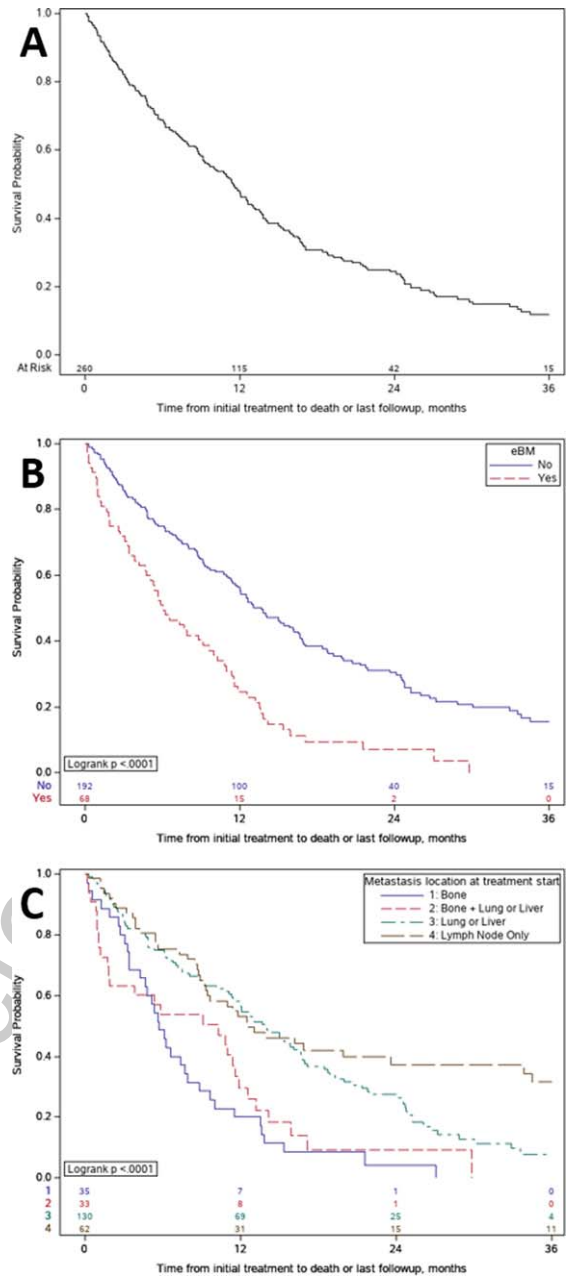


Fig. 1. Kaplan-Meier Overall Survival. A. Overall survival for the entire cohort was 11.5 months; B. Overall survival for patients with early bone metastases versus no bone metastases. Median overall survival was 6.1 versus 13.7 months ($p < 0.0001$), respectively; C. Overall survival subgroup comparisons amongst those with bone-only, mixed, and non-bone shows, C1 Bone without other visceral sites OS was 5.7 months, C2 Bone and other visceral sites OS was 10.3 months, C3 Non bone visceral sites OS was 13.8 months and C4 Neither visceral nor bone OS was 12.5 months; grouping includes one patient with only CNS metastases.

Table 3
Multivariable Cox Regression Analysis for Overall Survival

Factor	HR	95% CI	P-Value
eBM (Yes vs No)	2.52	(1.75 – 3.63)	<0.0001
Liver Metastases (Yes vs No)	1.47	(1.01 – 2.12)	0.042
Lung Metastases (Yes vs No)	0.91	(0.64 – 1.30)	0.610
Lymph Node Only Metastases (Yes vs No)	0.84	(0.56 – 1.27)	0.416
De-Novo Metastases (Yes vs No)	0.94	(0.65 – 1.36)	0.736
Age	1.00	(0.99 – 1.02)	0.982
Sex (Male vs Female)	0.91	(0.66 – 1.26)	0.563
Smoking (Yes vs No)	1.21	(0.86 – 1.71)	0.267
Upper vs Bladder Primary	0.66	(0.45 – 0.95)	0.027
Histology (Urothelial Ca vs. Variant)	0.76	(0.53 – 1.10)	0.147
ECOG PS 1 vs 0	1.56	(1.05 – 2.32)	0.027
ECOG PS ≥ 2 vs 0	2.33	(1.48 – 3.69)	<0.001
ECOG PS Missing	0.89	(0.53 – 1.49)	0.662
Initial Treatment: Platinum vs CPI	0.60	(0.42 – 0.85)	0.004
Initial Treatment: Other vs CPI	0.85	(0.54 – 1.33)	0.474

eBM, early bone metastases; CPI, checkpoint inhibitor; HR, hazard ratio; CI, confidence interval

