Advances in Radiation Oncology (2024) 9, 101377

advances in radiation oncology
www.advancesradonc.org

Critical Review

Radiation Therapy in the Management of Leptomeningeal Disease From Solid Tumors

Andrew B. Barbour, MD, PhD,[a] Rupesh Kotecha, MD,[b] Stanislav Lazarev, MD,[c] Joshua D. Palmer, MD,[d] Timothy Robinson, MD,[e] Divya Yerramilli, MD,[f] and Jonathan T. Yang, MD, PhD[a,*]

[a]Department of Radiation Oncology, University of Washington − Fred Hutchinson Cancer Center, Seattle, Washington; [b]Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida; [c]Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, New York; [d]Department of Radiation Oncology, The James Cancer Hospital, The Ohio State University Wexner Medical Center, Columbus, Ohio; [e]Department of Therapeutic Radiology, Yale University, New Haven, Connecticut; and [f]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

Received 24 March 2023; accepted 3 September 2023

Purpose: Leptomeningeal disease (LMD) is clinically detected in 5% to 10% of patients with solid tumors and is a source of substantial morbidity and mortality. Prognosis for this entity remains poor and treatments are palliative. Radiation therapy (RT) is an essential tool in the management of LMD, and a recent randomized trial demonstrated a survival benefit for proton craniospinal irradiation (CSI) in select patients. In the setting of this recent advance, we conducted a review of the role of RT in LMD from solid tumors to evaluate the evidence basis for RT recommendations.

Methods and Materials: In November 2022, we conducted a comprehensive literature search in PubMed, as well as a review of ongoing clinical trials listed on ClinicalTrials.gov, to inform a discussion on the role of RT in solid tumor LMD. Because of the paucity of high-quality published evidence, discussion was informed more by expert consensus and opinion, including a review of societal guidelines, than evidence from clinical trials.

Results: Only 1 prospective randomized trial has evaluated RT for LMD, demonstrating improved central nervous system progression-free survival for patients with breast and lung cancer treated with proton CSI compared with involved-field RT. Modern photon CSI techniques have improved upon historical rates of acute hematologic toxicity, but the overall benefit of this modality has not been prospectively evaluated. Multiple retrospective studies have explored the use of involved-field RT or the combination of RT with chemotherapy, but clear evidence of survival benefit is lacking.

Conclusions: Optimal management of LMD with RT remains reliant upon expert opinion, with proton CSI indicated in patients with good performance status and extra-central nervous system disease that is either well-controlled or for which effective treatment options are available. Photon-based CSI traditionally has been associated with increased marrow and gastrointestinal toxicities, though intensity modulated RT/volumetric-modulated arc therapy based photon CSI may have reduced the toxicity profile. Further work is needed to understand the role of radioisotopes as well as combined modality treatment with intrathecal or central nervous system penetrating systemic therapies.

Sources of support: This work had no specific funding.
There are no data to make available for this work.
Noted—An online CME test for this article can be taken at https://academy.astro.org.
*Corresponding author: Jonathan T. Yang, MD, PhD; E-mail: yang1@uw.edu

https://doi.org/10.1016/j.adro.2023.101377

Introduction

Leptomeningeal disease (LMD) is the spread of malignancy into the cerebrospinal fluid (CSF)-filled leptomeningeal space surrounding the brain and spinal cord of the central nervous system (CNS). Although 20% to 30% of patients with metastatic disease and neurologic symptoms harbor LMD at autopsy,[1-3] LMD is clinically detected in only 5% to 10% of patients with solid tumors.[4] The incidence of LMD varies with histology, with lung and breast cancers being most commonly associated with LMD (5%-25%), followed by melanoma (6%-18%) and gastrointestinal malignancies (4%-14%).[3,5-7] Mutation status may also relate to LMD risk, particularly for the epidermal growth factor receptor family of mutations.[8,9] The incidence of clinically detected LMD is thought to be rising because of a combination of improved imaging techniques[6] and improved control of extra-CNS disease (ECD).[10-12]

Dissemination of tumor cells through the CNS results in a diverse presentation of neurologic symptoms that may include severe headaches with nausea and vomiting, cranial neuropathies, cerebellar dysfunction, radiculopathy, and cauda equina syndrome. Symptoms can be debilitating and life-threatening, resulting in substantial morbidity and mortality and requiring multidisciplinary management. The median overall survival (OS) of patients with LMD is often measured in months but can be highly variable in relation to multiple factors such as patient performance status, status of ECD, tumor histology, and systemic therapy options.[13] Given the historically poor prognosis, the primary goals of treating LMD with radiation therapy (RT) have been to stabilize or improve neurologic symptoms, reduce tumor bulk, and restore CSF flow.

