Original Study

Prostate Cancer Central Nervous System Metastasis in a Contemporary Cohort

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Abstract

Central nervous system (CNS) metastasis from prostate cancer (PCA) is a rare event, but one with significant prognostic impact. We retrospectively identified 6596 cases of PCA, with 29 confirmed cases of CNS metastases from PCA. The incidence of CNS metastases in PCA is considerably increased in patients who receive medical therapy beyond first-line androgen deprivation therapy.

Introduction: Central nervous system (CNS) metastasis from prostate cancer (PCA) is a rare event, but one with significant prognostic impact for those affected. There are limited data on its impact in contemporary cohorts treated with modern agents. **Patients and Methods:** A retrospective institutional review was performed to characterize the occurrence/outcome of PCA CNS metastasis on all cases of PCA from 2011 to 2017. A manual chart review was performed to confirm PCA CNS metastases in all cases identified through a diagnostic code screening of the health data. **Results:** A total of 6596 cases of PCA were identified, with 29 (20 dural and 9 intraparenchymal) confirmed cases of CNS metastases from PCA. The median survival from the time of diagnosis of CNS metastasis was 2.6 months (95% confidence interval, 2.04-10.78 months) and 5.41 months (95% confidence interval, 3.03 months to not reached) for dural and parenchymal metastases, respectively. Among those who developed CNS metastases, approximately 79% of patients had prior exposure to abiraterone and/or enzalutamide, of whom 50% had $\geq$ 6 months of exposure. Four (0.07%) of the 5841 patients developed CNS metastases prior to the initiation of therapy or on androgen deprivation therapy alone. In contrast, 24 (8.6%) of the 279 patients with 2 or more lines of medical therapy developed CNS metastases. **Conclusions:** Our analysis highlights the continued poor prognosis of parenchymal and dural CNS metastases from PCA. CNS metastases in PCA remain a rare event with a 0.4% incidence in this series, but this incidence is considerably increased in patients who receive medical therapy beyond first-line androgen deprivation therapy.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■
Keywords: Brain metastasis, CNS metastasis, Dural metastasis, Prostate cancer

Introduction

Within the United States, prostate cancer is the most common cancer among men and second most common cause of cancer-related death.[1] Historically, the occurrence of CNS metastases in patients with prostate cancer has been extremely low.[2,3] A retrospective study of 16,280 patients with prostate cancer at a tertiary referral center between 1944 and 1998 revealed only 103 (0.63%) patients who were diagnosed with parenchymal metastases.[4] Interestingly, contemporary analysis suggests that, though still rare, the incidence of CNS metastases in patients with prostate cancer is gradually increasing.[2,5] A recent analysis of the Surveillance Epidemiology and End Results database between 2010 and 2015 identified over 23,000 men who were diagnosed with metastatic prostate cancer. Of these, CNS metastases were identified in 208 (0.89%) and 11 (3.57%) patients with adenocarcinoma and neuroendocrine tumors, respectively.[5]

This possible increase in the incidence of CNS metastases in prostate cancer has been attributed to improved systemic therapy that has increased life expectancy in patients with metastatic prostate cancer. Indeed, in the last decade, prostate cancer treatment has seen

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Submitted: May 17, 2020; Accepted: Jul 30, 2020

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1558-7673/$ - see frontmatter
https://doi.org/10.1016/j.clgc.2020.07.012

a rapid expansion in the number of therapeutic options, including new chemotherapeutics (cabazitaxel)[6] and potent hormonal agents (enzalutamide, abiraterone acetate, apalutamide),[7-9] that have quickly become the standard of care in advanced disease. Although there has been a considerable examination of the incidence, location, and treatment of CNS metastases of prostate cancer, there is, to date, a lack of research examining the association between the incidence of CNS metastases and longer survival owing to the availability of more effective therapies.[2,10] If such an association exists, it is unclear if it is owing purely to an increased length of survival or to a drug-induced change in disease phenotype. To explore the possibility of these associations, we performed a single-institution retrospective review of patients with prostate cancer and CNS metastasis treated over a 6-year period. This analysis focused on the site of metastasis as well as the medication exposures of patients prior to developing CNS involvement.

