Long-term Survival of Bladder Cancer Metastatic to Femoral Neck Treated with Chemotherapy, Radiation, and Arthroplasty: A Case Report

John Defant  
*Wright State University - Main Campus*, defant.2@wright.edu

Scott Huff  
*Wright State University*, scott.huff@wright.edu

Joseph D. Henningsen  
*Wright State University*, joseph.henningsen@wright.edu

Anil Krishnamurthy  
*Wright State University*, anil.krishnamurthy@wright.edu

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Long-term Survival of Bladder Cancer Metastatic to Femoral Neck Treated with Chemotherapy, Radiation, and Arthroplasty: A Case Report
John Defant 1, Scott Huff 2, Joseph Henningsen 3, Anil Krishnamurthy 4

Abstract

Case: A 64-year-old male suffered a pathologic left femoral neck fracture. Biopsy demonstrated metastatic urothelial cancer with a non-muscle invasive bladder cancer primary confirmed by cystoscopy. Patient underwent hemiarthroplasty, chemotherapy, radiation, and eventually, a conversion to total hip arthroplasty. Today, over a decade from initial surgery, the patient remains alive and highly functional. To our knowledge, this is the only report of bone metastatic bladder cancer with over 10-year survival.

Conclusion: Bladder cancer metastatic to bone has a 5-year survival rate of 3%. Surgical resection of metastasis with reconstruction may confer a survival benefit in bony oligometastatic bladder cancer.

Introduction

Bladder cancer represents a spectrum of disease from less aggressive, non-muscle invasive to highly aggressive forms, of which all maintain the ability to metastasize. Metastasis to bone is somewhat common when the carcinoma is muscle invasive, ranging from approximately 14% – 32% of all metastatic bladder carcinoma cases.1 2 Non-muscle invasive bladder cancer (NMIBC) metastasizes in less than 10% of cases, typically to lymph nodes.3 Depending on the type, bladder cancer is treated with either radical cystectomy or transurethral resection, combined with radiation and chemotherapy.
Overall, once bladder cancer has metastasized to bone there is a very poor prognosis. There currently remains no consensus on surgical treatment of bony metastasis, with the strongest treatment recommendation being initiation of bisphosphonates or zoledronic acid to decrease skeletal related events. Management of pathologic or impending fractures is similar to that of other cancers including lung, breast, and prostate where intraleisional stabilization is typical. We report an extremely rare case of a gentleman who is cancer free and highly mobile over a decade following a diagnosis and surgical management of NMIBC metastatic to the left hip. Our patient was informed that information concerning his case would be described in this report and submitted for publication, to which he agreed.

**Case Description**

A 64-year-old gentleman presented to our orthopedic clinic with a one-month history of left hip pain. Plain radiographs revealed a lytic lesion of the left femoral neck (Fig. 1). A CT guided biopsy was scheduled to evaluate the etiology of the lesion, with plans for prophylactic stabilization if metastatic versus wide resection if primary.

Before scheduled biopsy, on September 17th, 2008, the patient had a near fall when his hip suddenly “buckled”. Radiographs demonstrated a new pathologic, displaced femoral neck fracture (Fig. 2). Patient was admitted and underwent CT guided biopsy. Following the return of pathology consistent with metastatic disease, patient underwent left hip cemented bipolar hemiarthroplasty (Fig. 3). As standard procedure, the femoral head and neck were resected, essentially performing a surgical metastasectomy of the lesion.
Final pathology demonstrated transitional cell type morphology and was positive for cytokeratin (CK) 7 and CK20 confirming urothelial malignancy. Biopsy stained negative for thyroid transcription factor (TTF), CD45, chromogranin, prostate specific antigen (PSA), and S100 protein, helping to rule-out other primaries, including lung cancer, lymphoma, neuroendocrine, prostate, and melanoma (Fig. 4).

A CT thorax/abdomen/pelvis did not reveal other metastases or sites concerning for primary tumor. PET scan demonstrated increased uptake in the left proximal femur and right pubic bone with physiologic uptake in the bladder. The patient began palliative radiation therapy of bony metastasis, which consisted of 3000 centigrays (cGy) in ten fractions to left hip and 2000 cGy in five fractions to the right pubic bone. During work-up to identify the primary tumor, cystoscopy was performed where an exophytic bladder lesion was identified, underwent transurethral resection, and sent for pathology. Biopsy was consistent with transitional carcinoma, papillary, non-invasive, and low grade with muscularis propria present. During cystoscopy prostate core needle biopsy was also performed and was positive for adenocarcinoma in 3 out of 6 cores. Concurrent prostate adenocarcinoma is found in 25-46% of patients undergoing cystoscopy for bladder cancer.7 Hematology/oncology began simultaneous treatment for both bladder and prostate primaries with combination chemotherapy and radiation. Gemcitabine 1000 mg/m² and cisplatin 70mg/m² cycles were completed followed by 4600 cGy of radiation to the bladder and prostate in 23 fractions. At a little over 2 years from initial fracture patient remained alive and asymptomatic. Patient was given a 4-week course of zoledronic acid by Hematology/Oncology, and considered cancer free with no plans for future imaging or studies without new symptoms.
Upon orthopedic follow-up 2½ years out from initial hemiarthroplasty, there was evidence of hemiarthroplasty hardware migrating proximally into the acetabular dome (Fig. 5). As patient was now cancer free per hematology/oncology patient underwent conversion to a total hip arthroplasty (THA) (Fig. 6). Over the next 24 months, the patient continued to do well despite the development of a chronic draining sinus. 2-stage revision was discussed, however patient declined and instead was placed on Bactrim DS for chronic suppression.

