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Original Article

Descriptive Analysis of Patients with Urothelial Cancer Brain Metastases Treated with Stereotactic Radiosurgery and Surgical Resection

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Abstract

Background and objectives: Information on the survival of urothelial cancer (UCa) patients with brain metastases (BM) is largely unreliable due to the rarity of such cases. Previous studies that have attempted to capture the prevalence and survival of these patients are limited to case series and retrospective studies with small cohort sizes. This study aimed to explore patient characteristics and treatment outcomes based on treatment modalities from a large sample of patients with UCa and BM.

Methods: In this retrospective study, we utilized the TriNetX Research Network, a real-world and in-house database with longitudinal electronic medical records from 92 institutions. The database was queried for patients with UCa who also had BM. Kaplan–Meier plots were used to assess overall survival (OS). Log-rank tests were applied for stratified outcomes. The Cox proportional hazards model was used for continuous data.

Results: We identified 357 patients with UCa and BM, representing 4.7% of the 7,521 patients diagnosed with primary UCa. The mean age at diagnosis was 65.6 years, with a predominance of male patients (67%). The median OS from BM diagnosis was 18.6 months. For patients treated solely with stereotactic radiosurgery (SRS), the median OS was 20.8 months. For those treated with both SRS and surgical resection, the median OS was 18.6 months. There was no significant difference in survival between patients treated with SRS alone and those treated with both SRS and surgical resection ($p = 0.875$). For patients treated only with gemcitabine chemotherapy, the median OS was 15.4 months.

Conclusions: This study represents the largest known retrospective analysis of UCa patients with BM. Survival trends for patients treated with surgical resection, SRS, and systemic therapies are described in detail.

Introduction

Metastasis of urothelial carcinoma (UCa) to distant organs, although rare, is associated with high morbidity and mortality. The five-year relative survival rate for stage IV UCa is 22%, compared to 97% for stage I disease.[1] While UCa of the bladder can metastasize to almost any organ, the most common sites are the lymph nodes, liver, lung, bone, and peritoneum.[2] Metastasis in the brain is extremely rare, with reports limited to case studies and small retrospective cohorts.[2–6] The frequency of brain metastases (BM) in patients with UCa has been previously reported to be 1–7%,[7,8] though these estimates may be unreliable due to the rarity of reported cases. Consequently, studying patient outcomes with Uca and BM at any single institution presents a clinical challenge due to the small number of cases.

The main treatments for patients with BM are surgical resection or stereotactic radiosurgery (SRS). Whole brain radiotherapy is rarely used due to the superior safety and efficacy of SRS for local control of BM.[9,10] Despite abundant evidence on survival for patients with more common BM such as those from lung, breast,

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and melanoma cancers, there is limited information on survival for patients with Uca and BM. Data on survival following surgical resection and SRS in Uca with BM are particularly scarce. In this study, we report the largest retrospective cohort to date, aimed at elucidating survival trends for patients with Uca and BM treated with various modalities.

Materials and methods

Data source

The TriNetX Research Network (TriNetX Inc., Cambridge, MA), a real-world and in-house database, is a global federated health research network that combines real-time access to longitudinal electronic medical records and administrative claims data. It includes a diverse range of healthcare organizations (HCOs) spanning various geographic locations, age groups, and income levels. This report utilizes data from a network called the Global Collaborative Network, which comprises 92 HCOs. The TriNetX platform complies with the Health Insurance Portability and Accountability Act and the General Data Protection Regulation. Most contributing HCOs are located in the USA and the European Union.

Data collection

As TriNetX is a federated database, an institutional review board waiver was granted for its use. Given that this is a retrospective study with minimal risk, a waiver of authorization and informed consent was approved. The study protocols adhered to the ethical guidelines outlined in the latest version of the Declaration of Helsinki (as revised in 2013). Data were queried using the International Classification of Diseases, Tenth Revision, Clinical Modification, and Current Procedural Terminology codes. The use of this database was supported by literature validating its application for similar projects, and the specific details of this research network have been previously described.[11–13]

The database was queried for patients with a diagnosis of urothelial cancer who also had metastases to the brain or other parts of the central nervous system (CNS). The cohort was generated in November 2022 and includes patients from November 2002 to November 2022. The analysis covered several treatment modalities, including stereotactic radiosurgery, craniotomy, navigational procedures, and various drugs such as gemcitabine, methotrexate, enfortumab, atezolizumab, axitinib, carboplatin, sunitinib, lenvatinib, pazopanib, everolimus, cisplatin, nivolumab, pembrolizumab, and cabozantinib.

