Review

Advances in Prostate Cancer Research

Current Urology

OPEN

Leptomeningeal metastases in prostate cancer: A review of the current literature

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Abstract

Leptomeningeal metastasis/leptomeningeal carcinomatosis (LMC; terms used interchangeably) is an inflammatory complication of primary tumors that involves the spread of the disease to the meninges (specifically the arachnoid and pia maters) and spinal cord. In the United States, approximately 110,000 new cases are diagnosed each year, and the prognosis is usually poor. Complications of LMC include cognitive impairment, cranial nerve dysfunction, ischemic stroke, and mortality. The survival times of untreated and treated LMC are approximately 4–6 weeks and 2–4 months, respectively. Leptomeningeal carcinomatoses are usually metastatic cancers that spread to the central nervous system. Although lung and breast cancers have a clearly defined relationship with LMC, it remains unclear whether prostate cancer (PC) is also directly associated with LMC. To determine whether such association exists, we conducted a PubMed review of the literature on patients with PC with coexisting LMCs. Our search yielded 23 case reports of patients with preexisting PC who developed LMC. In addition, 2 retrospective cohort studies were examined.

Various findings were identified in the revised cases and studies. The first 3 findings were related to the progression of the disease: patients presenting with neurological disease symptoms were in remission from PC for 7 years on average, LMCs tended to occur after other cancer diagnoses, and the disease had already rapidly progressed by the time the symptoms were present. Regarding diagnosis, the major finding was that most LMCs were detected by magnetic resonance imaging (which does not detect early dissemination), and it was suggested that single-photon emission computed tomography or positron emission tomography imaging could be used for earlier detection. Finally, in terms of treatment, the main finding was that treatment was palliative rather than curative and that prognosis remained poor despite treatment. On the basis of these results, we recommend for individuals with risk factors, such as high-grade PC and hormonal PC, to be evaluated on a case-by-case basis for increased surveillance of LMC development.

Keywords: Leptomeningeal carcinomatosis; Prostate cancer; Prostate cancer metastasis

1. Introduction

Leptomeningeal metastasis/carcinomatosis (LM/LMC; terms used interchangeably) is a rare form of metastasis occurring in certain cancers, extending from a preexisting tumor site to form meningeal tumors in the brain and spinal cord.[1] It occurs more commonly in patients with breast cancer, lung cancer, and melanoma.[2] In rare cases, LM can occur in patients with genitourinary cancers, such as prostate and urological cancers.[1] Although LMs are rare, prostate cancer (PC) is the second leading cause of cancer-related deaths in men. Therefore, it is important to highlight the clinical relevance of LM in patients with PC.[3] The diagnose of LM often occurs during cancer relapse, with a median survival time of a few weeks to months from diagnosis.[1] Its symptoms include cerebellar ataxia, limbic/brain stem encephalitis, neuropathies, and spinal cord compression with subsequent lower back pain and headache.[3,4] Other complications include sensory loss, limb weakness, bowel dysfunction, infarction, and seizures. Therefore, despite the low reported incidence of LM in PC, significant complications and poor survival outcomes upon diagnosis indicate a need for further studies.

Although there are case reports on the disease course, few recent studies have reviewed these articles holistically to recommend treatment options and provide clinical suggestions for this population. Because of the significant neuropathological risks of LM and its poor prognosis, the objective of this systematic review was to use relevant literature to develop treatment guidelines for patients with PC and LM, considering its symptoms, diagnosis, and treatment recommendations.

2. Materials and methods

The protocol for this systematic review follows the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols.[5]

2.1. Literature search

On March 1, 2023, three research team members (A.A., A.P., and U.D.) independently searched the PubMed/MEDLINE databases

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Current Urology, (2024) 18, 3, 159–166

Received July 30, 2023; Accepted January 3, 2024.

http://dx.doi.org/10.1097/CU9.0000000000000245

for articles pertaining to keywords in English. Using search engine filters, the searches were limited to case reports in humans and English language. The searches were not limited to a single timeframe. Search queries were structured to match primary and secondary search terms sequentially. The primary search terms were related to various terminologies associated with LM: leptomeningeal carcinomatosis, carcinomatous meningitis, neoplastic meningitis, and malignant leptomeningitis. The secondary search terms were prostate cancer and prostate adenocarcinoma.

