Presentation, Treatment, and Outcomes of Dural Metastases in Men with Metastatic Castrate-Resistant Prostate Cancer: A Case Series

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Abstract

Purpose: Men with metastatic castrate-resistant prostate cancer (mCRPC) have shown increased survival since the introduction of docetaxel-based chemotherapy in 2004. While bone metastases are common in prostate cancer, cranial dural metastases (DM) are not. We hypothesize that longer survival in patients with mCRPC may increase the incidence of uncommon metastatic sites, including the cranial dura. We describe 10 cases of DM in men with mCRPC and review the relevant literature.

Materials and Methods: We conducted a retrospective chart review of 10 subjects with mCRPC, diagnosed ante-mortem with DM at our institution between August 1, 2003 and June 1, 2008. Variables analyzed included prognostic factors at prostate cancer diagnosis, number of therapies prior to DM, treatments administered for DM with response achieved, and survival following diagnosis of DM.

Results: Median age at prostate cancer diagnosis was 59 years (range, 52–80), with a median Gleason's score of 9 (range, 8–10) and prostate-specific antigen (PSA) of 37 ng/dL (range, 4.9–118). Fifty percent had metastatic disease at initial diagnosis. A median of 5 therapies (range, 1–13) were administered prior to diagnosis of DM, including a median of 1 course of chemotherapy (range, 1–3). Cranial neuropathies were the most common presenting symptoms of DM, and 8 of 10 patients received treatment for their DM, most often radiotherapy. Median survival for this group was 6.17 months (range, <1–15).

Conclusions: Treatment advances in mCRPC may lead to an increased incidence of previously rare metastatic sites. CNS symptoms in men with mCRPC should prompt evaluation for DM.

Introduction

PROSTATE CANCER is the second leading cause of cancer death in men, with an expected 32,050 deaths in 2010.¹ Advanced or metastatic prostate cancer remains incurable, and androgen ablation, the current initial standard-of-care treatment, affords men with this disease a median of 2-year time to progression.² For patients with castrate-resistant prostate cancer, defined either by progression of disease by serum prostate-specific antigen (PSA) or by radiographically measurable disease despite a castrate level of serum testosterone, the development of docetaxel-based chemotherapy in 2004 has led to increased overall survival.^{3,4}

While bone, lymph nodes, and even viscera are relatively common sites of metastases in prostate cancer, metastases to the central nervous system (CNS) and meninges remain

uncommon as sites of disease spread. More specifically, metastasis to the dura mater has rarely been reported in prostate cancer literature, with only sporadic mention found in case reports and autopsy series.^{5–21} Penley et al.⁵ reported the first case of discrete DM from prostate adenocarcinoma in 1981, and since then, there have been 14 other case reports of DM from prostate cancer in the literature,^{6–18} with additional cases mentioned only briefly in autopsy series.^{19–21} Presented here, to the authors' knowledge, is the first case series ($n = 10$) of DM diagnosed ante-mortem in patients with metastatic prostate cancer, with a review of the relevant literature. We hypothesize that the improved treatment regimens and resultant increased survival now enjoyed by patients with mCRPC may allow for the progression of disease in previously rare sites of metastasis, including the cranial dura.

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Accepted April 16, 2010.

Materials and Methods

A retrospective chart review of cases of DM diagnosed at the Medical College of Wisconsin between August 1, 2003 and June 1, 2008 in patients with castrate-resistant prostate cancer was undertaken for descriptive purposes. Of 124 total subjects seen with prostate cancer at the medical oncology clinic in this time period, 61 had documented metastatic disease, and 70% received chemotherapy for mCRPC. Ten subjects with mCRPC were found to have evidence of dural metastases. Institutional Review Board approval was obtained prior to review of all patient records. Variables extracted from the charts included age, Gleason's score and PSA at prostate cancer diagnosis; initial therapy following diagnosis; time from prostate cancer diagnosis to diagnosis of metastatic disease; time from completion of first hormone therapy to next treatment; median number of sites of metastasis; PSA at diagnosis of DM; symptoms of DM; number of systemic treatments prior to diagnosis of DM; type of and response to treatment for DM; and length of survival following diagnosis of DM.

Results

Median age at prostate cancer diagnosis was 59 years (range, 52–80) with a median Gleason's score of 9 (range, 7–10) and a median PSA of 37 ng/dL (range, 4.9–118; Table 1). Fifty percent of subjects had metastatic disease at the time of diagnosis, while those with early stage disease had a median 28 months (range, 2–120) until development of metastatic prostate cancer. A median of 20 months (range, 1–84) lapsed between initial systemic hormone therapy and the next systemic treatment administered. Subjects had a median of 2 additional sites of metastatic disease (range, 1–3) at the time of diagnosis of DM, with bone and lymph node involvement being most common. Additional sites of metastases are listed