Statistical analysis

Kaplan–Meier plots were created to assess time-to-event variables, such as overall survival (OS), including time intervals from the date of development of intracranial metastases. Log-rank tests were used for stratified outcomes, while the Cox proportional hazards model was applied to continuous data. Chi-square analysis was used for categorical variables. All statistical tests were two-tailed, and a *p*-value of less than 0.05 was considered statistically significant.

Results

Cohort demographics

Patient characteristics and treatment parameters are shown in Table 1. The mean age at diagnosis of BM was 65.6 years (±12.4).

Table 1. Patient demographic characteristics

Characteristic	N = 357[a] patients
Mean age, years	65.4 (12.4)
Gender	
Male, %	241 (67%)
Female, %	103 (29%)
Other, %	13 (4%)
Race	
White, %	259 (72%)
Black or African American, %	23 (6%)
American Indian or Alaska Native, %	10 (3%)
Asian American, %	10 (3%)
Unknown Race, %	55 (15%)
Comorbidities	
Hypertension, %	250 (70%)
Cerebrovascular diseases, %	89 (25%)
Diabetes, %	90 (25%)
Obesity, %	68 (19%)
Colorectal cancer, %	36 (10%)

[a]Mean (Standard Deviation); n (%)

Among the patients, 241 (67%) were male and 103 (29%) were female. The racial distribution was as follows: 259 patients (72%) were White, 23 patients (6%) were Black or African American, 10 patients (3%) were American Indian or Alaska Native, and 10 patients (3%) were Asian American. The predominant comorbidities in the cohort were hypertension (70%), ischemic heart disease (39%), cerebrovascular diseases (25%), diabetes (25%), and obesity (19%). The most frequently identified cancer outside of the genitourinary tract was colorectal cancer, found in 10% of patients.

Survival

We examined a total of 119,653,901 patients in the database and identified 7,521 patients with UCa (0.6%). The survival rate for patients diagnosed with primary UCa 19.9 years after the initial cancer diagnosis is 88%. Consequently, the majority of patients in this cohort were in the Ta or T1 stage of UCa (non-muscle invasive bladder cancer).[14] Of the patients with UCa, 357 developed BM (4.7%).

At the time of analysis, 170 patients were deceased, and 187 were alive. Ninety-nine patients had undergone surgical resection of the primary tumor site. The median OS from the time of BM diagnosis was 18.6 months. Actuarial survival rates were 64%, 54.1%, 45.6%, and 36.1% at six months, and at one, two, and five years, respectively (Fig. 1a). Forty-one patients underwent SRS alone, with a median OS from BM diagnosis of 20.8 months. Actuarial survival rates were 70.3%, 62.3%, 44.5%, and 35.6% at six months, and at one, two, and five years, respectively (Fig. 1b). Seventy patients underwent SRS with craniotomy, with a median OS from BM diagnosis of 18.6 months. Actuarial survival rates were 69.5%, 55.7%, 44%, 36%, and 35.6% at six months, and at one, two, and five years, respectively (Fig. 1c). There was no significant difference in OS between patients treated with SRS alone

