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Review

Intradural Cauda Equina Metastases: A Systematic Review of Clinico-radiological Features, Management, and Treatment Outcomes

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Abstract. *Background/Aim: Intradural cauda equina metastases (ICEM) are rare tumors that reduce functional status. Surgery and radiation are feasible and effective treatments but may have debilitating complications. We systematically reviewed the literature on ICEMs. Materials and Methods: PubMed, Scopus, Web of Science, and Cochrane were searched for studies reporting clinical data of patients with ICEMs. Clinical characteristics, management strategies, and treatment outcomes were analyzed. Results: We included 40 studies comprising 123 patients. Median age was 57 years. The most frequent primary tumors were lung (18.7%), breast (13%), and renal carcinomas (11.4%). Median time from primary tumor diagnosis to ICEMs' presentation was 36 months. The most common presenting symptoms were lower back pain (74%) and motor deficits (62.6%), with acute cauda equina syndrome documented in 36 patients (29.3%). Most lesions were diagnosed at magnetic resonance imaging (56.9%) or computed tomography myelography (32.5%). All cases were treated with decompressive laminectomy and tumor resection, with partial resection (82.1%) more often than complete (15.4%). Adjuvant radiotherapy (83.7%) and/or chemotherapy (10.6%) were often administered. Most patients experienced post-treatment symptom improvement (86.2%) and favorable radiological response (82.9%). ICEM recurrences were reported in 4 cases (8.5%) with median local tumor control of 7 months. At last follow-up, most patients were dead (62.9%) with median overall-survival of 10 months. Conclusion: Patients with ICEMs have poor prognoses and significant tumor burden. Surgery and locoregional radiotherapy may offer optimal clinical and radiological outcomes but have a limited role in improving local tumor control and overall survival.*

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The cauda equina is the conglomeration of lumbar and sacral nerve roots distally to the terminal portion of the spinal cord, starting at the L1-L2 vertebral level in most people. Cauda equina syndrome (CES) frequently results from nerve root compression and damage from herniated lumbar discs, spinal stenosis, post-traumatic fractured vertebral fragments, or tumors, which result in devastating morbidity (1). The clinical presentation is characterized by a combination of symptoms and signs, including lower back pain (LBP), radicular pain, lower extremities weakness, reduced deep tendon reflexes, saddle/perianal sensory deficits, bowel, bladder, and sexual dysfunction (2). Early diagnosis and timely intervention are critical to prevent symptom progression and, when feasible, promote neurological recovery (3, 4).

Neoplastic CES may arise from cauda equina primary tumors or secondary metastases, which may involve the vertebral bones, resulting in fracture and external nerve compression (5). A subset of neoplastic CES, intradural cauda equina metastases (ICEM), represent a rare but challenging entity (6, 7). The initial symptoms may be limited to LBP and paresthesia, but the prolonged neuropathic damage may become irreversible, severely affecting patients' quality of life (8). The diagnosis of ICEM is often delayed, particularly when there is no known history of cancer, as patients frequently present with a long and nonspecific disease course due to slow tumor growth and gradual nerve roots compression (5, 9). Surgery with decompressive laminectomy and/or tumor resection may relieve symptoms and improve functional status in eligible patients, but locoregional radiotherapy may also be delivered as adjuvant or stand-alone treatment in selected cases (5, 10).

Due to the rare incidence of ICEMs, most treatment paradigms derive from few case reports and series with heterogeneous clinical features and treatments. In this systematic review, we aimed to summarize the clinical characteristics, management strategies, and treatment outcomes of patients with ICEMs.

Materials and Methods

Literature search. A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). PubMed, Scopus, Web of Science, and Cochrane were searched from inception to November 11, 2021, using the combination of the Boolean operators "OR" and "AND" and the search terms: "cauda equina", "conus medullaris", "metastasis", and "metastases". Articles were uploaded to Mendeley, and duplicates were deleted manually.