Patients and Methods

Health Data Compass (HDC) is an institutional data warehouse housed on the Anschutz Medical Campus in Aurora, Colorado. HDC integrates data from UCHealth and Colorado Children's Hospital, as well as outside sources such as the Colorado State Death Registry. HDC contains inpatient and outpatient electronic medical data for patient encounters, diagnoses, procedures, medications, laboratory results, and survival. HDC was used to identify patients with both a prostate cancer and CNS diagnosis from 2011 to 2017.

Regarding HDC, patient data is integrated into the data warehouse through processes that extract data from various source systems, transform that data into a common schema (OMOP CDM V5), and load the data into the data warehouse. The source data systems include clinical operational systems such as electronic health records, research databases, biorepositories, and processed genomics data (VCF files). Integration and linkage of these separate data sources creates a comprehensive longitudinal patient record. HDC has achieved NIST 800-53 compliance with external third-party validation. The HDC Informatics environment has been certified as HIPAA compliant.

Cases identified in the initial review as having CNS metastases and a concurrent prostate cancer diagnosis were then manually reviewed to ensure the metastases were of prostate origin. This manual chart review was done with an institutional review board-authorized protocol. Cases were excluded if they did not have imaging or biopsy confirmation of CNS disease. In addition, cases that had an alternative diagnosis such as an infection, demyelinating disease, or other secondary cancer that was more likely to explain a CNS imaging finding were excluded (see Supplemental Table 1 in the online version). Lesions originating in bone (eg, skull, but not in the dura or parenchyma) were excluded.

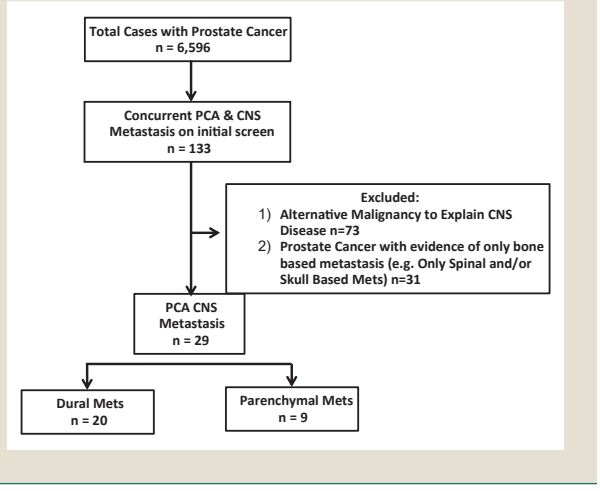
To examine possible relationships between medical therapy and the development of CNS metastasis, medication records were collected on all patients with prostate cancer via HDC. Data was collected on all commonly used agents in the medical therapy of advanced prostate cancer at the time of patient treatment. This included androgen deprivation therapy (leuprolide, degarelix, and/or goserelin), enzalutamide, abiraterone acetate, docetaxel, and cabazitaxel. To further verify the accuracy of the medication records, medication records were manually extracted during the chart review for all patients with confirmed prostate cancer CNS metastasis. The manually collected data from these 31 charts was compared with the HDC medication data from these same patients to assess congruency.

In this study, the incidence of CNS metastases and patient characteristics, including a detailed analysis of medication use, was collected. Among the individuals who developed CNS metastases, a Kaplan-Meier survival analysis was used to examine time from prostate cancer diagnosis to the time of CNS metastasis development and survival time following CNS development. The log-rank test was used to assess differences in the time to CNS development following prostate cancer diagnosis and survival following CNS disease development based on CNS location (ie, dural or intraparenchymal). The Fisher exact test was used to assess whether the rate of CNS metastasis differed between those that received 1 line of medical therapy compared with those that received 2 or more lines of therapy. Statistical analyses were conducted using R version 3.4.1, and an alpha level of 0.05 was used to assess significance.

Results

Of the 6596 cases of prostate cancer, there were 133 cases with diagnoses codes of prostate cancer and CNS (dural or parenchymal) neoplasm. Of these, 104 were excluded when detailed manual medical record review revealed they were unlikely to be related to prostate cancer. The majority (73/104) had a diagnosis of low-risk prostate cancer with a concurrent alternative malignancy deemed a more likely cause of the CNS metastasis (eg, metastatic lung cancer in a patient with a history of low-risk prostate cancer and a suppressed prostate specific antigen blood level). The additional 31 cases were coded as having CNS metastases, but excluded when records showed only spinal- or skull-based prostate cancer bone metastasis that did not have dural or intraparenchymal origin (Figure 1; Supplemental Table 1 [in the online version]). Twenty-nine cases of confirmed CNS prostate cancer metastases were

Figure 1 Flow Chart of Search and Selection Process for Included and Excluded Cases



Abbreviations: CNS = central nervous system; Mets = metastasis; PCA = prostate cancer.