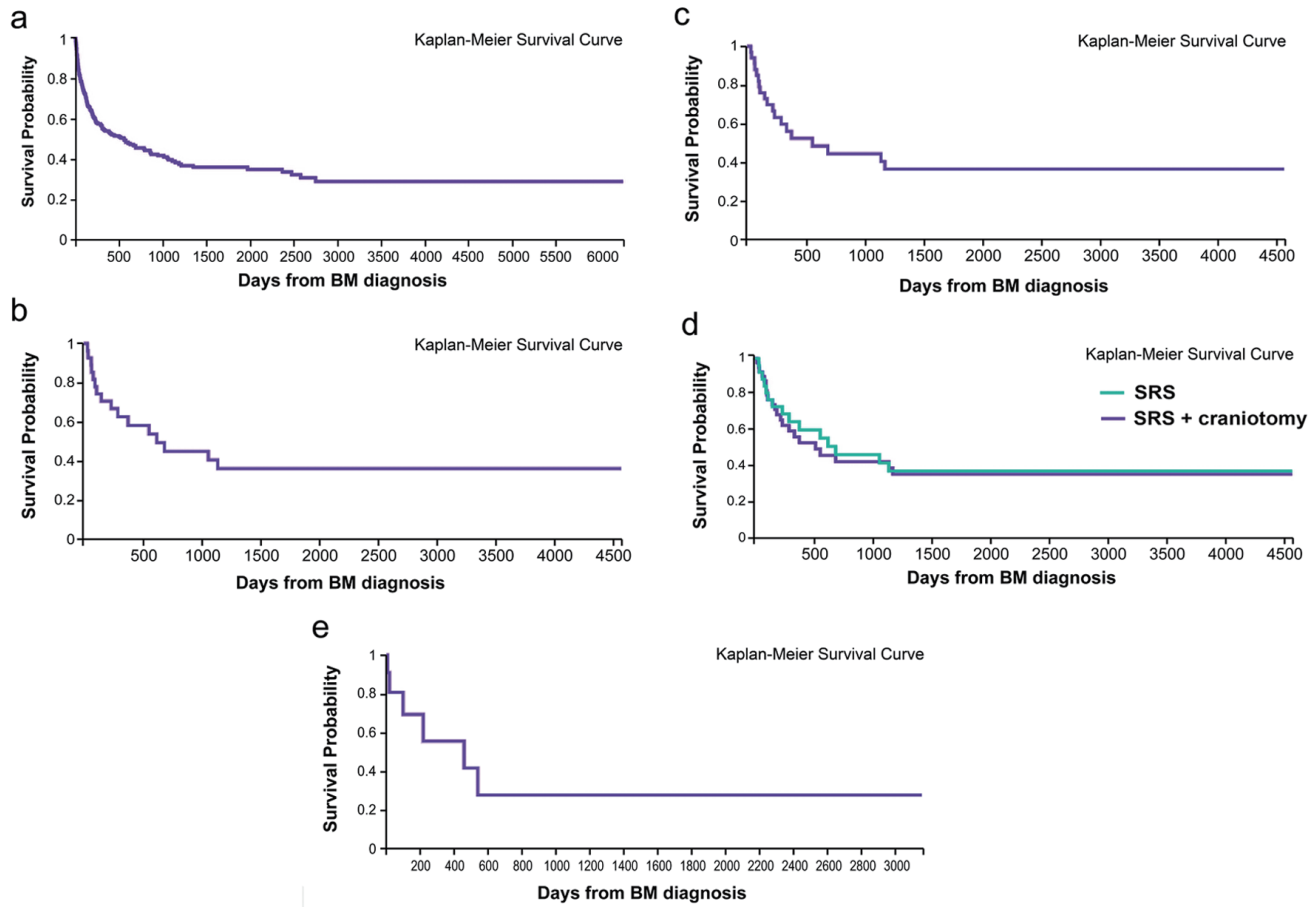

Fig. 1. Overall Survival Curves. (a) Kaplan-Meier graph showing overall survival (OS) for all patients (n = 357) from the time of brain metastases (BM) diagnosis. (b) Kaplan-Meier graph showing OS from the time of brain metastases diagnosis for patients who underwent stereotactic radiosurgery (SRS) alone (n = 40). (c) Kaplan-Meier graph showing OS from the time of brain metastases diagnosis for patients who underwent SRS and craniotomy (n = 70). (d) Log-rank graph comparing OS between patients who underwent SRS alone (n = 40) and those who underwent SRS with craniotomy (n = 70) (p = 0.8747). (e) Kaplan-Meier graph showing OS from the time of brain metastases diagnosis for patients treated with gemcitabine alone without any surgical intervention (n = 37).

and those treated with SRS and surgical resection (Hazard Ratio (HR)1.089, 95% Confidence Interval (CI) .564–2.101, p = 0.8747) (Fig. 1d).

Gemcitabine and cisplatin chemotherapy regimens are now considered the standard treatment for advanced UCa.[15] Additionally, these regimens have been shown to have high CNS penetration for the treatment of UCa with BM. Thirty-seven patients were treated with gemcitabine alone, without neurosurgical intervention. Their median OS from BM diagnosis was 15.4 months, with actuarial survival rates of 69.3%, 55.4%, and 27.8% at six months, and at one and two years, respectively (Fig. 1e).