2 years following THA conversion, our patient presented with a significant increase in hip pain, which was determined to be loosening of the femoral components (Fig. 7). At this time the patient was agreeable to a 2-stage revision and subsequently underwent explant and antibiotic spacer placement. 3 months later, patient underwent the second stage with revision to a long stem, uncemented femoral component (Fig 8). Unfortunately, the patient developed an acute infection and was taken back for irrigation and debridement (I&D) with polyethylene exchange. The patient was initiated on ceftaroline acutely followed by chronic suppressive Bactrim DS and Rifampin, for which he has taken since 2013.

For the past 6 years this patient has had good functional use of the hip, without major complication besides intermittent development of a draining sinus. Suppressive therapy has allowed hardware to be retained and functional without any episodes of systemic infection. He was cleared to return to work as a painter in 2014. As of this publishing, the patient remains alive and highly mobile with minimal hip pain eleven years following metastatic transitional cell carcinoma diagnosis.

Discussion
Bladder cancer is a relatively common malignancy that, when metastasizes, portends a poor prognosis. Bladder cancer is generally categorized as muscle invasive or non-muscle invasive. The literature has limited descriptions of NMIBC metastatic to bone. In one study only 5 patients developed bone metastases without evidence of primary site invasion, among 1,000 total patients with bladder cancer.\textsuperscript{10} Case reports have described bony metastatic NMIBC which include metastases to the hand, foot, and knee.\textsuperscript{11,12,13} When any form of bladder cancer metastasizes to bone, the outcome is poor. 5-year survival rate is about 3% with mean survival time from 6 to 26 months.\textsuperscript{5,6,14} As of the writing of this manuscript we are aware of no metastatic bladder cancer patients with over 10-year survival.

There are several reasons that may have contributed to our patient’s remarkable course. Although, the initial hemiarthroplasty surgery was not intended to be curative, by removing the femoral head and neck a metastasectomy of the lesion was performed. There are no studies that have evaluated wide versus marginal resection in metastatic bladder cancer, however there is evidence that wide resection improves survival in single and oligometastatic renal cell carcinoma (RCC).\textsuperscript{15,16} Some controversy does remain with data suggesting any debulking of metastatic RCC, including intralesional resection, improves survival.\textsuperscript{17} Our patient appears to have been oligometastatic with lesions of the femoral neck and pubic bone, however only the primary tumor and femoral neck lesion were biopsy confirmed. While initial plans were for intralesional stabilization, following fracture, hemiarthroplasty was pursued given the displaced nature of the femoral neck fracture. By subsequently removing the entire femoral head and neck, the patient may have benefited from surgical metastasectomy. The survival of this patient raises the
question of whether oligometastatic NMIBC patients, similar to RCC patients, may benefit from undergoing surgical tumor debulking.

Of note, our patient did suffer from a long-standing infection of the THA prompting suppression chronically with Bactrim DS and Rifampin. Traditionally chronic infection and/or inflammation has been associated with immunosuppression and a tumor-friendly microenvironment.\textsuperscript{18} There are well-established relationships between infectious agents, including viruses and bacteria, and certain cancer types.\textsuperscript{19} Some viruses appear to exhibit oncolytic properties, thought to be a result of preferential infection of tumor cells and/or priming of the immune response.\textsuperscript{20} Currently we are aware of no evidence that suggests bacterial infection may impede tumor growth, however it is possible this had some effect on our patient’s local tumor environment. Interestingly there is some preliminary research demonstrating tumor suppressive effects of Rifampin primarily via anti-angiogenic properties.\textsuperscript{21} Importantly, in the case presented, chronic antibiotic intervention was begun over 2 years after diagnosis and Rifampin was not initiated until over 4 years after diagnosis.

Given the rarity of oligometastatic bladder cancer to bone, there is very little literature to guide surgical management. When curative radical cystectomy is not possible, combined chemotherapy and radiation are the recommended treatments. Surgical metastasectomy may increase survival rates in bony oligometastatic bladder cancer, similar to single and oligometastatic renal cell carcinoma. Due to persistently low survival rates in metastatic bladder cancer, future research should investigate this possibly life-prolonging measure in a larger cohort.

Conclusion
NMIBC metastasis to bone is a rare event, with a poor prognosis. We present the exceptional case of a patient who remains alive and highly functional over 10 years following NMIBC pathologic femoral neck fracture. Combined chemotherapy, radiation, and **surgical metastasectomy with reconstruction** may confer a survival benefit in metastatic bladder cancer.

**Figure Legend**

Figure 1. Painful lytic lesion of the left femoral neck
Figure 2. Pathologic femoral neck fracture

Figure 3. H&E stain, CK7 stain, CK20 stain, TFF, and Chromogranin stains consistent with urothelial (transitional) cell carcinoma
Figure 4. Evidence of proximal migration of hemiarthroplasty into the acetabular dome

Figure 5. Conversion to Total Hip Arthroplasty
Figure 6. Loosening of the femoral components of the THA with lucency around the femoral stem

Figure 7. THA revision to long stem prothesis
References


