

Clival Metastases in Cancer Patients

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Abstract

Purpose

This study aimed to describe clinical features, radiotherapy (RT), and symptom outcomes in cancer patients with cranial nerve palsies associated with clival metastases.

Methods

A retrospective record review for the period in between 2000 and 2020 was conducted for patients with primary metastatic cancers, who developed distal clival metastases, or were treated with RT at the Karmanos Cancer Institute (Detroit, Michigan). The patients' demographics and clinical characteristics, including their symptoms and improvement of symptoms after RT are described.

Results

Forty-four patients were identified who met inclusion criteria. The most common primary cancers were breast cancer, prostate cancer, and multiple myeloma. Magnetic resonance images and computed tomography scans were used for the diagnosis of clival metastasis, as well as for the evaluation after RT. Thirty-two patients (73%) with clival metastases also had cervical spine metastases. Prevailing neurologic symptoms were headache, diplopia, lateral gaze paralysis, blurry vision, chin numbness, and tongue deviation. Fifteen of 23 RT-treated patients (65%) received clivus only RT, and 8 patients (35%) were given whole brain RT. Post-RT symptom improvement was observed in patients with diplopia (5/6; 83%), headache (8/10; 80%), chin numbness (2/4; 50%), blurry vision (2/5; 40%), lateral gaze deficit (2/6; 33%), and tongue deviation (1/4; 25%).

Conclusions

These results suggest that early detection and rigorous cranial nerve examination, in addition to RT treatment, should be considered in patients with breast cancer, prostate cancer, and multiple myeloma, who developed bone metastasis, especially cervical spine metastasis.

Introduction

Breast cancer, prostate cancer, kidney cancer, lung cancer, thyroid cancer and bladder cancer are cancer types that commonly spread to the bones [1]. About 70% of patients with advanced breast cancer and prostate cancer have metastatic bone disease [2]. Typically, metastases spread to the bones of the spine, pelvis, ribs, upper arms and thighs. Rarely, metastases can end up at the base of the skull in the clivus region. Clival tumors represent only 0.1–0.4% of all intracranial tumors, and clival metastases are an extremely rare subset of clival tumors, with only 57 cases reported in the literature [3–5]. In the clivus,

cranial nerve VI (CNVI) runs through Dorello's canal, and many patients with clival metastases present with unilateral or bilateral CNVI palsy [4, 6]. Given that CNVI channeled by Dorello's canal reaches the neighboring cavernous sinus, through which other cranial nerves traverse, involvement of cranial nerves other than CNVI, indicates spread of clival metastasis into the cavernous sinus [5, 6]. Because clival metastasis spreads proximal to critical structures that include, besides cranial nerves, basilar artery, internal carotid arteries, and brain stem, considerable morbidity and mortality burden is associated with the condition in the absence of timely treatment [5]. The overall median survival of patients with clival metastases is about 2.5 years [7], and the average survival of patients with cranial nerve palsy involvement is only 5 months [7].

Clival metastases originate most frequently from prostate cancer, kidney cancer, and liver cancer [4]. Other primary tumors from which clival metastasis can spread include breast cancer, melanoma skin cancer, tonsillar cancer, lung cancer, gastrointestinal and blood cancers [8, 9]. Prostate cancer is the most common cancer type associated with clival metastasis, often accompanied by multiple cranial nerve deficits [3, 6].

McDermott and coworkers [10] reported cranial nerve deficits suffered by 15 patients with metastatic prostate cancer. The presenting symptoms included facial numbness, tongue weakness, headache, diplopia, ptosis, proptosis, and unilateral blindness. All patients received external beam radiotherapy (RT) to the brain or the base of the skull. Ten of 15 patients (67%) had complete resolution of their cranial neuropathies, and 4 patients (27%) experienced improvement in symptoms, notwithstanding incomplete resolution of the neurologic impairments. Because of its potential for symptom improvement, RT was proposed as a treatment for metastatic prostate cancer patients with cranial nerve deficits. To add to this body of work, we report in the present study clinical features, RT, and symptom outcomes in cancer patients with cranial nerve palsies associated with clival metastases.

Methods

Data collection

Under the Wayne State University Institutional Review Board approval, we conducted a retrospective record review for the period in between 2000 and 2020 for patients with primary metastatic cancers, who developed distal clival metastases, or were treated with RT at the Karmanos Cancer Institute (Detroit, Michigan). The selection criteria included identifying individuals who were > 18 years of age, who were diagnosed with a metastatic cancer and went on to develop clival metastasis, as verified by radiology imaging results, and/or received RT treatment. Data were collected on the patients' demographics, the primary site of a metastatic cancer, the diagnostic imaging, the type of RT, neurologic symptoms present at the time of clival diagnosis, and symptom responses to RT.