Involved-field RT (IFRT), such as whole brain (WBRT) and focal spine RT, is effective in symptom management, but does not generally improve OS, and out-of-field failure is common.[13] This can partially be attributed to LMD tumor dissemination affecting the entire neuroaxis, thus requiring the craniospinal compartment to be considered as the target volume. However, delivery of craniospinal irradiation (CSI) with traditional photon-based techniques can lead to significant hematologic and gastrointestinal morbidity and is generally not recommended for adults with LMD from solid tumors. In contrast, proton beam therapy can permit a safe delivery of CSI thanks to protons' negligible exit dose, potentially improving safety and efficacy of the treatment. A recent phase 2 randomized trial of proton CSI versus photon IFRT for LMD from breast and non-small cell lung cancer (NSCLC) demonstrated a significant survival benefit of proton CSI with no increase in high-grade radiation toxicities.[14] Given this recent advance, we conducted a review of the role of RT in the management of LMD from solid tumors to assess the current state of the literature and inform modern RT recommendations, supplemented by expert commentary.

Methods and Materials

In November 2022, we conducted a search of the relevant literature in PubMed and of ongoing clinical trials listed on ClinicalTrials.gov to inform a discussion on the role of RT in the management of solid tumor LMD. We used search terms including, but not limited to, combinations of such keywords as "leptomeningeal metastases," "leptomeningeal disease," "leptomeningeal carcinomatosis," "neoplastic meningitis," and "carcinomatous meningitis," as well as "radiotherapy," "radiation therapy," "irradiation," "radioisotope," and "radionuclide." Only studies written in the English language that included patients with LMD from solid tumors were reviewed. Studies of LMD from primary CNS tumors (eg, medulloblastoma) or hematologic malignancies (eg, leukemia) were excluded. All publication years were considered. Because of the paucity of high-quality published evidence, discussion was informed more by expert consensus and opinion, including a review of societal guidelines, than evidence from clinical trials.

Results and Discussion

Overview of current guidelines

National Comprehensive Cancer Network (NCCN) guidelines version 1.2023 stratifies patients with LMD into "good risk" (Karnofsky performance score [KPS] $\geq$60; no major neurologic deficits, minimal systemic disease, reasonable systemic treatment options) versus "poor risk" (KPS <60; multiple, serious, major neurologic deficits; extensive systemic disease with few treatment options; bulky CNS disease; encephalopathy).[15] The recommended management of poor-risk patients includes best supportive care and palliative measures such as the consideration of IFRT to painful or neurologically symptomatic sites. The recommended management of good-risk patients includes systemic therapy, intra-CSF systemic therapy, RT, and palliative and/or best supportive care. RT is recommended to be given as stereotactic radiosurgery (SRS) or IFRT and/or WBRT to bulky disease and neurologically symptomatic or painful sites. Consideration of CSI is recommended in selected patients, although patient selection guidelines are not provided. When employing CSI, NCCN guidelines recommend consideration of advanced modalities such as intensity modulated RT or protons where available.

The European Association of Neuro-Oncology and European Society for Medical Oncology guidelines do not incorporate risk stratification. European Association of Neuro-Oncology/European Society for Medical Oncology guidelines instead recommend palliative approaches for patients with life expectancies less than 1 month. For other patients, treatment recommendations are algorithmically stratified by CSF cytology, presence of brain metastases (BMs), status of ECD, and LMD subtype.[16,17] For circumscribed symptomatic lesions, including CSF flow obstruction, IFRT is recommended.[17] WBRT may be considered for extensive nodular or symptomatic linear LMD. In exceptional circumstances of radiographically occult cauda equina syndrome or cranial nerve palsies, IFRT may be considered. No specific recommendations were made regarding the use of CSI.