2.2. Study selection

Two reviewers (A.P. and U.D.) independently assessed the articles deemed relevant to assess eligibility based on the study inclusion and exclusion criteria. The studies were not limited to treatment interventions or outcomes to maintain a broad scope. The inclusion criteria were broad enough to consider any study that discussed LM in the setting of confirmed primary PC. Accordingly, studies were excluded if they did not report patients with confirmed LM and confirmed PC, were duplicates of previous studies, or had noticeable deficiencies in methodology. To avoid the risk of individual bias, a team-based approach was used to evaluate all the selected studies, with each record independently assessed by both reviewers before determining inclusion or exclusion. Figure 1 presents a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the systematic process of study selection.

2.3. Data extraction

From each study included in this review, the following data were collected: type of cancer, location of metastasis, patient status or outcome, time to status or outcome, drugs used during treatment, reason for drug use, drug dosage, surgeries performed, Gleason score, radiation therapy, serum prostate-specific antigen (PSA) level at LMC diagnosis, and cerebrospinal fluid (CSF) PSA level, if applicable. In addition, qualitative data from each study sample (ie, symptoms, diagnostic techniques, and hospital course or treatment) were used to conduct a descriptive analysis of each patient in each study. Table 1 outlines a synopsis of each included study. Table 2 outlines patient descriptions and disease courses.

3. Results

We reviewed 23 case reports of patients with a history of PC that progressed to LMC. Two retrospective cohort studies were also reviewed. The first study by Yust-Katz et al.[1] examined all patients with genitourinary cancers between 1979 and 2011 in the Monroe Dunaway Anderson database. Their search yielded 93,960 patients who met the inclusion criteria, of whom 41,830 had PC. In the PC group, 7 patients (0.016%) had LMC.[1] The second retrospective cohort study looked at castration-resistant PC (CRPC) from 2002 to 2010 across 9 hospitals in Italy.[19] Their review included 943 cases of CRPC, of which 31 were found to have brain or leptomeningeal metastases (22 in the brain and 9 in the leptomeninges).[19]

Through our review, we identified some common themes in disease progression, clinical presentation, diagnosis, treatment, and prognosis of this rare complication of PC.

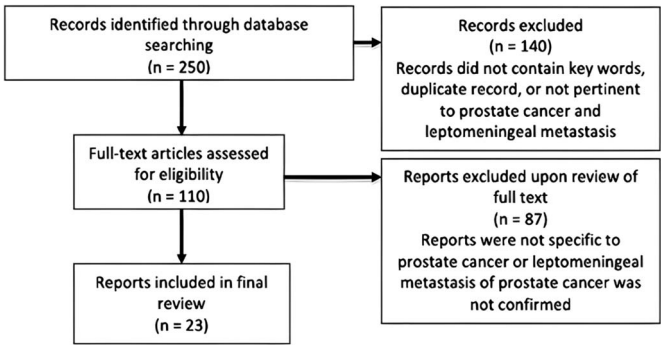

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

3.1. Disease course and progression

A common finding that we identified was that, in numerous cases, the patients were treated for an initial cancer diagnosis and subsequently went into remission before presenting with symptoms of metastasis. The remission time ranged from 6 months to 21 years, with an average time in remission of 7 years.[2,3,6–17,19–22] Furthermore, in all patients, LMC was always preceded by another metastasis, as is common in PC; bone metastases to the axial skeleton frequently precede leptomeningeal spread, with the most common being to the vertebrae.[11,13,17,18,20,22,25] Finally, the disease progresses rapidly from the time of the onset of neurological symptoms. As calculated from 20 case studies, the average survival time after the onset of neurological symptoms was 30 weeks.[2,3,6–16,19–22] The only exception to this trend was 1 case study in which the patient survived and was alive for 5 years at the time the article was written.[26]

3.2. Clinical presentation and diagnosis

In all the case reports reviewed, the patients presented with neurological signs and symptoms. The most common symptom reported was headache (n = 20).[2,3,6–17,19–22] Ahmed and Halmagyi[24] reported 3 cases of LMC that presented with symptoms of pseudotumor cerebri. In another article, Nunno et al.[23] presented 12 cases of dural metastasis of prostate adenocarcinoma with a clinical presentation that resembled an infarct in the middle cerebral artery territory and subdural hematoma. However, during surgery, it was found to be a metastatic prostatic adenocarcinoma that resulted in subdural fibrosis and hemorrhage.