Statistical analysis

Baseline patient characteristics were summarized using count and percentage for categorical variables, and median with range for continuous variables. All statistical analyses were descriptive and did not include p value calculations.

Results

Patients' characteristics

As shown in Table 1, 44 patients (24 men and 20 women) were identified who met the selection criteria. The median age was 62.5 years (range, 39-88 years). Twenty-six patients (59%) were white, and 16 patients (36%) were black. Nineteen patients (43%) had breast cancer, 18 patients (41%) had prostate cancer, and 6 patients (14%) had multiple myeloma. Additional cancer types included thyroid cancer, tongue squamous cell carcinoma, olfactory neuroblastoma, lung carcinoma, B-cell lymphoblastic leukemia, and diffuse large B-cell lymphoma, and were diagnosed in one patient (2% each; not shown).

Diagnostic procedures

Imaging procedures were performed before and during diagnosis of clival metastasis, including magnetic resonance imaging (MRI) of the brain in 41 patients (93%), abdominal and thoracic computed tomography (CT) scans in 34 patients (77%), pelvic CT in 33 patients (75%), and whole body bone scan in 32 patients (73%; Table 1). Of note, 32 of all 44 patients (73%) diagnosed with clival metastases were also diagnosed with cervical spine metastases. Bone marrow biopsy of the pelvis was done in 7 of 44 patients (16%) as part of their clinical care, irrespective of clival metastasis diagnosis.

RT treatment

Twenty-three patients of 44 patients (52%) were treated with RT. Median time from diagnosis of clival metastasis to the start of RT was 9 days (range, 0-405 days). Sixteen patients of 23 RT-treated patients (70%) had cervical spine metastasis. The time from the diagnosis of cervical spine metastasis to completion of RT treatment ranged from 7 to 419 days, with the median time of 23 days. As depicted in Table 1, 16 of 24 men (70%) received RT, whereas only 7 of 20 women (30%) did. The median age of RT-treated patients was 63 years (range, 41-88 years). Fourteen patients of 23 RT-treated patients (61%) were whites, and 8 patients (35%) were African Americans. Among 23 RT-treated patients, 6 patients (26%) were with breast cancer, 10 patients (43%) were with prostate cancer, and 4 patients (17%) were with multiple myeloma. Twenty patients of 23 RT-treated patients (87%) received MRI of the brain, 15 patients (65%) got either abdominal CT or thoracic CT scan, or whole body bone scan, and 14 patients (61%) received pelvic CT. Bone marrow biopsy of the pelvis was done in five patients of 23 RT-treated patients (22%; not shown).

Fifteen patients of 23 RT-treated patients (65%) received clivus only RT, and 8 patients (35%) had whole brain RT. Of all 15 patients who were treated with clivus only RT, 2 patients (13.3%) also received RT to the cervical spine (not shown). Among clivus only RT-treated patients, 12 patients received 30 Grays (Gy; in 3

Gy x 10 fractions), one patient had a total 20 Gy treatment (in 4 Gy x 5 fractions), and one patient was given an 8 Gy x 1 treatment only. One patient, previously treated in the base of skull region, received a lower dose of 2.5 Gy x 10 fractions using intensity-modulated RT to minimize overlap with the previous treatment. Among whole brain RT-treated patients, 6 patients were given 30 Gy in 10 fractions, one patient received 25 Gy in 10 fractions, and one patient was treated with a total of 12 Gy (3 Gy x 4) out of 30 Gy (3 Gy x 10) planned treatment prior to discontinuing due to worsening of the performance status.

Of all 44 patients in the study, 7 patients (15.9%) expired within 3 months after the diagnosis of clival metastasis, and ended up receiving no RT treatment (Table 2). Among them, 5 patients (11.4%) were with prostate cancer, one patient (2.3%) was with breast cancer, and one patient (2.3%) was diagnosed with both breast cancer and multiple myeloma. Of note, 14 patients (31.8%), who received care outside our institution, were with unknown RT status. Among them, 2 patients (4.5%) were with prostate cancer, 11 patients (25.0%) were diagnosed with breast cancer, and one patient (2.3%) was with both prostate cancer and multiple myeloma.

Types of neurologic symptoms

Common neurologic symptoms noted in all 44 patients are depicted in Table 3. Thirteen patients (30%) suffered from headache, 7 patients (16%) experienced diplopia, 6 patients (14%) had lateral gaze paralysis, 5 patients (11%) presented with blurry vision or chin numbness, and 4 patients (9%) suffered from tongue deviation. Some patients experienced more than one symptom.