Study selection. Inclusion and exclusion criteria were defined *a priori*. Studies were included if they: 1) presented ≥1 patients with histologically confirmed secondary intradural metastases involving the cauda equina region, as explicitly mentioned within their text or extracted from radiological images; 2) reported primary data on clinical features, treatment strategies, and post-treatment outcomes; 3) were written in English. Studies were excluded if they were: 1) reviews, autopsy reports, or animal studies; 2) studies with insufficient data on management and outcomes; 3) studies with no clear differentiation of patients with ICEM and patients with different spine metastases. ICEM were intended as intradural metastases involving the cauda equina nerve roots or the medullary cone, excluding cases with vertebral bone metastases and/or leptomeningeal metastases.

Two independent authors (P.P. and N.S.S.) screened titles and abstracts of all collected articles, and then evaluated full texts of studies that met inclusion criteria. A third author (A.S.H.) resolved any disagreements at both stages of screening. Eligible articles were included based on the pre-specified criteria and references were screened to retrieve additional studies.

Data extraction. One reviewer (S.E.Z.) extracted data from all articles, which were then confirmed by two independent reviewers (P.P. and N.S.S.). Extracted data included: authors, year, sample size, age, sex, primary tumors, systemic metastases, time interval between primary tumor diagnosis and ICEM onset, presenting symptoms, diagnostic protocol, ICEM location, surgery and extent of resection, radiotherapy, chemotherapy, treatment complications, clinical and radiological outcomes, recurrence, local tumor control (LC), overall survival (OS), survival status. Extent of resection was defined as "complete" for 100% tumor resection and "partial" for <100% Clinical and radiological responses were assessed at last available follow-up. Radiological responses were assessed using the "spine response assessment in neuro-oncology (SPINO)" criteria, describing: complete response (CR, complete tumor resolution), partial response (PR, decreased tumor volume), stable disease (SD, no volume change), progressive disease (PD, increased volume) (12).

Data synthesis and quality assessment. The primary outcomes of interest were the clinical-radiological features, treatment, and outcomes of patients with ICEMs. Levels of evidence were determined following the 2011 Oxford Centre For Evidence-Based Medicine guidelines (13). A study-level meta-analysis was precluded because all included articles had levels IV and V of evidence and hazard ratios could not be deducted. However, individual patient data were extracted for individual patient data meta-analysis. For each study, risk of bias was independently evaluated by two reviewers (P.P. and O.B.A.) in accordance with the Joanna Briggs Institute checklists for case reports and case series (14, 15). The risk of bias for this study overall was determined by considering the risk of bias of all included studies in aggregate.

Statistical analysis. The software SPSS V.25 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses. Continuous variables are presented as medians and ranges, and categorical variables as frequencies and percentages. The time intervals between surgery and ICEM recurrence (LC curve) or death (OS curve) were estimated using the Kaplan–Meier method.

Results

Study selection and overview. The Supplementary File 1 displays the literature search and study selection flowchart. The initial search returned 1,082 citations (PubMed: 368; Scopus: 446; Web of Science: 245; Cochrane: 23). In total, 5 case series and 35 case reports were included, respectively categorized as level IV and V of evidence (Supplementary File 2) (6, 7, 10, 16-52). Critical appraisal resulted in low risk of bias for all included articles (Supplementary File 3), predisposing this study to a low risk of bias overall.

Demographics and primary tumors' characteristics. A total of 123 patients diagnosed with ICEMs were analyzed. Patients were mostly male (57.7%), with a median age of 57 years (range=11-87 years) (Table I). The most frequent primary tumors comprised lung cancer (18.7%), breast cancer (13%), renal cell carcinoma (11.4%), and prostate cancer (10.6%). Two patients had primary brain tumors, consisting of one pituitary carcinoma (36) and one cerebellar hemangiopericytoma (25). Primary tumors were mostly treated with surgery (98.4%) coupled with adjuvant radiotherapy (82.9%) and/or chemotherapy (8.1%). Systemic metastases were described in 55.3% of patients, commonly involving the lungs (50%), bones (26.9%), and/or brain parenchyma (26.9%). Metastatic peritoneal seeding was found in 1 patient with anal carcinoma (52) and 1 patient with ovary adenocarcinoma (7).