The diagnosis was always made by computed tomography (n = 3) or magnetic resonance imaging (MRI) (n = 14), although MRI was more specific in most cases, along with clinical presentation evaluation, serum PSA level (n = 20), and the patient's medical history.[2,3,6–17,19–22] In some cases, CSF analysis was performed for further confirmation (n = 11).[3,6,7,9,10,12,13,17,20,22] From the 11 reports of CSF analysis, in 2 of the cases, the CSF analysis was negative for any abnormalities.[13,20] In the remaining 9 samples, all showed elevated CSF proteins, and 6 had atypical or malignant cells.[7,9,10,12,17,22]

Finally, a higher initial Gleason score correlated with a higher probability of progression to LMC, with an average reported Gleason score of 8.69 with a range of 7–10 (n = 13).[2,3,6,7,9,10,15–17,20,22]

3.3. Treatment and outcome

In terms of treatment, we identified 1 theme across all case reports worth considering. From the 23 cases we reviewed, 11 patients received whole-brain radiation therapy (WBRT).[2,3,11,14,16–18,20–22] In all cases in which WBRT was used, a significant improvement in neurological symptoms was observed. However, patients still passed away shortly after, with an average survival time of 139 days for 10 out of 11 patients in this cohort.[2,3,11,14,16,18,20–22] The patient who received WBRT was the only one reported to

Table 1

Summary of studies evaluating patients with leptomeningeal metastases in prostate cancer.

Study author	Type of cancer	Age of patient at the time of diagnosis, yr	Location of the metastasis	Castration-resistant prostate cancer	Patient status/ outcome	Gleason score	Time to status/ outcome	Drugs used during treatment	Reason for use	Dosage of drugs	Surgery	Chemotherapy	Radiation	Serum PSA at LMC diagnosis, ng/mL	CSF PSA if measured, ng/mL
Dehghani et al.[2]	Prostate adenocarcinoma	69	Dura and bone	Yes	Deceased	9	~2 mo after onset of neuro sx	Dexamethasone		4 mg/6 hr	No	Yes	Yes	300	—
Cone et al.[3]	Prostate adenocarcinoma	76	Left skull base and right cerebellum and bone (no skull)	Yes	Deceased	8	4 d after neuro sx	Dexamethasone		High dose	Prostatectomy No for LMC	Yes	Yes	459	90
Bernstein et al.[6]	Prostate adenocarcinoma	65	Leptomeninges thickening in the anterior cortex	Yes	Deceased	9	6–7 mo of neuro sx	Intrathecal liposomal cytarabine	LMC		No	Yes	No	775	191
Neelapu et al.[7]	Prostate adenocarcinoma	66	Dura	Yes	Unknown	8	N/A	N/A			Not reported	Not reported	Not reported	1131	28
Gupta et al.[8]	Prostate adenocarcinoma	81	Dura	No	Deceased		2 wk from neuro sx	Phenytoin Corticosteroids	Developed generalized seizures		Yes	Yes	No		
Honda and Miyagawa[9]	Prostate adenocarcinoma	68	CNS	No	Deceased	9	5 mo from primary diagnosis 4 mo from neuro sx	Bicalutamide Leuprolide acetate		Bicalumatide: 80 mg daily Leuprolide acetate: 3.75 mg	Yes	No	No	4.1	N/A
Yamada et al.[10]	Mixed small cell lung carcinoma and adenocarcinoma of prostate	65	Meninges	No	Unknown	9	3 mo				No	Yes	No	Undetectable	Undetectable
Hentschel et al.[11]	Prostate adenocarcinoma	60	Intradural extramedullary spinal lesion (L1–L2)	No	Deceased		5 mo				Yes (palliative operation to lessen the burden of tumor)	Yes	Yes (30 Gy in 12 fractions)		
Rubins and Guzman-Paz[12]	Prostate adenocarcinoma	65	Leptomeninges	No	Deceased		3 wk				No	No	No		
Mahadevia and Kiely[13]	Prostate adenocarcinoma	66	Leptomeninges	No	Deceased		1 mo				No	No	No		
Cante et al.[14]	Prostate adenocarcinoma	70	LM	Yes	Deceased	9	4 mo				No	Yes	Yes	20	6
Okoye et al.[15]	Prostate adenocarcinoma	48	LM	No	Deceased	10	1 mo				Yes	Yes	No		