Table 3 also shows neurologic symptoms based on cancer type. Patients with breast cancer experienced headache (6/13; 46%), and blurry vision or chin numbness (1/5; 20% each). Patients with prostate cancer had diplopia (4/7; 57%), tongue deviation (2/4; 50%), blurry vision or chin numbness (2/5; 40% each), lateral gaze deficit (2/6; 33%), and headache (3/13; 23%). The symptoms noted in patients with multiple myeloma were tongue deviation (2/4; 50%), lateral gaze deficit (2/6; 33%), diplopia (2/7; 29%), and headache (3/13; 23%), in addition to blurry vision or chin numbness (1/5; 20% each).

Symptom improvement after RT

Symptom improvement after RT was defined as lessening or resolution of a symptom based on patients' reports. As shown in Table 4, symptom improvement after RT was experienced by 5 of 6 patients (83%) with diplopia, 8 of 10 patients (80%) with headache, 2 of 4 patients (50%) with chin numbness, 2 of 5 patients (40%) with blurry vision, 2 of 6 patients (33%) with lateral gaze deficit, and one of 4 patients (25%) with tongue deviation.

A classic example of the patients in this study is a 58-year old patient with metastatic castrate-resistant prostate cancer, who initially presented with severe headaches. The clival involvement was noted using the MRI scan (Fig. 1a). In this case, the RT treatment plan was 3000 centigrays (cGy) delivery in 10 fractions using opposed laterals and 6 megavolts (MV) photons. The total dose of 3000 cGy was

delivered to the entire gross tumor volume, and to 95% of the planning target volume (Fig. 1b). The RT treatment resulted in significant improvement of headaches.

Discussion

Although 70% of patients with advanced breast cancer and prostate cancer have metastatic bone disease [2], the presence of clival metastases is not a common occurrence [3-5]. When clival metastases are present, however, the resulting neurologic symptoms, such as facial numbness, visual changes, and tongue paralysis, can be devastating. Dramatic clinical findings associated with clival pathology are known to be nonspecific, and the time interval from the diagnosis of the primary tumor to the diagnosis of the clival metastasis has a wide range from 2 months to 33 years [4, 11]. In this study, ascertaining the time interval from the onset of neurologic symptoms to the diagnosis of clival metastasis by brain MRI was a challenge. In addition, the diagnosis of clival metastasis was delayed, possibly due to the heterogeneous nature of the cranial neuropathies and symptoms.

The RT-treated patients in this study experienced symptom improvement with variable responses. Patients with headache and diplopia improved after RT. However, patients with blurry vision, eye gaze paralysis, and tongue deviation are not guaranteed any improvement. This may be due to the rapid progression of the disease, which is consistent with the observation that 7 patients who did not receive RT (16%; 7/44) died 3 months after the diagnosis of clival metastasis. The development of clival metastasis typically occurs later in the patient's disease continuum. However, when the condition is diagnosed early, and the RT treatment is planned; the median time from the diagnosis to the start of RT is 9 days. Early recognition and treatment of clival metastasis may provide improved symptom relief.

Among 23 patients who received RT, 16 patients (70%) were men and 7 patients (30%) were women. Furthermore, of all 23 RT-treated patients, 14 patients (61%) were whites and 8 patients (35%) were blacks. The data suggest trends in gender and racial disparities. A literature review found a preponderance of men who were reported with clival metastases (72%, 31/43) [11]. In our study, however, the gender disparity may be apparent, because 11 women with breast cancer (25%; 11/44) received care outside our institution, and possibly were treated with RT elsewhere.

Understanding the pathophysiology of clival metastasis may be improved by our knowledge of chordoma, a rare type of sarcoma that develops de novo from the base of the skull. The most prominent single nucleotide polymorphism rs2305089 in the T (brachyury) gene has been associated with a 6-fold increase in the risk of developing chordoma, and has been implicated in the prognosis of individuals with chordoma [12, 13].

Genomic profiles of 27 clivus chordoma patients derived from the biopsy samples were reported in [14]. These patients were among the youngest in the chordoma patient group, with the median age of 43 years, and had genomic alterations in CDKN2A, CDKN2B, PBRM1, and PTCH1. In our study, however, these genomic changes were not observed in the genomic profiling data obtained from a small subgroup of patients (not shown). Consistent with an important role of genomic sequencing in the management of

solid tumor cancer patients, future evaluation of genomic signatures associated with clival metastases is warranted.