256 received initial ICI, median OS was also shorter when
 257 compared to patients who received platinum-based
 258 chemotherapy, but this difference was non-significant
 259 on pairwise comparison with stratified log-rank test
 260 (11.8 vs 15.8 months; $p=0.11$) (Fig. 2B).

261 DISCUSSION

262 Multiple prognostic models have identified the
 263 presence of visceral metastases as a negative prognos-
 264 tic biomarker, and historically, bone metastases have
 265 been included in the definition of visceral metastases
 266 along with liver and lung metastases [3, 5–7]. Our
 267 study found that the presence of eBM, independent
 268 of other sites of metastases, was associated with a
 269 7.6-month decrease in median OS when compared to
 270 patients with nBM and a 2.5-fold increase in the risk
 271 of death. Lung metastases were not associated with
 272 increased risk, a finding which has previously been
 273 reported by other groups [13, 14]. These results sug-
 274 gest that eBM is a biomarker of poor prognosis. Lung,
 275 liver, and bone metastatic sites may represent differ-
 276 ing underlying biology or tumor microenvironment,
 277 and therapeutic responses may differ across sites of
 278 metastases; a hypothesis which should be tested in
 279 future prognostic models.

280 Additionally, we demonstrated that those patients
 281 with eBM had longer OS when treated with initial
 282 platinum-based chemotherapy regimens in the
 283 metastatic setting when compared to those who
 284 received ICI. Although the number of patients within
 285 this subset is small, and there are selection and con-
 286 founding biases in this retrospective cohort study, this
 287 represents an intriguing hypothesis which deserves

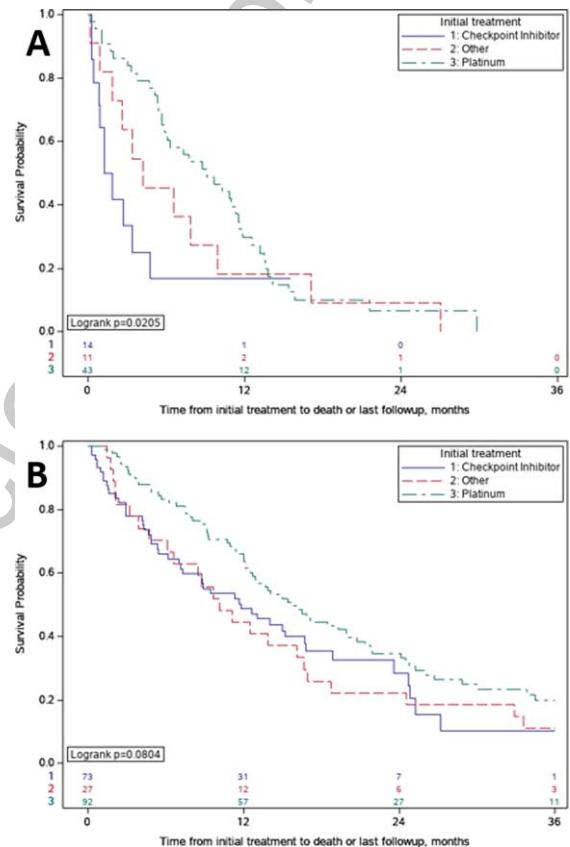


Fig. 2. Overall Survival Comparisons by Initial Treatment. A. Early Bone Metastases (eBM); For patients with eBM treated with immune checkpoint inhibitors versus platinum, overall survival was 1.6 vs 9.1 months ($p=0.02$). B. No Early Bone Metastases (nBM). For patients with nBM treated with immune checkpoint inhibitors versus platinum, overall survival was 11.8 vs 15.8 months ($p=0.11$).