in Table 1. All patients had 14 or more discrete sites of bone metastases, and all subjects had extra-axial skeletal disease. Median time from prostate cancer diagnosis to diagnosis of DM was 40 months (range, 21–164). Prior to development of DM, the most common pattern of disease progression was biochemical. Median PSA at diagnosis of DM was 193.7 ng/dL (range, 2.4–3011.3). Subjective symptoms reported at time of diagnosis with DM included dysphagia, chin numbness, dysarthria, blurred vision, and headache (Table 2). Objective findings included cranial neuropathies, specifically affecting the hypoglossal nerve and manifesting as tongue deviation (Table 2). Eight of 10 patients received treatment for their DM, primarily radiation therapy (Table 3). While complete resolution of symptoms was seen in only 1 patient, partial symptom resolution was reported in 5 of the 8 treated patients. Seven of the 8 treated patients had known pretreatment and post-treatment PSA values, and of these 7 patients, 3 demonstrated a decline in PSA following treatment for DM. Median PSA posttreatment for DM was 266 ng/dL (range, 3.8–2764.5). Three of the 8 treated subjects had imaging studies following therapy for DM, and of these 3 subjects, 1 had radiographic evidence of regression of DM (Fig. 1). In the months prior to DM diagnosis, patients showed a median weight loss of 5.5 pounds (range, –12.2 to +1.6 lbs). Following treatment, 3 patients gained weight while 2 patients had further reduction in body weight. Prior to the onset of DM, patients received a median of 3 systemic therapies (range, 1–5; Table 3). Following treatment for DM, palliative therapies including blood transfusions, radiotherapy, and radioisotope were most common (Table 3), although 3 patients went on to receive further systemic treatment with chemotherapy. For the 9 of 10 patients for whom survival status is known, median survival following diagnosis of DM was 6.17 months (range, <1 to 15 months). One patient transferred care following treatment and survival status is unknown.

TABLE 1. PATIENT DISEASE PROGRESSION

Subject	Age at prostate cancer diagnosis (years)	Gleason's score at prostate cancer diagnosis	PSA at prostate cancer diagnosis (ng/dL)	PSA at diagnosis of DM (ng/dL)	Other Sites of metastatic disease	Evidence of disease progression prior to diagnosis of DM	Time lapsed from diagnosis of prostate cancer to diagnosis of DM (months)
1	54	10	37	507.4	Bone	New bone metastases	22
2	61	9	118	2731.3	Liver Bone Lymph nodes Brain parenchyma	New bone metastases	44
3	52	7	37	197.9	Bone Lymph nodes	Rising PSA	46
4	80	9	4.9	8.6	Bone	New bone metastases	23
5	57	7	Not available	1344.9	Bone	Rising PSA	124
6	65	9	57	3011.3	Bone Lymph Nodes Lung	New bone metastases	36
7	56	8	30	2.4	Bone	New bone metastases	54
8	57	Not available	24	189.5	Bone	New bone metastases	24
9	66	Not available	Not available	168.8	Bone Lymph nodes	New bone metastases	21
10	67	9	76.6	46.3	Bone	New bone metastases	164

PSA, prostate-specific antigen; DM, dural metastases.

TABLE 2. SIGNS AND SYMPTOMS OF DURAL METASTASES (N=10)

Sign or symptom at diagnosis of DM	Number of subjects
Dysphagia	6
Chin numbness	6
Dysarthria	4
Blurry vision or diplopia	4
Headache	3
Tongue deviation	2

Total subjects, *n* = 10.
DM, dural metastases.

Discussion

PSA testing has led to diagnosis of earlier stage prostate cancer; however, once advanced cancer occurs, the most common sites of metastases include bone and retroperitoneal or pelvic lymph nodes.²² Treatment advances in recent years have resulted in increased therapy options for patients, including the use of bisphosphates and docetaxel-based chemotherapy. Consequentially, men with advanced prostate cancer are now undergoing more therapies, both in number and type, and have a documented survival advantage over historical controls.^{3,4}

DM are more common in other solid tumors including breast and lung, but continue to be a rare finding in prostate cancer.^{23,24} In a 2003 chart review series of 16,280 patients with prostate cancer, Tremont-Lukates et al.²¹ found only 19 cases of DM. This study also found cranial DM to be less common than intraparenchymal brain metastases, of which the authors identified 103 cases, and yet more common than leptomeningeal metastases, of which there were 5 cases. While Kleinschmidt-DeMasters²⁰ found that DM are rare in prostate cancer, the finding was somewhat more common among prostate cancer subjects in an autopsy series, versus

subjects in a surgical series. This suggests that DM are associated with late-stage, advanced disease and may not be identified ante-mortem.²⁰

Several mechanisms for metastatic spread from the prostate to the cranium have been proposed. Batson's theory suggests a direct, retrograde flow of tumor cells to the cranium through the vertebral veins.²⁵ A multistep or cascade theory suggests that metastasis occurs first in the bone and then moves to more distal locales.²² Our findings seem more consistent with the cascade theory, as all 10 subjects developed extensive bone metastases prior to DM. Six of our 10 subjects had skull metastases documented on imaging reports prior to development of DM, while the other 4 subjects had no known calvarial metastases during their care. For our 6 cases with skull metastases, a process of dural invasion by direct extension from calvarial bone deposits, first suggested by Lewis et al.,²⁶ seems plausible. In fact, upon review of computed tomography and magnetic resonance imaging reports for these 6 subjects, 3 were found to have documentation of extension of calvarial bone metastases to the dura. This mechanism of direct extension has also been supported by several other case reports of DM in prostate cancer.^{7,15,20}