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Table 1 *(Continued)*

Study author	Type of cancer	Age of patient at the time of diagnosis, yr	Location of the metastasis	Castration-resistant prostate cancer	Patient status/ outcome	Gleason score	Time to status/ outcome	Drugs used during treatment	Reason for use	Dosage of drugs	Surgery	Chemotherapy	Radiation	Serum PSA at LMC diagnosis, ng/mL	CSF PSA if measured, ng/mL
Lin et al.[16]	P1: PA P2: PA P3: PA P4: PA	P1: 72 P2: 78 P3: 77 P4: 57	P1: LM P2: LM P3: LM P4: LM	P1: Yes P2: Yes P3: Yes P4: Yes	P1: Deceased P2: Deceased P3: Deceased P4: Deceased	P1: Not reported P2: 10 P3: Not reported P4: 9	P1: 5 mo P2: 2 mo P3: 7 mo P4: 2 mo	P1: Dexamethasone P3: Oral cyclophosphamide	P3: second-line chemotherapy		P1: No P2: No P3: No P4: No	P1: Yes P2: Yes P3: Yes P4: Yes	P1: No P2: Yes P3: Yes P4: Yes	P2: 115	
Zhang et al.[17]	Prostate adenocarcinoma	87	LM	No	Alive	8	5 yr at the time of article	Leuprolide acetate	Hormonal therapy for elevated PSA		No	No	Yes		
Deinsberger et al.[18]	Prostate adenocarcinoma	61	Thoracic and lumbar spine	Yes	Alive		6 mo				Yes, debulking	No	Yes		
Caffo et al.[19]	Prostate adenocarcinoma	Median, 62 Range, 51–78	31 patients (22 brain and 9 LM)		Deceased		4 mo (only 6 patients >1 yr)								
Tawadros et al.[20]	Prostate adenocarcinoma	67	LM	Yes	Deceased	7	3 mo	Dexamethasone		High dose	No	Yes	Yes, WBR	502	
Santos et al.[21]	Prostate adenocarcinoma	72	LM	No	Deceased		4 mo				Yes	No	Yes, WBR		
Orphanos and Ardavanis[22]	Prostate adenocarcinoma	72	Skull	Yes	Deceased	8	5 wk	None reported	—	—	No	Yes	No	1500 1729	439 678

CNS = central nervous system; CSF = cerebrospinal fluid; Gy = gray (a radiation unit); L = lumbar spine level; LM = leptomeninges; LMC = leptomeningeal carcinomatosis; N/A = non-applicable; PA = prostate adenocarcinoma; PSA = prostate-specific antigen; P1 = Patient 1; P2 = Patient 2; P3 = Patient 3; P4 = Patient 4; sx = symptoms; WBR = whole-brain radiotherapy; N/A = not applicable.

Table 2

Patient descriptions and disease course.