Table 1 Total Incidence of CNS Metastasis in Patients With Prostate Cancer and Overview of Results Comparison Between Dural and Intraparenchymal-based CNS Metastasis

	Dural (n = 20), n (%)	Intraparenchymal (n = 9), n (%)
Patient race		
Non-Hispanic white or caucasian	27 (93.1)	
Latino or Hispanic American	2 (6.9)	
Median age at PCA diagnosis, y (IQR)	58.43 (53.01-65.89)	
Total incidence	29/6596 (0.44)	
Median time from PCA diagnosis to diagnosis of CNS metastases, y (IQR)	3.62 (2.48-8.47)	8.36 (3.59-NR)
Median overall survival after diagnosis of CNS metastases, mos (IQR)	2.6 (2.04-10.78)[a]	5.4 (3.03-NR)[a]
Median Gleason score (IQR)	9 (7-9)[b]	8 (8-8.75)[b]
Percentage high-grade (Gleason 8-10), %	69+	83+
History of abiraterone or enzalutamide exposure pre-CNS metastasis, %	85	67
Small-cell histology, %	11	17

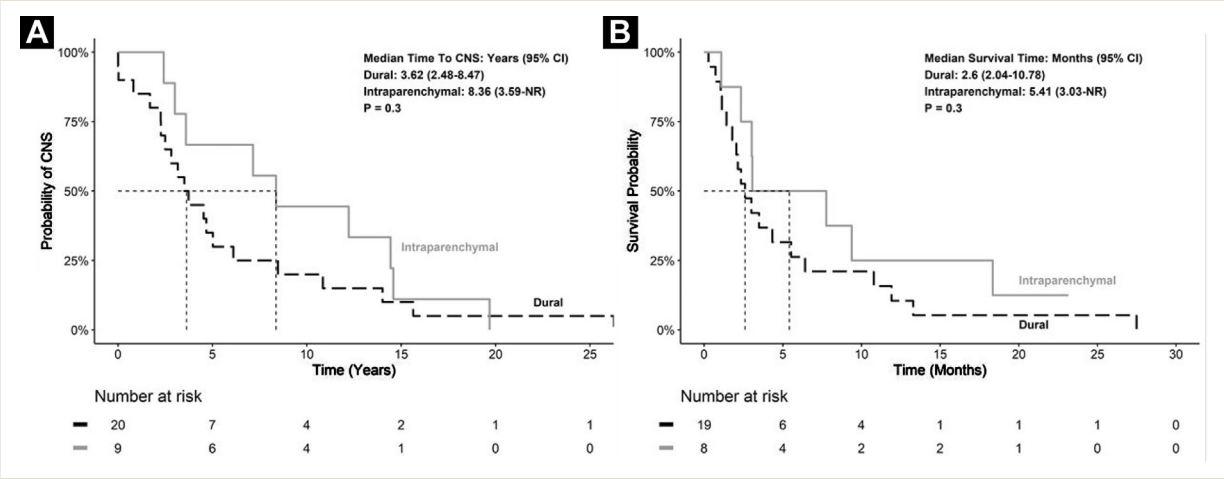
Abbreviations: CNS = central nervous system; IQR = interquartile range; PCA = prostate cancer.
[a]The sample size was slightly smaller for overall survival data; only 19 patients with dural metastases and 8 with intraparenchymal metastases had follow-up data available.
[b]Gleason score data was available for only 16 patients with dural metastases and 6 with intraparenchymal metastases.

identified with 9 representing intraparenchymal metastases and 20 representing dural metastases (Table 1).

The total incidence of CNS metastases for both dural and intraparenchymal events was found to be 0.44% in this series. This corresponded to 29 cases of prostate cancer CNS metastasis from the 6596 cases of prostate cancer examined. There was no evidence that patients who developed dural as opposed to intraparenchymal metastases differed in their time from prostate cancer diagnosis to CNS development ($P = .35$) (Figure 2). Although not significant, CNS metastases generally developed earlier for those with dural metastases compared with those with intraparenchymal metastases, with median times of 3.6 years versus 8.4 years, respectively. Although we did not see a significant difference in overall survival based on CNS location ($P = .3$), the median overall survival was longer for those with intraparenchymal CNS metastases compared with those with dural CNS metastases; 5.4 years versus 2.6 years, respectively (Figure 2).

