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Long-term survival in bone-predominant metastatic urothelial carcinoma

Jorge D. Ramos¹, Heather H. Cheng¹, and Evan Y. Yu¹

¹Department of Medicine, Division of Oncology, University of Washington School of Medicine, Seattle, WA 98109, USA.

Introduction

Bladder cancer is the most commonly diagnosed malignancy of the genitourinary tract. In 2013, an estimated 74,690 new cases were diagnosed and there were 15,580 deaths from bladder cancer in the United States.[1] The predominant histologic subtype is urothelial, accounting for 90% of cases in developed countries.[2] Superficial, non-muscle invasive urothelial carcinoma accounts for 70% of new bladder cancer diagnoses.[3] High-risk, typically high grade and T1 lesions, will progress to invade the muscularis propria in 20-25% of patients.[4] The remainder of new diagnoses are either muscle-invasive, locally advanced or metastatic urothelial carcinoma. Approximately 50% of patients with muscle-invasive disease will have a distant recurrence after radical cystectomy.[5]

Unfortunately, metastatic urothelial carcinoma portends a very poor prognosis. Treatment with standard first-line chemotherapy regimens such as gemcitabine/cisplatin (GC) or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) leads to a median overall survival of only approximately 15 months.[6, 7] Furthermore, despite better detection modalities and molecular understanding of the disease, there has been no significant improvement in survival over the past twenty years. Interestingly, a small subset of patients with metastatic disease are long-term survivors, with 5-year survival rates of 6.8%.[7], but there is limited data describing which patient- or tumor-related features associate with long-term survival. Here, we present two patients with bone-predominant metastatic urothelial cancer who have had prolonged survival with limited treatment. We also discuss current understanding of prognostic factors in metastatic urothelial carcinoma, and summarize potential future areas of investigation.

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Corresponding author: Evan Y. Yu, MD Seattle Cancer Care Alliance 825 Eastlake Ave E – G4-800 Box 358081 Seattle, WA 98109-1024 evanyu@u.washington.edu tel: (206) 288-6292.

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Case 1

A 65-year-old male with a long-standing smoking history presented with gross hematuria. A computed tomography (CT) scan showed a mass in the left lateral bladder wall and indeterminate size right-sided pelvic lymph nodes. The patient then underwent cystoscopy and transurethral resection of bladder tumor (TURBT) with pathology showing a high-grade urothelial carcinoma with evidence of muscle invasion with focal areas concerning for lymphovascular invasion. The patient then completed 3 cycles of dose-dense MVAC with follow-up imaging showing only some irregular wall thickening in the left bladder wall. He was then, unfortunately, lost to follow-up for several months. Approximately 11 months following initial presentation, the patient re-established care and was found on imaging to have evidence of recurrence in the left lateral bladder wall. This was completely resected and pathology was consistent with the earlier specimen. Following this TURBT, the patient underwent concomitant chemoradiation with low-dose weekly cisplatin and subsequent imaging revealed no evidence of disease. Approximately 21 months from initial diagnosis, he developed severe right shoulder pain with subsequent pathologic fracture. The patient was taken to the operating room for fixation and biopsy with pathology showing metastatic urothelial carcinoma. He was then treated with palliative radiotherapy. Restaging bone scan showed multiple osseous metastases involving both the axial and appendicular skeleton. There was no evidence of liver or lung metastases on CT. He was enrolled on a clinical trial of combination docetaxel and vandetanib for 4 months until restaging imaging showed progression into the soft tissue of the pre-existing bony metastatic lesions in the right ischium and right posterior 5th rib. The patient then received 4 cycles of gemcitabine and paclitaxel before going on a treatment holiday with every 3-6 month surveillance imaging. After 3 years off therapy and almost 6 years since diagnosis, bone scan continued to not show any signs of recurrence (Figure 1). However, surveillance CT imaging revealed new jejunal thickening. He underwent a small bowel resection with pathology confirming recurrence of previously diagnosed urothelial primary with evidence of perineural and lymphovascular invasion. The patient has now been surveyed for 6 months since the surgery, with reimaging every 3 months without any further evidence of disease recurrence.