Author name	Patient disease course/treatment description (maximum of 5 sentences)
Dehghani et al.[2]	**Presentation:** Presenting with headache, true vertigo, impaired vision in the right eye, diplopia, and balance disturbances approximately 4 mo after discovery of bone metastases of prostate adenocarcinoma. **Diagnosis:** MRI and serum PSA **Hospital course:** Patient presented 7 d after initial onset of neuro symptoms. After 7 d in the hospital on dexamethasone, it was determined the patient had poor prognosis, and whole-brain radiation was performed (30 Gy/10 fractions). One month after completing WBR, neuro symptoms progressed, and the patient died.
Cone et al.[3]	**Presentation:** Presented with a 5-d history of confusion, right-sided HA in the frontoparietal and vertex regions. **Diagnosis:** MRI, serum PSA, and CSF PSA **Hospital course:** Patient initially diagnosed 10 yr prior for prostate cancer and had total prostatectomy. He was cancer-free for 6 yr before recurrence, which was treated with thalidomide. PSA levels were elevated 3 yr later and treated with chemotherapy. A year and a half later, PSA levels rose again with no response to mitoxantrone and prednisone. Five months later, the patient presented with neuro symptoms. He died after a 4-d hospital stay with attempted treatment using WBR and dexamethasone.
Bernstein et al.[6]	**Presentation:** Various weeks of worsening headache, nausea, decreased cognitive function, 4 mo of right lateral gaze diplopia, broad-based gait, and right-sided facial numbness extending from the maxilla to the chin. **Diagnosis:** MRI **Hospital course:** Patient presented improvement in headache, nausea, and diplopia within 2 wk of initiating intrathecal liposomal cytarabine (ARA-C). He received 4 more ARA-C doses at 2-wk intervals. On the fourth dose, the patient developed hepatic failure. He declined any further therapy and died.
Neelapu et al.[7]	After 2 yr of diagnosis of metastatic prostate cancer and undergoing treatment, the patient presented with cranial nerve 7 palsy and partial CN 12 palsy. The MRI showed diffuse dural enhancement and a 1-cm dural-based lesion in the right fossa with adjacent brain edema. CSF showed 6 malignant cells. Case outcome not reported.
Gupta et al.[8]	**Presentation:** Left side of face numbness and headache after ~30 mo of primary diagnosis of metastatic prostate adenocarcinoma. **Diagnosis:** Diagnosed with MRI + craniotomy and dural biopsy. Dural biopsy showed high-grade prostate adenocarcinoma. **Hospital course:** After craniotomy and dural biopsy, he was given corticosteroids, and plans were made for cranial radiotherapy. He developed generalized seizure before RT began. His performance declined so he was sent home on hospice and palliative care and died 2 wk later.
Honda and Miyagawa[9]	**Presentation:** Patient initially presented with complaints of urinary retention and herpetic rash. He was treated for the herpes, but the urinary retention persisted. He was then given a diagnosis of prostate adenocarcinoma for which he underwent a surgical excision. **Hospital course:** Shortly after operation, patient developed AMS, bilateral Babinski, and LE weakness. CT revealed hydrocephalus. LP showed elevated pressure. CSF analysis showed malignant cells staining positive for PSA. He was treated with bicalutamide for 7 d followed by leuprolide acetate every 4 wk. Two months after treatment, PSA levels were 0.10 ng/mL, and CSF was negative for malignant cells. However, his AMS persisted, and the patient died of pneumonia.
Yamada et al.[10]	**Presentation:** Patient presented 6 mo after primary diagnosis with headache, vomiting, and decreased level of consciousness. **Diagnosis:** MRI showed multiple brain metastases and meningeal carcinomatosis + malignant cells in CSF. **Hospital course:** Patient requested treatment despite advice for comfort care. Started on carboplatin AUC (Day 1, monthly) + irinotecan 60 mg/m^2 (Days 1, 8, and 15; monthly) for small cell lung carcinoma. Three months later, multiple brain metastases and meningeal carcinomatosis were drastically diminished on MRI. He also received hormonal therapy for 5 mo.
Hentschel et al.[11]	Patient presented 7 yr after being treated with chemotherapy, radiotherapy, and brachytherapy for prostate adenocarcinoma with lower back pain. Imaging showed an intradural extramedullary lesion of the spine at L1–L2. Palliative surgery was performed to debulk the lesion. The patient had a significant reduction in pain postoperatively and was treated with radiation. Three months after surgery, he developed confusion and AMS. CT revealed multiple brain metastases. Whole-brain radiotherapy was instituted. He died 10 days later from prostate adenocarcinoma: 4 mo after surgery, 5 mo from initial presentation of lower back pain.
Rubins and Guzman-Paz[12]	**Presentation:** Patient initially presented with signs and symptoms consistent with a viral infection. He was hydrated and treated. During his hospital stay, he developed alcohol withdrawal symptoms for which he was treated. He was discharged to an assistance facility to help with alcohol addiction. He returned 3 d later with nonfocal neuro symptoms. At this point, he had been given a diagnosis of metastatic prostate cancer 30 mo prior. **Diagnosis:** CT scan showed no abnormalities. CSF analysis showed malignant cells. **Hospital course:** Further treatment declined, and patient died 3 wk later from pneumonia.
Mahedevia et al.[13]	**Presentation:** Patient presented with episodes of loss of consciousness associated with marked elevation in blood pressure. **Diagnosis:** 2 spinal taps were normal. CT showed metastatic cancer to sacrum. Prostate adenocarcinoma with LMC diagnosed on autopsy.
Cante et al.[14]	**Presentation:** AMS, left-sided frontal headache, nausea with a history of metastatic prostate cancer. **Diagnosis:** MRI + PSA in CSF **Hospital course:** Treated with 3 cycles of docetaxel and prednisone followed by 30 Gy in 10 fractions of external beam radiotherapy. Patient had improved neurological symptoms post treatment but died 3 mo later because of sudden deterioration.
Okoye et al.[15]	Patient presented with difficulty voiding. He was given a diagnosis of prostate adenocarcinoma and was treated with 8 cycles of neoadjuvant chemotherapy (Taxol, VP-16, and cisplatin) with Lupron. He then underwent a prostatectomy. After a year of surgery, he was found to have widely metastatic cancer including leptomeninges and was discharged to hospice. He died 1 mo later.
Lin et al.[16]	Case report of 4 different patients all with prostate adenocarcinoma that became refractory to hormone manipulation therapy. All of the patients were treated with mitoxantrone + prednisone when disease became refractory. However, at some point, they presented with neurological symptoms. Diagnosis was made using MRI. In 3 of 4 patients, whole-brain radiation provided symptom relief, but they eventually passed away.
Zhang et al.[17]	Patient presented 21 yr after diagnosis of prostate cancer treated with radical prostatectomy with lower back pain. Whole-body scan and MRI showed metastasis to the thoracic spine and LM. CSF showed elevated protein and atypical malignant cells. He started leuprolide acetate therapy to which his PSA responded. He further received 3500-rad radiation. He presented 4 mo later with back pain and left leg weakness. MRI, PSA, and CSF were negative. His condition was attributed to toxicity from treatment. He underwent physical therapy and continued to receive leuprolide injections. Patient was still alive 5 yr later at the time of case report publication.
Nunno et al.[23]	A case report of a patient with prostate adenocarcinoma presenting with symptoms indicating an MCA stroke and subdural hematoma. On surgery, it was found to be metastatic adenocarcinoma to the dura with subsequent fibrosis and hemorrhage. Article includes a review of 12 other cases with similar presentations.