Gleason scores were available for 22 of the 29 patients that developed CNS metastasis. The median Gleason score was 9 (range, 6-10) for dural metastasis and 8 (range, 7-9) for intraparenchymal

Figure 2 Kaplan-Meier Analysis of Median Time From PCA Diagnosis to CNS Metastasis for Dural and Intraparenchymal PCA CNS Metastasis (A); Median Overall Survival of PCA CNS Metastasis (B). The Log-Rank Test was Used to Assess Differences Between Dural or Intraparenchymal Metastasis for Time to CNS Development Following PCA Diagnosis and Survival Time Following CNS Development



Abbreviations: CNS = central nervous system; PCA = prostate cancer.

Table 2 Comparison of Dural- and Intraparenchymal-based Prostate Metastasis in Patients Who Received Abiraterone or Enzalutamide During Their Treatment Course Prior to CNS Development

	Dural Metastasis (n = 20), n (%)		Intraparenchymal Metastasis (n = 9), n (%)	
	Yes	No	Yes	No
History of abiraterone or enzalutamide exposure	17/20 (85)	3/20 (15)	6/9 (67)	3/9 (33)
>6 months of abiraterone or enzalutamide exposure	10/20 (50)	10/20 (50)	5/9 (56)	4/9 (44)
Median time to development of CNS metastasis	58.1 mos 4.8 y	31.7 mos 2.6 y	85.7 mos 7.1 y	159.8 mos 13.3 y

Abbreviation: CNS = central nervous system.

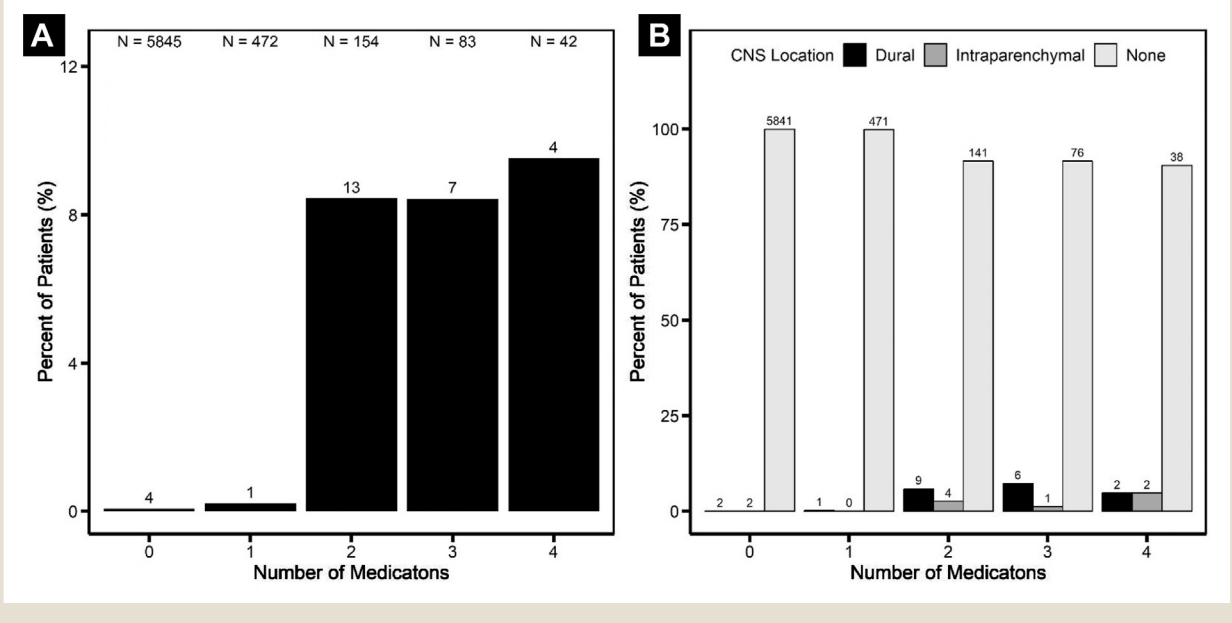
metastasis. The percentage of high-grade Gleason scores (8-10) was 69% versus 83% for each group, respectively, showing that the majority of those developing CNS metastases had high-grade prostate cancer. There were 2 cases of small-cell carcinoma in each group. Only 1 case from the dural group was diagnosed with small-cell carcinoma at the time of initial diagnosis. The additional 3 cases were found to have a small-cell component from a biopsy of a metastatic site, which occurred months to years after having an original diagnosis of adenocarcinoma.