IFRT

IFRT, typically in the form of WBRT and/or focal spine RT, does not comprehensively treat the entire CNS compartment at risk for LMD tumor cell dissemination. Because of the overall simplicity in patient set-up and treatment delivery, IFRT allows for rapid initiation of therapy to stabilize neurologic symptoms in a majority of patients.[18] Clinical application of IFRT is based on retrospective or noncomparative prospective studies, as the only randomized prospective evaluation of photon IFRT was conducted in comparison to proton CSI.[14] Dose fractionation typically ranges from 20 to 40 Gy in 5 to 20 fractions. Prior reviews of IFRT in the management of LMD have not found reliable evidence of an OS benefit, and the vast clinical and methodological differences of past studies have hindered the ability to perform a meta-analysis.[13,19,20] Inadequate data exist to guide treatment based on primary tumor histology; however, patients with gastrointestinal malignancies have lower likelihood of benefit from IFRT[13] and mutational status has correlated to treatment benefit in retrospective work.[21] Radiographic patterns of LMD are being elucidated, but as they have not been routinely reported, insufficient data exist to evaluate their ability to inform use of IFRT.[22-24] Given the lack of high-level evidence guiding the use of IFRT, there exists a diversity of expert opinion on IFRT application.[25]

WBRT is the most prescribed form of RT for the management of LMD.[25] Retrospective studies demonstrate an inconsistent relationship between WBRT and OS, but in general, patients completing a course of WBRT live longer.[13,26-29] Similar to WBRT for the management of BM, WBRT is unlikely to improve survival in poor-risk patients.[30] However, the results of multiple studies suggest a symptomatic benefit of WBRT, justifying its palliative use.[22,31-35] Although there are no clear guidelines for proper patient selection, WBRT is typically indicated in patients of adequate functional status who are not eligible or able to be treated with proton CSI, have intracranial CSF flow blocks, have symptoms of increased intracranial pressure, or otherwise have symptomatic intracranial lesions. Although a small retrospective analysis of patients with breast cancer suggested improved survival with higher RT doses,[26] WBRT for LMD is typically prescribed as 30 Gy in 10 or 20 Gy in 5 fractions given the palliative nature of treatment. Moreover, because prolonged fractionated schedules have not demonstrated benefits in patients with BM without LMD, a lack of benefit for prolonged fractionation in patients with LMD would be anticipated.[36] Hippocampal avoidance WBRT has not been studied in the management of LMD and is not recommended at this time because of the potentially reduced coverage of at-risk CSF spaces. WBRT should be delivered with 2 lateral opposing fields encompassing the cribriform plate and the inferior border placed at the C2/C3 intervertebral space to ensure coverage of the inferior aspect of the posterior fossa. In cases of isolated cranial neuropathies, IFRT to the skull base, including the interpeduncular cistern and extending to include the first 2 cervical vertebrae, can be considered in lieu of WBRT with the goal of palliation of symptoms for patients who would prefer to defer a more comprehensive approach.

The use of focal spine RT can be guided by radiographic and/or clinical findings. For patients with cauda equina syndrome, the lumbosacral vertebrae should be targeted with a multifield 3-dimensional technique. For radiculopathies or other neurologic symptoms above the cauda equina, focal spine RT treatment fields are guided by radiographic findings and symptoms. Focal spine RT may be targeted to areas of CSF flow blocks, as these areas are associated with decreased survival and have a reasonable probability of response to focal spine RT.[37-41]

A limited number of retrospective studies have examined the role of focal intracranial RT, such as SRS, in the setting of LMD. One retrospective review identified 16 patients of good performance status who had LMD treated with SRS, achieving a median OS of 10 months.[42] Of patients with imaging follow-up, 50% developed distant LMD at a median interval of 7 months. Prospective work is required to guide patient selection when using focal intracranial RT in the management of LMD. Given that LMD is a disseminated disease, SRS is not recommended as a first-line radiation treatment. However, SRS may be useful as a salvage option for focally recurrent or symptomatic disease in patients who have had prior RT.