288 further investigation. It is also interesting to inves- 340
289 tigate whether or not ICI therapy is beneficial in 341
290 patients with tumor progression within the bone 342
291 microenvironment. In other tumor types, such as non- 343
292 small cell lung cancer, patients with bone metastases 344
293 when compared to patients without bone metastases 345
294 have also demonstrated inferior responses to ICI [15, 346
295 16]. The efficacy of ICI in patients with mUC and 347
296 bone metastases is not well understood, and our data 348
297 support the need for further research on the bone mar- 349
298 row niche, host immune-tumor microenvironment, 350
299 and molecular mechanisms. 351

300 Recently Khaki et al. demonstrated that patients 352
301 with poor performance status (ECOG 2-3) may have 353
302 shorter OS when treated with ICI in the first-line 354
303 setting vs. those with ECOG PS 0-1; however, differ- 355
304 ences in ECOG PS at the time of initiation of systemic 356
305 therapy between patients with eBM and those with 357
306 nBM approached but did not reach statistical signif- 358
307 icance in our study [17]. The presence of eBM was 359
308 associated with a similar increase in risk of death as 360
309 that of ECOG performance status ≥ 2 , demonstrat- 361
310 ing the significant prognostic impact of early bone 362
311 metastases. After adjusting for ECOG performance 363
312 status and other factors, eBM remained a significant 364
313 independent negative prognostic factor in multivari- 365
314 ate analysis. 366

315 This study is the first to report on survival and 367
316 pain outcomes of patients with eBM who received 368
317 immune checkpoint inhibitors as an initial systemic 369
318 therapy in the metastatic setting. Few publications 370
319 exist in the pre-immune checkpoint era which address 371
320 outcomes of patients with mUC and early bone 372
321 metastases. A population-based study utilizing the 373
322 National Cancer Institute Surveillance, Epidemiology 374
323 and End Results (SEER) database demonstrated 375
324 similarly poor median OS of just 4 months in patients 376
325 with bone metastases at diagnosis [18]. Necchi et al. 377
326 evaluated outcomes in the subgroup of patients with 378
327 mUC with exclusive bone metastases compared to 379
328 those with no bone metastases and both bone and 380
329 other sites of metastases [2]. Similar to our findings, 381
330 patients with bone metastasis had worse prognosis 382
331 irrespective of other sites of disease. For patients 383
332 with bone-only metastatic sites, median OS was 14.4 384
333 months, those with bone and other metastatic sites 385
334 had median OS of 12 months [2]. In patients who 386
335 received first-line platinum-based chemotherapy, the 387
336 presence of bone metastases was associated with 388
337 lower response rate to chemotherapy [2]. 389

338 Patients with mUC have multiple sources of mor- 390
339 bidity due to prior chemotherapy, past surgeries, as 391

well as metastatic disease burden, all of which may 340
impact a patient's functional status and, ultimately, 341
treatment options. Bone metastases specifically may 342
lead to bone-related pain, pathologic fractures, hyper- 343
calcemia, and epidural spinal cord compression. We 344
demonstrated that patients with eBM were more 345
likely to present with *de-novo* metastatic disease 346
in bone and more likely to develop progressive or 347
new metastases within bone sites. Patients with eBM 348
required higher doses of opioid analgesics and more 349
palliative radiation (to bone, or to any site) than their 350
nBM counterparts. Overall, these results emphasize 351
that patients with eBM suffer higher disease-related 352
morbidity and emphasize the need for clinical care 353
approaches that adopt early, integrated palliative care. 354