Discussion

The first documented case of UCa with BM was reported by Watkins and Lower in 1924.[16–18] Since then, similar reports have been scarce, mainly limited to case series. The limited literature on this topic is partly due to other organs being more favorable sites for UCa metastasis compared to the CNS, as evidenced by our finding that only 4.7% of UCa patients present with BM. Furthermore, once metastases reach the CNS, the poor prognosis complicates thorough analysis. Bladder cancer commonly spreads distally through hematogenous and lymphatic dissemination.[2,17,19] While the exact biological process through which UCa metastasizes to the CNS remains unclear, it likely involves hematogenous spread via the vertebral venous plexus (Batson's plexus) (Fig. 2).[17] Historically, aggressive treatment options for UCa with BM were limited due to poor CNS penetrance, resulting in the CNS acting as a sanctuary site for distant metastases. However, the advent of radiosurgery and platinum-based agents for BM treatment has led to increased survival for UCa patients.[15]

This large-scale retrospective study using real-world data from TrinetX contributes to the emerging literature on UCa patients with BM, being the largest study to capture the OS of patients managed with various treatments. Our study found that the mean age at diagnosis of UCa is 65.6, with a male-to-female ratio of more than 2:1, consistent with prior reports.[20,21] We observed that the survival rate for patients diagnosed with primary UCa is favorable, with 88% surviving 19.9 years after diagnosis. In contrast, UCa that has spread to the CNS has a median OS rate of 18.6 months from the onset of BM detection. When analyzing survival based on treatment type, we found that patients treated with SRS alone exhibited a median OS of 20.8 months, while those treated with SRS plus resection had a median OS of 18.6 months. However, due to data-

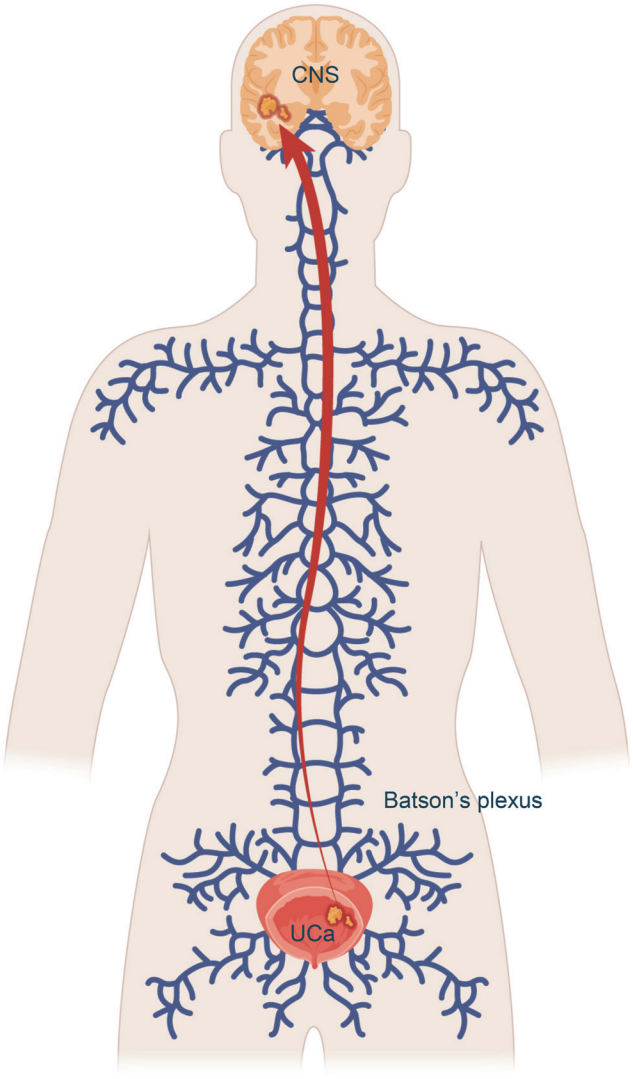

Fig. 2. Illustration depicting Batson's plexus as a possible route for hematogenous spreading of UCa to the CNS. CNS, central nervous system; UCa, urothelial cancer.

base limitations and sample size, we could not make statistically or clinically significant comparisons between these two groups. As expected, patients treated with chemotherapy alone carried the lowest median OS of 15.4 months.