Medication data showed 17 of 20 dural metastasis and 6 of 9 intraparenchymal metastasis cases had a history of abiraterone and/or enzalutamide exposure in the metastatic castrate-resistant setting. Approximately 52% of patients in both groups had ≥ 6 months of abiraterone and/or enzalutamide exposure (Table 2). In terms of any medication exposure, only 1 (0.2%) of the 472 patients who received 1 line of medical therapy for prostate cancer developed CNS metastasis. In contrast, 24 (8.6%) of the 279 patients who received 2 or more lines of medical therapy developed CNS metastasis (Figure 3). The difference in the rate of CNS metastases was significantly higher among those patients who received 2 or more lines of therapy compared with those who received 1 line of therapy ($P < .001$).

Discussion

The rate of parenchymal and dural metastases (0.44%) observed in our retrospective cohort is similar to that observed in other institutional analyses. A study of 7994 patients diagnosed with prostate cancer between 1980 and 1998 reported an incidence of

Figure 3 A, Incidence of CNS Metastasis by the Number of Different Medications a Patient Received. Medications Include Enzalutamide, Docetaxel, Abiraterone, or Androgen Deprivation Therapy (which Includes Lupron, Degarelix, and/or Goserelin). Counts for Those that Developed CNS are Shown Above Each bar, and the Total Number of Patients that Received the Given Number of Mediations in Each Column Shown at the Top of the Plot which Includes Those Without CNS Metastasis. Note that the y Axis Ranges From 0% to 12%. B, Breakdown Showing the Number of Medications Received by Patients including Those Without CNS Metastasis as Well as CNS Metastasis Broken Down by Dural and Intraparenchymal Locations



Abbreviation: CNS = central nervous system.

0.7%, whereas, as noted above, the study performed by Tremont-Lukats et al reported a rate of 0.63% (parenchymal metastases).[4,11] The slight differences in the rate of incidence in these other reports may be attributed to the fact that we manually reviewed all cases of CNS metastases to ensure accuracy after initial identification through diagnostic codes, which excluded many cases. It is not clear that preceding studies took this additional step. Referral bias for a particular institution may also play a role. Regardless, CNS metastases remains a rare event in the general population of men diagnosed with prostate cancer.

Our study demonstrates that patients who developed dural metastases did so on average almost 5 years sooner than those patients who developed parenchymal metastases (median, 3.0 years after diagnosis vs. 7.7 years). Despite this significant difference, once a patient was diagnosed with a CNS metastasis, either parenchymal or dural, location had no statistically significant impact on the very poor survival observed.

We identified that the rate of CNS metastasis was significantly ($P < .001$) higher among those that received 2 or more lines of medical therapy (8.6%) compared with those treated with 1 line (0.2%) (Figure 3). Given the limitations of this assessment (ie, potential confounders and specific follow-up time information was not collected), there may be other factors associated with this increased rate of CNS metastasis. However, to our knowledge, this study is the first to examine the association between modern medical therapies for advanced prostate cancer and the incidence of CNS metastases.

Limitations of the analysis include the retrospective nature of the study as well as the limited number of events precluding more powerful statistical analysis. Additionally, given the limited number of events and limits of the data collected, assessment of potential confounders, such as prostate-specific antigen, Gleason score, age, etc, were not performed. Nevertheless, the profound increase of risk observed in patients with $\geq$ 2 lines of therapy suggests the existence of a population that is at an elevated risk of developing CNS metastases, a clinically relevant finding in the management of advanced prostate cancer. Whether that risk is owing to increased survival given modern treatment, improved imaging modalities,[12] a phenotypic change owing to drug exposure, or a specific disease phenotype itself, is unclear. Given the substantial changes advanced prostate cancer treatment has undergone, it is important for clinicians to appreciate that, although rare in the prostate cancer population in general, CNS metastases are not rare in patients with advanced disease after multiple lines of therapy.