Clinical and diagnostic features of ICEMs. The median time interval from primary tumor diagnosis to ICEMs onset was 36.0 months (range=0-360.0 months), with synchronous ICEMs identified in 12 patients (9.8%). The most frequent presenting symptoms were LBP (74%), motor deficits (62.6%), including paraparesis with walking impairment (21.1%), and radicular pain (59.3%) (Table II). Acute CES was documented in 36 cases (29.3%). Strong *et al*. (35) described one asymptomatic patient with renal cell carcinoma who was diagnosed with ICEM at oncological imaging follow-up. The diagnosis of ICEMs was mostly obtained at magnetic resonance imaging (MRI) T1-contrast scans (56.9%), showing contrast-enhancing lesions encasing the cauda equina nerve roots. CT myelography and X-Ray myelography were performed in 40 (32.5%) and 10 (8.1%) patients, respectively, showing complete block of the contrast dye. Most lesions occurred in the lumbar (78.9%) and lumbar-sacral (10.6%) spine. Of note, Wu *et al*. (38) reported one patient with hepatocellular carcinoma presenting with an ICEM located at the T12-S1 spine levels. Concurrent extradural vertebral metastases were found in 8 patients, mostly involving the thoracic (4, 50%) and lumbar (4, 50%) spine (7, 10, 18, 37, 38, 40, 43, 49). Skoch *et al*. (37) described one case of ICEM from testicular choriocarcinoma with concomitant metastases of the brain parenchyma and the C3 vertebra.

Management strategies. All patients received decompressive laminectomy with tumor removal (100%) (Table III). Partial tumor resection was obtained in most cases (82.1%), whereas complete tumor resection (15.4%) and biopsy (2.4%) were less frequent. In 12 patients (9.8%), the cauda equina nerve roots were transected during tumor removal and intraoperative neuromonitoring, but no post-surgical complications were noted. Locoregional radiotherapy was delivered in 103 patients (83.7%) at a median dose of 30 Gy (range=10-50 Gy). Most patients received external beam radiotherapy targeting the lumbar-sacral spine, while the whole spine axis was radiated only in 2 patients (7, 25). Pagano *et al*. (10) reported the use of palliative stereotactic radiosurgery in one patient with lung ICEM. Systemic chemotherapy was administered in 13 patients (10.6%), mostly with methotrexate (47, 48) (2, 15.4%) and cisplatin plus etoposide (37, 39) (2, 15.4%). No treatment-related complications were reported across all included articles.

Table I. Summary of patients' demographics and primary tumors' characteristics.

Characteristics (no. of patients with available data)	Value
Cohort size (no.)	123
Demographics (n=123)	
Age (years), median (range)	57 (11-87)
Gender (male)	71 (57.7%)
Primary tumor (n=123)	No. (%)
Lung	23 (18.7%)
Breast	16 (13%)
Renal	14 (11.4%)
Prostate	13 (10.6%)
Lymphoma	6 (4.9%)
Endometrial	5 (4.1%)
Others	45 (36.6%)
Treatment primary tumor (n=123)	No. (%)
Surgery	121 (98.4%)
Radiotherapy	102 (82.9%)
Chemotherapy	10 (8.1%)
Secondary metastases (n=47)	No. (%)
Patients with systemic metastases	26 (55.3%)
Lung	13 (50%)
Bone (Long bones, Spine, Skull base)	7 (26.9%)
Brain	7 (26.9%)
Lymph nodes	5 (19.2%)
Peritoneal seeding	2 (7.7%)
Adrenal gland	2 (7.7%)
Colon	1 (3.8%)
Liver	1 (3.8%)
Muscle/Soft tissue	1 (3.8%)
Skin	1 (3.8%)
Time from primary tumor to ICEMs (months), median (range)	36.0 (0-360.0)
Synchronous ICEMs	12 (9.8%)

Treatment outcomes and survival. Patients were followed-up for a median of 10 months (range=0.5-152 months) (Table III). Most patients (86.2%) had post-treatment symptomatic improvement. Restoration of the ambulatory status was reported in all the 26 patients with pre-treatment walking impairment. Radiological responses were evaluated in 47 patients, documenting: CR in 16 (34%), PR in 23 (48.9%), SD in 2 (4.3%), and PD in 6 (12.8%). Median local tumor control was 7 months (range=0.5-36.0 months) (Figure 1), with 4 patients (8.5%) experiencing local ICEMs recurrences and 2 (4.3%) presenting concurrent new leptomeningeal metastases (LMs) (10, 31, 36, 40). Median OS was 10 months (range=0.5-152.0 months), with most patients dead at last follow-up (62.9%).