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Table 2 *(Continued)*

Author name	Patient disease course/treatment description (maximum of 5 sentences)
Deinsberger et al.[18]	Patient presents 3 yr after diagnosis and treatment of prostate adenocarcinoma with lower back pain. He had multiple metastases to the vertebrae with lumbar and thoracic spinal lesions. Debulking surgery was performed, and histology showed metastatic adenocarcinoma. He underwent radiotherapy of all spine and was ambulatory and doing well 6 mo post surgery (time of article).
Caffo et al.[19]	Retrospective cohort study of patients with metastatic castration-resistant prostate cancer from 2002 to 2010 across 9 hospitals in Italy. Thirty-one patients were found to have CNS metastases (22 in the brain and 9 in the LM). Diagnosis was made by CT or MRI. No report of CSF studies. Symptoms included headache (35%), confusion (10%), coma (10%), and hyposthenia (10%). Average survival post BLM was 1 mo for LMC and 4 mo for brain. Study looked at the incidence of LMC and brain metastasis in patients treated with docetaxel.
Tawadros et al.[20]	Patient with a history of prostate adenocarcinoma 5 yr ago presented with PSA increase. Patient was found to have bone metastases as well as LMC on MRI imaging. CSF was negative. Diagnosis was made by temporal meningeal biopsy. Treated with dexamethasone and whole-brain radiation, which helped his symptoms of headache, nausea, and vomiting. He died 3 mo later.
Santos et al.[21]	**Presentation:** Patient presented with headache, left facial nerve palsy, and right upper extremity weakness. He has a history of prostate adenocarcinoma diagnosed 16 yr prior. **Diagnosis:** MRI showing carcinomatous meningitis and thick subdural collection in the left hemisphere **Treatment:** Surgical evacuation of subdural collection. The collection returned and was worse 4 d post surgery. Patient was given whole-brain radiation to which the collection disappeared and his symptoms stabilized. He passed away 4 mo after diagnosis.
Ahmed and Halmagyi[24]	Case report of 3 different patients presenting with signs and symptoms of pseudotumor cerebri. All were given a diagnosis of LMC later and eventually died. Two of the 3 patients had interventions to preserve vision.
Orphanos and Ardavanis[22]	**Presentation:** Patient is a 72-year-old man with a 4-yr history of prostate adenocarcinoma treated with goserelin and flutamide who presented with elevated PSA and bone metastases. Patient received 5 cycles of chemotherapy. Four weeks later, he presented with confusion, lethargy, and weakness. CSF analysis showed malignant cells. Diagnosis: MRI + CSF **Treatment:** Docetaxel and zoledronic acid every 3 and 4 wk, respectively. The patient did not respond to this therapy. CSF shows malignant cells, and thus, methotrexate intrathecal treatment is initiated.
Hébert-Blouin et al.[25]	Clinical article presenting 3 cases of prostate adenocarcinoma with metastases to the lumbosacral plexus and shows, using MRI imaging, that it is a direct perineural spread.
Yust-Katz et al.[1]	Retrospective cohort study looking at all patients with GU cancers from 1979 to 2011 (MD Anderson database). • 93,960 patients met inclusion and exclusion criteria. • Of those, 41,830 had prostate cancer. • Of those, 7 patients developed LMC or 0.016%. • Mean time from primary diagnosis to LMC diagnosis was 141 ± 244 wk (0–410). • Mean survival after diagnosis 24 ± 29 wk (0–143). • Imaging used to diagnose 9 patients, cytology in 14 patients, and combination in 8 patients. • No significant difference in survival regardless of treatment (radiation, chemotherapy, combination, or neither). • 19 patients presented with cerebral symptoms (seizures, HA, vomiting, confusion). • 12 patients presented with cranial nerve symptoms. • 13 presented with spinal cord symptoms.