In conclusion, our data suggest that (i) early detection and incorporation of detailed cranial nerve examination are needed, especially in patients with breast cancer, prostate cancer, and multiple myeloma, who developed metastases in the cervical spine, and that (ii) palliative RT should be considered in these patients, given its potential for symptom improvement. Our data imply that providers need to recognize a potential link between neurologic deficits and metastatic carcinomas, in order to effectively diagnose and treat the patients, with the goal of symptom improvement. This is consistent with the findings that treatment of neurologic defects is associated with improvement of patients' emotional wellbeing and quality of life, and that psychological wellness and positive health outcomes are related [15, 16].

Declarations

Funding Not applicable.

Conflicts of interest Not applicable.

Data availability All electronic medical records were obtained primarily from Cerner, Mosaic, and iSITE that enabled us to identify patients who meet study criteria. Clinical variables were accessed via chart review. Datasets analyzed may be obtained from the corresponding author Dr. Elisabeth Heath upon request.

Code availability Not applicable.

Author contributions Rebecca Sturgis, MD Candidate, Department of Oncology, Wayne State University School of Medicine, Detroit, MI, USA, Contributed to the acquisition and the analysis of the data; drafted the manuscript; approved the final manuscript. Alleda Mack, MD, Department of Oncology, Wayne State University School of Medicine, Detroit, MI, USA, Contributed to the acquisition of the data; approved the final manuscript. Seongho Kim, PhD, Department of Oncology, Wayne State University School of Medicine, Detroit, MI, USA, Contributed to the study's design; major role in the acquisition and the analysis of the data; interpreted the data; revised the manuscript for intellectual content; approved the final manuscript. Jordan Maier, MD, Department of Radiation Oncology, Wayne State University School of Medicine, 4100 John R, Detroit, MI 48201, USA, Contributed to the study's design; major role in the acquisition and the analysis of the data; interpreted the data; revised the manuscript for intellectual content; approved the final manuscript. Elisabeth I. Heath, MD, Department of Oncology, Wayne State University School of Medicine, Detroit, MI, USA, Designed the study and supervised the study's design; revised and supervised the acquisition and the analysis of the data; interpreted the data and supervised the interpretation of the data; revised and supervised the manuscript for intellectual content, as well as the manuscript's final write-up; approved the final manuscript.

Ethics approval This study was approved by the Wayne State University Institutional Review Board. The protocol will be made available to the journal reviewers upon their request. The interpretation and conclusions in this manuscript are those of the author/s alone.

Consent to participate A waiver of informed consent and the Health Insurance Portability and Accountability Act (HIPAA) privacy rule was requested due to retrospective nature of this study.

Consent for publication The corresponding author Dr. Elisabeth Heath transfers to Springer Nature the publication rights and she warrants that her contribution is original and that she has full power to give this granting.

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Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures

(a)



(b)

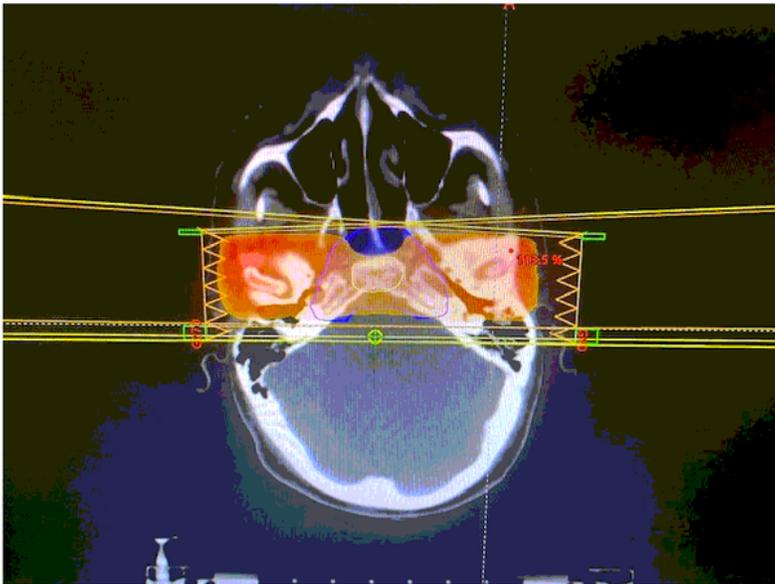


Figure 1

a Brain MRI (sagittal view, with an arrow pointing to the clivus) and b radiation treatment plan (axial view showing GTV (yellow) and PTV (blue)). The MRI was obtained from a 58-year old patient with prostate cancer (stage 4). The total dose (3000 cGy) was delivered to the entire GTV, and to 95% of the PTV. cGy centigray, GTV gross tumor volume, MRI magnetic resonance imaging, MV megavolts, PTV planning target volume

Supplementary Files

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