Table II. *Summary of clinical and radiological features of intradural cauda equina metastases.*

Characteristics (no. of patients with available data)	Value
Presenting symptoms (n=123)	No. (%)
Acute cauda equina syndrome	36 (29.3%)
Lower back pain	91 (74%)
Motor deficits	77 (62.6%)
Paraparesis (cannot walk)	26 (21.1%)
Radicular pain	73 (59.3%)
Sensory deficits	38 (30.9%)
Incontinence	31 (25.2%)
Urine retention	6 (4.9%)
No symptoms	1 (0.8%)
Diagnostic protocols (n=123)	No. (%)
MRI	70 (56.9%)
CT myelogram	40 (32.5%)
X-Ray myelogram	10 (8.1%)
CT spine	5 (4.1%)
Location (n=123)	No. (%)
Lumbar	97 (78.9%)
Lumbar-Sacral	13 (10.6%)
Thoracic-Lumbar	7 (5.7%)
Sacral	3 (2.4%)
Thoracic-Lumbar-Sacral	1 (0.8%)

Table III. *Summary of management strategies and treatment outcomes.*

Characteristics (no. of patients with available data)	Value
Management (n=123)	No. (%)
Decompressive laminectomy + Resection	123 (100%)
Complete	19 (15.4%)
Partial	101 (82.1%)
Biopsy	3 (2.4%)
Radiation therapy	103 (83.7%)
Dose (Gy), median (range)	30 (10-50)
Systemic chemotherapy	13 (10.6%)
Post-treatment symptom improvement (n=123)	106 (86.2%)
Radiological response (n=47)	No. (%)
Complete response (CR)	16 (34%)
Partial response (PR)	23 (48.9%)
Stable disease (SD)	2 (4.3%)
Progression (PD)	6 (12.8%)
Recurrence of ICEMs (n=47)	4 (8.5%)
Leptomeningeal metastases	2 (4.3%)
Outcome (months)	Median (range)
Local control (n=47)	7.0 (0.5-36.0)
Overall survival (n=123)	10.0 (0.5-152.0)
Status (n=123)	No. (%)
Alive	46 (37.4%)
Dead	77 (62.6%)

Discussion

ICEMs represent late-stage complications of advanced systemic malignancies, and lead to major functional impairments in affected patients. Advances in imaging techniques and treatment strategies allow prompt and effective management, but outcomes have remained poor. We found that ICEMs commonly present with severe pain and motor deficits in known oncological patients. Current treatments offer short-term favorable clinical and radiological responses but are mostly intended only for palliation. This study aimed to provide useful insights into the management of ICEMs within the context of other spine metastases and primary cauda equina tumors.

In contrast to the more common extradural vertebral metastases, intradural spine metastases account only for 1-2% of all metastatic spine lesions (53). Metastases to the cauda equina are even rarer and mostly present with concurrent LMs (54), with only a few cases of focal space-occupying masses within the cauda dural sac described across the literature. In this review of ICEMs, the most frequent primary tumors were lung, breast, and renal carcinomas, in accordance with their prevalence in the general oncological population and in patients with spine metastases (55, 56). This likely suggests the presence of shared spreading routes among all spine metastases. A total of 5 different metastatic mechanisms have been hypothesized for ICEMs: 1) hematogenous spread through the arterial system, 2) the venous plexus of Batson, or 3) the perineural lymphatics; 4) cerebrospinal fluid dissemination; and 5) direct invasion from contiguous structures (18, 34). In our pooled cohort, we presume that most ICEMs originated from the arterio-venous and/or lymphatic spread of systemic cancers, owing to the high prevalence (55.3%) of patients with concurrent systemic metastases. Patients with gynecologic tumors, urologic neoplasms, and/or peritoneal seeding may have developed ICEMs from direct tumor invasion, especially from concurrent vertebral metastases (7, 37, 40). These preferred routes may also explain the delayed onset of ICEMs from primary tumor diagnosis found across our included studies (median 36 months). Of note, some aggressive neoplasms may have different metastatic mechanisms responsible for synchronous ICEMs, as reported in 12 of our pooled patients (9.8%) diagnosed with endometrial choriocarcinomas and stage 4 lung or renal cancers. Finally, the low rates of primary or metastatic brain tumors in our cohort may suggest that cerebrospinal fluid dissemination represents a less common route for ICEM development, as opposed to spine LMs (54).