AMS = altered mental status; AUC = area under the free carboplatin plasma concentration versus time curve; BLM = brain or leptomeningeal metastases; CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; GU = genitourinary; Gy = gray (a radiation unit); HA = headache; LE = left extremity; LM = leptomeninges; LMC = leptomeningeal carcinomatosis; LP = lumbar puncture; MCA = middle cerebral artery; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; RT = radiation therapy; WBR = whole-brain radiotherapy.

survive for a prolonged period, 5 years at the time of article publication.[17]

Surgical debulking was also performed to prevent the progression of neurological symptoms (n = 3). In other patients, high-dose dexamethasone was administered to alleviate symptoms (n = 5). In most cases, intrathecal chemotherapy was considered but not administered because of the poor prognosis of the disease.

These findings are consistent with those of a retrospective study by Yust-Katz et al.,[1] which reported no significant difference in patient survival regardless of treatment (radiation, chemotherapy, a combination of both, or neither).

Because there was a report of only 1 patient who survived for a minimum of 5 years, it is important to analyze their treatment plan.[17] The patient presented with lower back pain 21 years after an initial diagnosis of PC. A whole-body scan and MRI revealed metastases to the thoracic spine and leptomeninges. Leuprolide acetate therapy was started, and his PSA level responded. The patient subsequently received 3500 rad of WBRT. Four months after treatment completion, the patient presented with lower back pain and left leg weakness. Further workup using MRI, PSA level, and CSF analysis yielded negative results. The patient's symptoms were attributable to treatment toxicity. Therefore, he was administered physical therapy, and leuprolide injections were continued.

4. Discussion

The "Disease Course and Progression" category comprises the finding that patients presenting with neurological symptoms and subsequently rapid progression of disease were, on average, 7 years in remission from PC. This trend suggests that follow-up visits for patients in remission should include screening for tumor dissemination and potential brain metastases, particularly in those presenting with Gleason scores of 7 and higher. A study reported that 60%–75% of brain metastases are asymptomatic; this estimate is paired with the trend of carcinomatous meningitis usually being diagnosed only after neurological symptoms have already started, suggesting that the incidence of LM could be higher than current estimates report.[27] Furthermore, as presented in the "Clinical Presentation and Diagnosis" category, the case reports in this analysis primarily achieved diagnosis through the use of gadolinium-enhanced MRI. Gadolinium contrast-enhanced MRI is very sensitive and is thus the current standard of imaging for brain metastases. However, this approach is prone to false-negative results and relies on blood-brain barrier breakdown; thus, it tends to detect dissemination in the later stages of disease progression.[22] Because the early stages of brain metastases show robust glial activation, 1 study suggests that using single-photon emission computed tomography

(SPECT) imaging agents to detect translocator proteins (TSPO) on activated glia could allow for earlier detection of tumor dissemination than with MRI.[28] This study also indicates that glial activation occurs before the onset of neurological symptoms in some frontotemporal disorders. Therefore, it is possible that TSPO SPECT/PET may allow the detection of LM before symptom onset; however, this possibility requires further study. Discovering brain metastases before the onset of neurological symptoms could allow earlier intervention and potential improvements in disease outcomes.

The second finding presented in "Disease Course and Progression" showed that LM was always preceded by another metastasis, most commonly a vertebral metastasis. This suggests the presence of a specific pathway through which PC disseminates into the central nervous system (CNS). An initial theory by Batson[29] suggests that PC metastasizes to the CNS via the paravertebral plexus of the veins. Understanding the pathways and mechanisms of PC metastasis to the CNS will be helpful for developing interventions.