355 These inferior pain and symptom control find- 356
ings amongst those with eBM impact quality of 357
life, performance status, and ability to participate 358
in clinical trials especially whose criteria restrict 359
candidate patients who have escalating pain or anal- 360
gesia requirements, radiation washout periods, or 361
concurrent radiation. Prospective trials that include 362
palliative care intervention and patient reported 363
outcome endpoints in bladder cancer in the era 364
of immuno-oncology and antibody-drug conjugates 365
are needed. Intervention trials have often excluded 366
patients with mUC who have bone progression due to 367
non-measurable disease status, poor prognosis, esca- 368
lating pain, or poor performance status. An urgent 369
need amongst the bladder cancer research commu- 370
nity is for development of consensus for inclusion 371
criteria that reconciles the current knowledge- and 372
access-gaps for those with non-measurable disease, 373
as well as for reporting outcomes of patients with 374
non-measurable disease. 375

376 This study reports on a multi-institutional dataset 377
and large patient cohort outside the filter of clinical 378
trials. Our study analyzed OS from initiation of sys- 379
temic therapy in the metastatic setting and thus is 380
not confounded by prior therapies in the metastatic 381
setting. The specific effect of subsequent treatments 382
is hard to quantify in this analysis. The recent 383
FDA approval of switch maintenance avelumab 384
after platinum-based chemotherapy, current FDA 385
approved salvage therapies after chemotherapy and 386
ICI (enfortumab-vedotin and erdafitinib), as well as 387
other non-FDA approved therapies may impact sur- 388
vival and/or other clinical outcomes [19–25]. 389

390 Limitations of our study include its retrospective 391
design in only three academic centers with moderate 392
sample size, potential heterogeneity in data extrac- 393
tion, missing data, selection and confounding biases, 394

392 as well as lack of randomization, standardized base-
 393 line imaging and centralized radiographic review.
 394 There was also variability in therapy selection, inter-
 395 vals of assessment and follow up times. There was
 396 no assessment of PD-L1 status, other molecular or
 397 laboratory biomarkers. We did not identify those
 398 patients who were cisplatin eligible vs. ineligible. We
 399 did not measure progression-free survival, cancer-
 400 specific survival, toxicities and overall response rate
 401 to a particular therapy, bone fractures and other skele-
 402 tal related events. Despite these certain limitations,
 403 this study generated several intriguing hypotheses
 404 and supports further assessment of this important
 405 patient population.

406 In conclusion, we define eBM as the presence of
 407 at least one identified metastatic bone lesion before
 408 initiation of systemic therapy in the metastatic set-
 409 ting. The presence of eBM was associated with poor
 410 response to treatment, need for escalated palliative
 411 measures, and early death compared to patients with
 412 nBM. It is likely that this clinical phenotype will
 413 be further understood with molecular profiling and
 414 subtyping. Tumor tissue correlatives and incorpora-
 415 tion of stratification based on osseous involvement in
 416 trials can further enhance our understanding of the
 417 mechanisms underlying bone and other metastatic
 418 site tropism. Consensus for inclusion and reporting of
 419 patients' non-measurable disease, as well as palliative
 420 care endpoints, should be developed and incorporated
 421 into clinical trial design.

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426 AUTHOR CONTRIBUTIONS

427 AN: Conception, performance of data collection,
 428 interpretation of data and writing the article

429 RC: Performance of data collection

430 EL: Performance of data collection

431 AS: Analysis of data

432 AK: Performance of data collection

433 LD: Performance of data collection

434 PG: Writing the article

435 BN: Performance of data collection and writing the
 436 article

GM: Performance of data collection and writing
 the article 437 438

TZ: Writing the article 439

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 the article 440 441

442 CONFLICT OF INTEREST

AA Nelson has no conflicts of interest to report 443

RJ Cronk has no conflicts of interest to report 444

EA Lemke has no conflicts of interest to report 445

A Szabo has no conflicts of interest to report 446

AR Khaki has previously owned stocks in Merck
 and Sanofi, sold as of 4/28/20. 447 448

LN Diamantopoulos has no conflicts of interest to
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P Grivas: (all unrelated in the last 3 years): consult-
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 Genomic Health, and Sanofi Aventis; and consult-
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 Medicine, Janssen, Amgen, MJH Associates, and
 BMS. Stock ownership/employment (spouse) from
 Capio Biosciences, Archimmune Therapeutics, and
 Nanorobotics 466 467 468 469 470 471 472 473 474 475

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