Most ICEMs have a symptomatic but non-specific clinical presentation, often delaying diagnosis and leading to progressive worsening of neurological and functional status (6, 7). LBP is the most common presenting symptom, exacerbated by coughing, sneezing, and percussion to the lumbar spine, and frequently resulting in limited range of

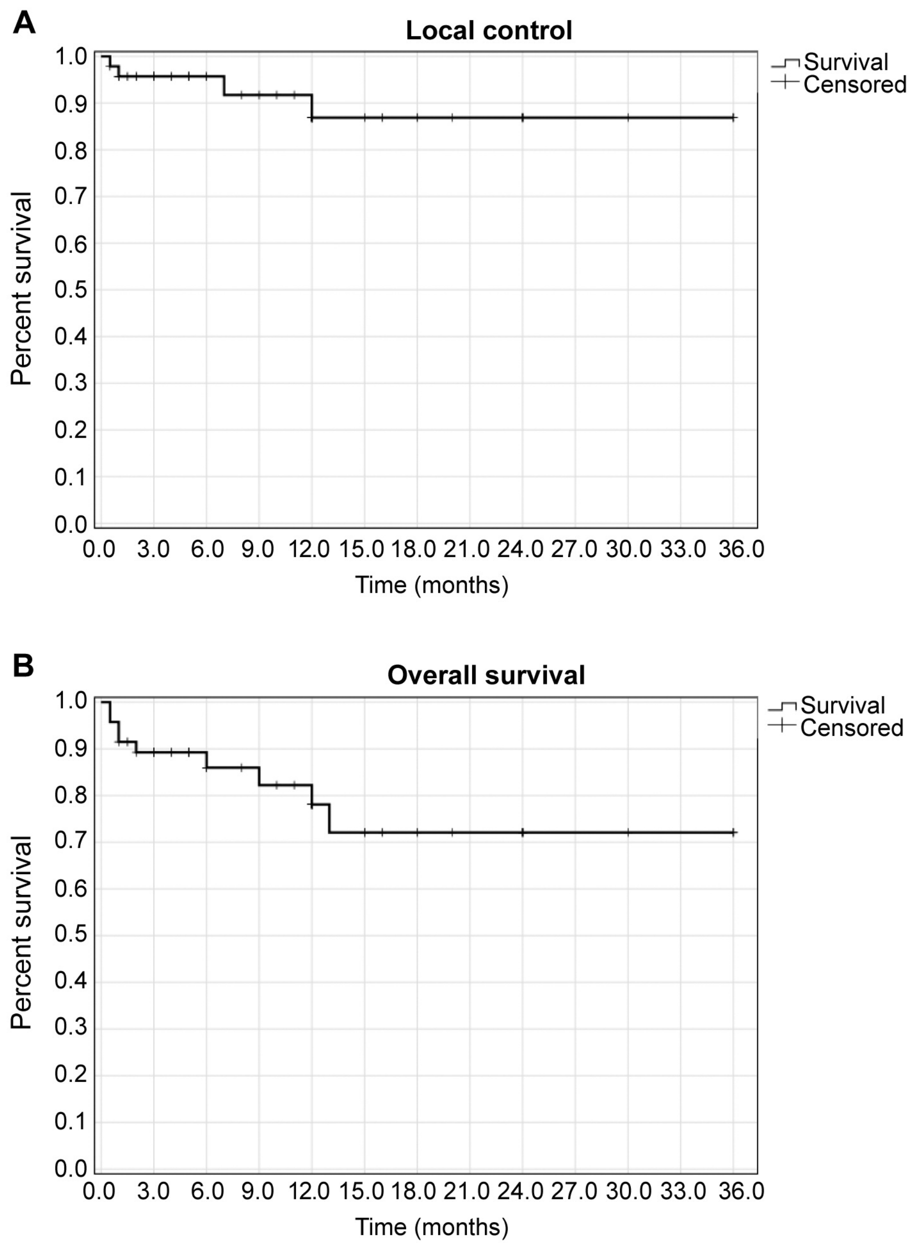

Figure 1. *Kaplan–Meier curves of (A) local control and (B) overall survival of the pooled cohort.*

spinal motion (33, 34). Due to tumor-induced direct compression of the cauda equina nerve roots, patients may gradually experience radicular leg pain and motor deficits, which can promote paraparesis, walking inability, and severe functional impairment if the nerve roots are not decompressed (7, 38, 42). Acute CES, with or without sphincter incontinence, may also occur, necessitating emergent planning of appropriate diagnostic and therapeutic strategies (5, 37, 46). Although these symptoms may simulate the presence of lumbar disc disease, their rapid progression and high severity may serve as "red flags" that require further assessment (57, 58). In earlier series, spine myelography was the most commonly used diagnostic tool, allowing clinicians to detect contrast dye block at the cauda equina level and increase suspicion regarding the presence of metastases in patients with a known tumor history (6, 36, 47-51). Contrast-enhanced MRI scans represent the current diagnostic standard, visualizing ICEMs as single or multiple lesions encasing the cauda equina nerve roots or located within the conus medullaris (6, 7). MRI of the whole spine may also detect the presence of concurrent LMs or extradural vertebral metastases, providing valuable information for accurate treatment planning (54, 56). In some cases, MRI may lack specificity in differentiating primary versus metastatic cauda equina lesions, especially in patients with no prior history of cancer and single spine lesions (59). Still, early diagnosis with MRI is mandatory in patients with acute CES and suspected ICEMs in order to design timely therapies and avoid irreversible neurological deficits.