Conclusion

CNS metastases in prostate cancer remain a rare event overall, but one with significant prognostic impact. The risk of developing CNS metastasis is associated more closely with the total amount of therapy given rather than the specific agents used or the initial risk factors at diagnosis such as Gleason score or histologic grade. Despite the small number of events of interest in this retrospective study, the $>$ 8% incidence of CNS metastases in patients with $\geq$ 2 lines of therapy is intriguing and makes prostate cancer CNS metastasis an important clinical consideration for patients who receive multiple lines of medical treatment.

Clinical Practice Points

- CNS metastasis from PCA is a rare event, but one with significant prognostic impact for those affected. There are limited data on its impact in contemporary cohorts treated with modern agents.
- A total of 6596 cases of PCA were retrospectively identified, with 29 (20 dural and 9 intraparenchymal) confirmed cases of CNS metastases from PCA. Among those who developed CNS metastases, approximately 79% of patients had prior exposure to abiraterone and/or enzalutamide, of whom 50% had $\geq$ 6 months of exposure. Four (0.07%) of the 5841 patients developed CNS metastases prior to the initiation of medical therapy or on ADT alone. In contrast, 24 (8.6%) of the 279 patients with 2 or more lines of medical therapy developed CNS metastases.
- The risk of developing CNS metastasis is associated more closely with the overall intensity and duration of medical therapy given rather than the specific agents used or the initial risk factors at diagnosis such as Gleason score or histologic grade. Despite the small number of events of interest in this retrospective study, the observation of $>$ 8% incidence of CNS metastases in patients with $\geq$ 2 lines of therapy is intriguing and makes PCA CNS metastasis an important clinical consideration for patients who receive multiple lines of medical treatment.

CRediT authorship contribution statement

Peter J. Boxley: Writing - original draft, Writing - review & editing, Investigation, Conceptualization, Methodology, Visualization. **Derek E. Smith:** Writing - original draft, Methodology, Formal analysis, Investigation, Software, Data curation, Visualization, Validation, Writing - review & editing. **Dexiang Gao:** Methodology, Formal analysis, Writing - review & editing. **Elizabeth R. Kessler:** Writing - review & editing, Conceptualization. **Benjamin Echalier:** Data curation, Validation, Investigation, Writing - review & editing. **Brandon Bernard:** Writing - review & editing, Visualization. **D. Ryan Ormond:** Writing - review & editing, Visualization. **Elaine T. Lam:** Writing - review & editing, Conceptualization. **Brian D. Kavanagh:** Writing - review & editing, Visualization. **Thomas W. Flaig:** Methodology, Writing - original draft, Writing - review & editing, Conceptualization, Supervision, Validation.

Acknowledgments

The authors gratefully acknowledge the Finlon-Glode Fellowship endowment, which supported this work and publication. The authors recognize the assistance of the Biostatistics Shared Resource of the University of Colorado Cancer Center (P30CA046934) and the Health Data Compass Data Warehouse Project (healthdatacompass.org). Additionally, the authors thank and acknowledge Paul Brittain for his contributions to this project.

Supplemental Data

Supplemental table accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2020.07.012.

Disclosure

Dr Flaig reports institutional payment for clinical trial costs from Pfizer, Safoni, Medivation, Dendreon, GTx, Janssen Oncology, Bavarian Nordic, Exelixis, Aragon Pharmaceuticals, Tokai Pharmaceuricals, Lilly, Astellas Pharma, SmithKline Beecham, Bristol Myers Squibb, and Genentech; institutional payment for clinical trial costs and research support from Novartis; and leadership, stock, and other ownership interests from Aurora Oncology. The remaining authors have stated that they have no conflicts of interest related to this work.

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Supplemental Data

Supplemental Table 1 List of ICD-9 and ICD-10 Codes Utilized in the Database Review to Find Patients With Prostate Cancer as Well as CNS Metastasis

ICD-9/10 Code	Diagnosis
C185/61	Malignant neoplasm of prostate
C191.9/71.9	Malignant neoplasm of brain, unspecified
C198.3/79.31	Secondary malignant neoplasm of brain
C198.4/79.4	Secondary malignant neoplasm of other parts of nervous system
C198.5/79.51	Secondary malignant neoplasm of bone

Abbreviations: CNS = central nervous system; ICD = International Classification of Diseases.