The "Treatment and Outcome" category indicates that most treatments were mainly palliative in nature and did not improve prognosis. In most studies, WBRT has not shown a survival benefit; thus, its use is decreasing, but it could still be useful for relieving neurological symptoms and for patients with extensive nodular disease or additional brain metastases.[30] In some of the patients in this analysis, dexamethasone was administered primarily for symptom alleviation; however, in most cases, intrathecal chemotherapy was not administered because of poor disease prognosis. It has been suggested that concomitant administration of intrathecal chemotherapy (methotrexate and dexamethasone) with involved-field radiotherapy can prolong the remission of neurological symptoms in LMC and increase overall survival.[31] Therefore, it may be beneficial to study the efficacy of this combination therapy for carcinomatous meningitis caused by PC.

As discussed in the "Treatment and Outcome" section, there was only 1 patient who displayed good treatment outcomes. This patient showed a decrease in PSA levels over time after undergoing hormone therapy, whereas the PSA levels of other patients in the sample who were treated with hormone therapy continued increasing. This finding indicates that patients with hormone-resistant PC may have a poorer prognosis due to limited therapeutic options and an increased incidence of LM. Hormone therapy, the first-line treatment of PC, is ineffective against CRPC. In addition, patients with CRPC have been found to acquire further resistance and progress to end-stage therapy-resistant PC.[32] Although treatment options are limited, studies have reported that in patients with CRPC, treatment with prostate-specific membrane antigen (PSMA) ligands can lead to the resolution of cerebral and skeletal metastases, as well as a reduction in PSA.[26] Further studies are necessary to determine the efficacy of this treatment in LM.

On the basis of our findings, it is recommended that those in remission from PC undergo routine follow-up screenings to detect LM before the disease progresses substantially. Most case reports in this analysis were published before novel PSMA-PET imaging techniques became available. Thus, it is important to consider PSMA-PET in screening for LM because it has been found to be more sensitive than conventional cross-sectional imaging and can detect lesions at PSA levels < 0.5 ng/mL.[33] As previously mentioned, SPECT/PET detection of TSPOs could help in the discovery of brain metastases before the development of neurological symptoms. However, further studies must be performed to determine its ability to specifically detect meningeal metastases.

Limitations

This study was limited by the small number of case reports in the literature, and the search was restricted to articles published in English. In addition, this analysis used secondary data; thus, the quality of the study design and primary data collection could not be controlled. These limitations make it difficult to confidently determine trends in treatment outcomes and disease presentation. The findings of this analysis highlight the need for future studies on the route of metastasis, screening methods, and treatment options to improve outcomes in patients with LM associated with PC.

5. Conclusions

Leptomeningeal metastasis tends to occur in patients with PC after cancer remission and often presents after vertebral metastasis. Although neurologic symptoms may present with LM, the disease can also progress asymptomatically. We recommend increased surveillance of high-risk cohorts (eg, high-grade hormonal PC). This type of surveillance could identify LM early, improving the prognosis of patients. However, each case should be individually assessed for the risks and benefits of using potentially invasive screening methods (eg, physical examination, brain imaging, and serology). We reaffirmed that brain imaging is the best method for LM detection. In addition, serological testing can be used to supplement the diagnosis when it is unclear. We also recommend WBRT as a treatment option for palliative pain and symptom management. This therapy was associated with the best outcomes in terms of symptomatic management, although mortality remained high. In the future, large-scale studies should be conducted on LM presentation, detection, and treatment to draw more definitive conclusions.

Acknowledgments

None.

Statement of ethics

The protocol for this systematic review follows the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols.

Conflict of interest statement

In compliance with the ICMJE uniform disclosure form, all authors declare that there are no conflicts of interest to disclose.

Funding source

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Author contributions

UD, AP, AA, WR, ZH: Research design, writing of the article, and data analysis;
KR: Writing of the article and performance of the research;
MA, ED, MP, FW, ZS: Writing of the article and data analysis;
EM: Research design and writing of the article.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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How to cite this article: Durrani U, Rifai K, Arshad M, Paracha A, Deol E, Paracha M, Waheed F, Siddiqui Z, Abid A, Mustafic E, Rodriguez W, Hamilton Z. Leptomeningeal metastases in prostate cancer: A review of the current literature. *Curr Urol* 2024;18(3):159–166. doi: 10.1097/CU9.0000000000000245