Given the rarity of UCa with BM at any single institution, literature capturing the survival of these patients is limited. Prior studies reported median OS for UCa patients from the time of BM diagnosis as between 3.1 and 12.8 months.[21,22] The nearly two-fold difference between prior studies and our results may be attributed to technological advancements and treatment selection. The difference can be partially explained by advancements in SRS for BM treatment compared to whole-brain radiation therapy.[10] SRS provides excellent local control of intraparenchymal tumors, with failure rates previously reported at 8%.[23] Conversely, new CNS tumors in BM patients are primarily due to poor systemic disease control rather than intra-CNS spread.[24–26] Advancements in radiosurgical techniques require time to be perfected and become widely available across institutions. The evolution of systemic therapy over the years may also explain the increased OS reported in our study. The advent of immunotherapy as a second-line treatment after platinum-based regimens and the increased use of targeted therapies for fibroblast growth factor receptor (FGFR)-mutated UCa contribute to the improved progression-free survival.[22,27]

From a treatment selection perspective, while surgical resection has been used for decades in the treatment of BM, resection alone is rarely employed if SRS can be performed on the surgical bed. For many BM histologies, applying SRS to the tumor cavity after surgical resection affords better local control of progression.[28,29] The synergistic effect of combining surgical resection with SRS for any residual tumors at the tumor bed appears to drive the increased survival observed in these patients.[30] In our data, no patient received surgical resection without adjuvant SRS. Conversely, a significant number of patients in our cohort received SRS alone. A cohort analysis of patients with Uca and BM showed a 30-day mortality rate of 10% after resection, largely attributable to surgical complications.[31] Although SRS is still considered a neurosurgical procedure, it has a much lower rate of complications, with a 5.4% rate of adverse radiation effects, which are often asymptomatic and non-life-threatening.[32]

Molecular profiling of BM has become increasingly relevant for treatment decision-making. Biopsy of the primary tumor alone is insufficient for BM molecular profiling, as cancer cells constantly mutate and there have been reports of genetic heterogeneity between BM and primary tumors.[33,34] In our study, 93 patients had biopsy-proven Uca with BM; however molecular profiling was not available for these patients. UCa has previously been characterized by mutations in breast cancer gene, FGFR, and ataxia-telangiectasia mutated.[35] Several targeted agents, such as poly (ADP-ribose) polymerase inhibitors and FGFR inhibitors, have shown promise in the treatment of Uca and BM with substantial penetration of the blood-brain barrier.[36,37] The absence of molecular profiling and targeted therapies for patients in our study may have contributed to the suboptimal performance of the current standard-of-care chemotherapeutics that we observed.

Our study is not without limitations. First, it is a retrospective study, which is susceptible to selection bias. Second, due to the nature of the data in the database, we were unable to collect patient-level data on specific outcomes. We could not obtain information on the number of BMs for each patient, the dosimetry of each SRS treatment, or the molecular mutations of each tumor. Thus, variations in these variables, such as the number of BMs, may account for different survival trends between treatment groups rather than the treatment modality itself. Third, the use of Current Procedural Terminology codes for patient identification has limitations in specificity and detail, which can lead to some misidentification. Therefore, any conclusions drawn from the results of this study regarding the effects of treatments on clinical outcomes should be carefully validated by prospective comparative studies.

Conclusions

This retrospective cohort study using real-world data is the largest analysis aimed at capturing the survival of UCa patients with BM. Survival trends for patients treated with surgical resection, SRS, and systemic therapies are described in detail. Our results represent the demographic characteristics, treatment patterns, and outcomes of a large number of patients with UCa and BM. Further prospective studies are needed to confirm these findings and compare outcomes between treatment groups.

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Conflict of interest

None.

Author contributions

Project conception (EM, DRH, EBR), data analysis (EM, DRH), manuscript drafting (EM), manuscript review and editing (EM, JDA, DRH, DAB, JH, EBR). All authors have approved the final version and publication of the manuscript.

Ethical statement

As TriNetX is a federated database, an institutional review board waiver was granted for its use in this study. As a retrospective study with minimal risk, a waiver of authorization and informed consent was approved. The data reviewed is a secondary analysis of existing data, involves no intervention or interaction with human subjects, and is de-identified according to the standards defined in Section §164.514(a) of the HIPAA Privacy Rule. The de-identification process has been formally determined by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. This formal determination by a qualified expert was last updated in December 2020. All study guidelines and protocols conform to the ethical guidelines of the latest version of the Declaration of Helsinki (as revised in 2013).

Data sharing statement

The dataset from TriNetX used in support of the findings of this study have not been made available because of licensing agreement.

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