The primary therapeutic goals in patients with spine metastases and cauda equina tumors are providing pain relief, neurological improvement and/or restoration in walking ability, and prolonged LC and OS rates (60). As compared to other spine oncological lesions, challenges in the management of ICEMs mostly derive from their complex surgical anatomy, coupled with the poor clinical condition of patients with systemic malignancies. When feasible, surgical laminectomy and resection of ICEMs represent the mainstay of treatment for providing both histological confirmation and relief of the compressive pathology (10, 42). However, as most tumors agglutinate the cauda equina nerve roots and lack a distinct cleavage plane, complete resection is rarely possible without posing severe risks of post-surgical complications (44). Similar to other series of primary cauda equina tumors, partial tumor resection was performed in most of our pooled patients, achieving optimal clinical and radiological outcomes and further suggesting that complete resection may not be necessary for ICEMs (42). In contrast, total en-bloc ICEM resection was carried out in some patients with aggressive lesions by transecting the encased nerve roots and/or the filum terminale, with no post-operative deficits were noted (24, 27, 33, 41). In these cases, neuromonitoring assistance allowed surgeons to evaluate the preserved motor functions and plan operative approaches to minimize the risk of iatrogenic complications. Additionally, adjuvant treatments have been also described in patients with ICEMs, which provide superior benefits relative to surgery alone. While chemotherapy agents varied based on primary tumors, radiotherapy protocols were mostly consistent across our included studies. Indeed, post-surgical spine radiotherapy has demonstrated to effectively reduce tumor remnant size and prolong local control in patients with metastatic spinal cord compression (61). In our pooled cases, locoregional radiotherapy was mostly delivered to the lumbar-sacral spine for targeting the lesions of interest or was extended to other spine regions in patients with concurrent vertebral metastases (43, 49). Radiotherapy to the whole spine axis was delivered only in patients with suspected cerebrospinal fluid dissemination, with no radiation-induced complications (7, 25). Although recent targeted molecular therapy and immunotherapy agents have been introduced in the multidisciplinary management of patients with systemic cancers, their role in patients with ICEMs is still uncertain and requires further evaluation (54, 62).