Case 2

A 74-year-old male presented with superficial, non-muscle invasive urothelial carcinoma and was treated with multiple TURBTs and intravesicular BCG. Three years after initial presentation, he developed hematuria. Cystoscopy with TURBT revealed progression to high-grade muscle-invasive urothelial cancer and evidence of carcinoma in situ but no lymphovascular invasion in the left lateral bladder wall. The patient underwent chemoradiotherapy with weekly paclitaxel at a dose of 50 mg/m² after declining radical cystectomy. Four months after completing concomitant chemoradiation, the patient presented with neck pain and was noted to have cervical spine metastases at C1, C3, and C4 on CT. A biopsy was consistent with metastatic urothelial cancer. He underwent proton beam radiation therapy to the cervical spine and subsequent spinal fusion. Restaging CT scan revealed prominent peri-aortic and aorto-caval lymph nodes, the largest measuring 1.6 cm in diameter. Bone scan imaging demonstrated new bony metastatic disease in the sternum, ribs, left scapula, and multiple thoracic vertebrae. He then completed 6 cycles of chemotherapy with gemcitabine and cisplatin with complete regression of all suspicious

retroperitoneal lymph nodes. He has continued with surveillance imaging every 3-6 months for 2 years without evidence of soft tissue or bony disease progression despite being off all treatment (Figure 2).

Discussion

Our early understanding of prognosis in metastatic bladder cancer is based on long-term follow-up of an intergroup trial comparing cisplatin to MVAC.[8] In this analysis, non-urothelial histology, poor performance status, and the presence of either bone or liver metastases were found to be poor prognostic features.[9] Subsequently, Bajorin et al. also demonstrated that patients with poor performance status and/or the presence of “visceral metastases” had worse outcomes in a cohort of patients treated with MVAC.[10] In this and later studies, “visceral metastases” were grouped and defined as the presence of either liver, lung, and/or bone metastases. Interestingly, though significant in the univariate analysis, liver, lung, and bone metastases were not independently prognostic in the multivariate analysis. Since then, multiple other studies have shown similar results indicating the importance of “visceral metastases” on outcomes in metastatic urothelial cancer.[11-14] However, none of these studies defined bone metastases as an independent predictor of poor outcome. Conversely, in two studies, the presence of liver metastases alone conferred worse outcomes, with bone metastases not influencing survival.[15, 16] Taken together, these studies suggest that the number of sites of metastases and possibly the presence of liver metastases drive the poor prognosis in metastatic urothelial cancer and bone involvement may not negatively affect prognosis.

Our report describes two cases of long-term survival in patients with bone-predominant metastatic urothelial cancer. In review of the literature, only one other report of this phenomenon was identified.[17] In that report, a 38 year old patient with biopsy-proven metastatic urothelial cancer only to bone received 6 cycles of carboplatin and gemcitabine with complete radiographic resolution of all sites of disease. He then underwent radical cystoprostatectomy and pelvic lymph node dissection with pathology also demonstrating a complete response in the surgical specimen. After two years, the patient did not have evidence of disease recurrence.

Bone is an unrecognized, relatively common site of metastasis of from urothelial carcinoma. Reports estimate the frequency of bone metastases range from 25-47%.[18] However, only 5-15% of patients with urothelial cancer will have bone as the only site of metastatic disease.[18, 19] Neither the prognosis nor mechanism of development of bone-predominant metastatic urothelial cancer have been clearly elucidated. One recent study indicated that older patients had a higher frequency of single-site metastasis, including to bone, based on ICD-9 coding of hospitalized patients.[20] Potentially, as evidenced in this report, bone-predominant disease may be indicative of a good prognosis.

One possible mechanism may be that the genetic changes in tumors of patients with bone only or bone predominant metastases may be associated with either a specific treatment-sensitivity or a less aggressive disease phenotype. An example of the former would be case 1, a patient whose disease progressed rapidly after initiating therapy with docetaxel and

vandetanib, but had a dramatic and prolonged response to gemcitabine and paclitaxel. Furthermore, recent work suggests that 69% of invasive urothelial bladder carcinomas have targetable genomic alterations, particularly along the PI3K/Akt/mTOR and RTK/MAPK pathways.[21] By utilizing gene sequencing panels to identify and subsequently target these actionable mutations, we may be able to achieve better long term outcomes, not only in bone-predominant disease, but all patients with metastatic urothelial carcinoma.

Conclusion

In summary, the prognosis of patients with bone predominant metastatic urothelial cancer is not well-defined by the current literature. Here, we described two cases with excellent long-term survival. Additional observations of this sort in patients with bone predominant metastatic urothelial cancer will facilitate further study into the underlying molecular mechanisms.

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Clinical Practice Points

- Performance status and visceral metastases are established prognostic features in patients with bladder cancer
- A small subset of patients with metastatic urothelial carcinoma have excellent long term overall survival
- Contrary to early reports, bone-predominant metastatic disease may have better clinical outcomes, though this requires further investigation
- Ultimately, molecular characterization and identification of individual targetable genomic alterations may improve patient outcomes in metastatic urothelial carcinoma

Figure 1.

A. Bone scan prior to initiation of chemotherapy with gemcitabine and paclitaxel

B. Bone scan 36 months after completion of chemotherapy

Figure 2.

A. Bone scan prior to initiation of chemotherapy B. Bone scan 20 months after completion of chemotherapy