The most common presenting symptoms of DM in our subjects were dysphagia, dysarthria, diplopia and facial numbness, and were consistent with other case report findings for DM in prostate cancer.^{11,15} The "numb chin syndrome," also noted by Confavreux et al.,¹¹ was found in 6 of our 10 patients. It should also be noted that several cases exist in the literature of prostate cancer first presenting as neurologic complications of intracranial metastases.^{15,27,28}

Our subjects, in general, represented a younger cohort with more aggressive disease, based both on a median age of 59 years and a median Gleason's score of 9 at initial diagnosis. Most subjects received numerous therapies prior to onset of DM, including docetaxel-based chemotherapy. Four of our patients, however, received no chemotherapy prior to DM, and 3 of these 4 received 2 or fewer hormone therapies prior to

TABLE 3. DETAILED PATIENT TREATMENT

Subject	Number of systemic therapies prior to development of DM ^a	Treatment for DM	Response to treatment for DM	Other treatments following treatment of DM
1	3	RT + Steroids	Complete symptom resolution	Docetaxel-based chemotherapy, palliative radioisotope therapy
2	5	RT	No response	Palliative therapy with blood transfusions
3	3	Steroids	Partial symptom resolution	Palliative care
4	2	None ^b	Not applicable	None
5	5	RT	Partial symptom resolution	Docetaxel-based chemotherapy, palliative radioisotope therapy
6	1	RT	Partial symptom resolution	Palliative care
7	3	RT	Partial symptom resolution	Palliative therapy with RT and blood transfusions
8	4	RT	Not available	Palliative care
9	2	RT	Partial symptom resolution	Docetaxel-based chemotherapy
10	3	None	Not applicable	None

^aSystemic therapies utilized included androgen deprivation alone; combined androgen blockade with one or more sequentially used anti-androgens; anti-androgen withdrawal; ketoconazole; docetaxel; and chemotherapy with experimental agents on clinical trials.

^bSteroids with RT planned for treatment of DM in subject 4, but patient expired before receiving treatment.

RT, Radiation therapy; DM, dural metastases.

FIG. 1. (A) T1-weighted magnetic resonance post-gadolinium image of a 69-year-old male demonstrating nodular dural metastases (arrows) in a patient with prostate cancer. (B) T1 weighted magnetic resonance post-gadolinium image of the same 69-year-old male, 3 months following radiation therapy, demonstrating marked improvement in dural metastases (arrows).

DM, suggesting that while more therapies may be associated with development of rare metastatic sites, a portion of our patient cohort may simply have had very aggressive disease.

We found that treatment of DM is largely beneficial to patients with mCRPC. Seventy-five percent of treated subjects

showed at least partial symptom resolution, and while life expectancy following diagnosis of DM was generally short (median 6.17 months), select subjects have shown longevity, including 3 patients who survived 9 months or longer. One subject survived 15 months postdiagnosis of DM, the longest in the series. This subject also showed one of the greatest lag times between initial prostate cancer diagnosis and onset of DM, at 125 months. Overall however, the time interval from prostate cancer diagnosis to development of DM was not significantly associated with survival post-DM diagnosis among our 10 patients. While our objective in presenting this case series is primarily for descriptive purposes, we also posit that improved therapies and increased survival in patients with mCRPC may lead to an increased incidence of previously uncommon metastatic sites. Other authors have also commented on this possible increased incidence of intracranial, and specifically dural, metastases in the setting of improved systemic therapies and survival for patients with advanced cancers.^{29,30} In considering other solid tumors, the introduction of trastuzumab therapy for patients with HER2-positive breast cancer in the late 1990s has been associated with a subsequent increased survival and increased incidence of CNS metastases in this patient population.³¹ It is merely our supposition that our 10 subjects may be evidence of a similar trend for DM in patients with metastatic prostate cancer who now experience the survival advantage of docetaxel chemotherapy. While yet unproven, the likelihood of such a trend may certainly become more evident over time.

Conclusions

Men with mCRPC enjoy improved survival due to availability of advanced treatments; therefore, unusual sites of metastasis, such as DM, may become more frequent, or may be increasingly recognized. We recommend that any patient with known mCRPC, as well as those with more aggressive prostate cancer phenotypes, who evidence CNS symptoms or cranial neuropathies should be considered as potentially having dural metastases, with appropriate counseling and diagnostic workup as indicated.

Acknowledgments

This project was funded by an R25 Education Grant from the National Cancer Institute.

The work presented here is original research and was presented in abstract and poster form at the 2009 Genitourinary Cancers Symposium, sponsored by the American Society of Clinical Oncology, the Society of Urologic Oncology, and the American Society for Therapeutic Radiology and Oncology.

Author Disclosure Statement

No competing financial interests exist.

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