Despite the current treatments, the prognosis of patients with ICEMs remains poor and is heavily dependent on the primary tumor histology and management (6, 10). We ascribe the low rates of LC (7 months) and OS (10 months) in our pooled cohort to the fact that most lesions occurred at later disease stages in patients with concurrent systemic metastases and high tumor burden. These factors, coupled with the limited availability of systemic therapies in ICEMs, may also explain the survival differences noted in comparison to patients with extradural vertebral metastases, who have OS rates ranging up to 2-years when treated with targeted molecular and immunotherapy agents (56). However, surgery and locoregional radiotherapy proved to be useful for palliation in patients with ICEMs. We found favorable rates of post-treatment clinical (86.2%) and radiological (82.9%) improvement, superior to those reported in patients with spine LMs (54). In particular, surgical decompression with tumor resection showed optimal outcomes in patients with pre-treatment paraparesis and walking impairment, leading to ambulatory restoration and improved quality of life in all cases (7, 48-50). However, due to the increasing survival of oncological patients and the growing incidence of spine metastases, novel patient-tailored treatments should be developed also for patients with ICEMs, to reduce neurological morbidity and improve quality of life.

Limitations. The limitations of this review should be considered. All included studies were retrospective case reports and case series likely subjected to publication and selection biases. Included studies also covered a 57-year time-period characterized by major advances in imaging and treatment protocols, which may have introduced some between-study heterogeneity in the analysis of radiological features and post-treatment outcomes. The low level of evidence of our included articles precluded a study level meta-analysis. By including only biopsy-proved cases, this review may have underestimated the overall prevalence and treatment-related outcomes of patients with ICEM, representing detection bias. However, our selective inclusion criteria were set a priori to minimize the risks of introducing confounding variables related to misdiagnoses of ICEMs from clinical and radiological assessments. Finally, pre- and post-treatment performance status scores could not be analyzed and compared due to the lack of granular data. Despite these limitations, we provide a methodologically rigorous, reproducible individual patient data meta-analysis of ICEMs to inform their management by neurosurgeons, neuro-oncologists, and radiation oncologists.

Conclusion

ICEMs comprise late-stage complications of systemic oncological diseases and lead to serious neurological and functional impairments in affected patients. ICEMs most commonly arise from lung, breast, and renal primary sources and present with acute cauda equina syndrome in one-third of cases. Surgical decompression and tumor resection, coupled with adjuvant locoregional radiotherapy and/or chemotherapy, demonstrate favorable rates of symptom improvement and positive radiological responses. However, rates of local tumor control and survival remain discouraging, with future studies required to evaluate the role of newer molecular and immune treatments.

Supplementary Material

Available at: https://www.dropbox.com/sh/u9nalvcbbsbasok/AADbPEkjKnI3lNYQan6TDRCYa?dl=0

Conflicts of Interest

The Authors have no relevant financial or non-financial interests to disclose.

Authors' Contributions

Paolo Palmisciano: Conceptualization, Methodology, Data analysis, Writing – Original draft preparation; Saif E. Zaidi: Resources, Writing – Reviewing and Editing; Nathan Shlobin: Resources, Writing – Reviewing and Editing; Navraj S. Sagoo: Resources, Writing – Reviewing and Editing; Othman Bin Alamer: Resources, Writing – Reviewing and Editing; Gianluca Scalia: Resources, Writing – Reviewing and Editing; Gianluca Ferini: Resources, Writing – Reviewing and Editing; Giuseppe E. Umana: Resources, Writing – Reviewing and Editing; Salah G. Aoun: Resources, Writing – Reviewing and Editing; Ali S. Haider: Methodology, Resources, Writing – Reviewing and Editing, Supervision.

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