CSI

LMD involves tumor dissemination through the entire CNS compartment, thus eradication of leptomeningeal tumor cells with RT requires CSI. CSI is standard-of-care treatment in select patients with LMD from hematologic malignancies, medulloblastoma, and germinomas.[43-45]

For LMD from solid tumors, retrospective studies have demonstrated efficacy of x-ray–based photon CSI for symptom alleviation, but widespread use of photon CSI is limited by toxicities and a lack of survival benefit.[18,31,46-48] Of particular concern are the high rates of hematologic toxicities as these patients have often undergone extensive prior treatment compromising bone marrow reserve, and myelosuppression may require early discontinuation of CSI or compromise future delivery of systemic therapy.[46,47] Modern techniques, such as helical tomotherapy or volumetric-modulated arc therapy, allow for improved dosimetry and organ sparing, thus improving upon historical rates of acute hematologic toxicity while increasing low-dose organ exposure.[48-52] However, modern photon CSI techniques have not been correlated with improved survival in retrospective studies of LMD,[18,31] but a prospective study is forthcoming.[52] Nonetheless, in cases where proton CSI is not available, the use of modern photon CSI to treat selected patients with good performance status and controlled ECD remains a reasonable option that has been anecdotally associated with favorable outcomes, with retrospective series suggesting a median survival of 7 months.[46]

Particle-therapy CSI, such as proton CSI, allows for improved organ and vertebral body sparing compared with all forms of photon CSI. In a study of adult patients with medulloblastoma comparing photon and proton CSI, proton CSI resulted in significantly fewer gastrointestinal and hematologic toxicities.[53] In 2021, Yang et al[54] reported a low toxicity profile for proton CSI through a phase 1 study of patients with solid tumor LMD. This finding led to the first prospective clinical trial of RT for solid tumor LMD, which randomized 63 patients in a 2:1 ratio to pencil beam scanning proton CSI or photon IFRT, including WBRT and/or focal spine RT.[14] Patients in each arm had systemic therapy held during RT and were prescribed 30 Gy in 10 fractions. Eligible patients had KPS $\geq$60, adequate bone marrow function, and NSCLC or breast cancer. At the time of planned interim analysis, the trial was discontinued because of a significant benefit of proton CSI for the primary outcome of CNS progression-free survival (PFS; 7.5 vs 2.3 months; $P <$ .001). Although not powered to evaluate differences in the secondary endpoint of OS, median OS was significantly higher in the proton CSI arm (9.9 vs 6.0 months; $P = .029$), which is likely a consequence of lower rates of CNS progression. There was no significant difference in the rate of grade 3 and 4 treatment-related adverse events ($P = .19$), with high-grade treatment-related adverse events occurring in a minority of patients. An exploratory proton CSI arm consisting of patients with other solid tumor histologies demonstrated a median CNS PFS of 5.8 months and median OS of 6.6 months.

Based on these results, it is reasonable to consider CSI, preferably proton-based, when considering RT in patients with NCCN good-risk solid tumor LMD for the intent of comprehensive CNS and CSF disease control. For patients desiring focal CNS disease control and symptom palliation, focal or IFRT continues to be an effective tool and has a role in the management of patients with good- and poor-risk LMD. Furthermore, it is important to note that a phase 3 study is planned to evaluate the survival benefit observed in the phase 2 trial, and ongoing work in biomarker identification will further help elucidate which patients benefit most from proton CSI.

Quantitative CSF tumor cell (CSF TC) count has been shown to have improved diagnostic performance for LMD compared with magnetic resonance imaging (MRI) and CSF cytology.[55-58] In a large retrospective cohort of patients with CNS metastases, quantitative CSF TC count was associated with survival.[59] For patients undergoing proton CSI, CSF TC before treatment and change in CSF TC after treatment have been shown to correlate with CNS PFS and OS. In a 58-patient retrospective study, Wijetunga et al[60] were able to group patients based on baseline CSF TC and change in CSF TC at the time of proton CSI, with the most favorable group of patients having low CSF TC count before proton CSI, resulting in a median CNS PFS of 12 months and OS of 17 months. In patients with high baseline CSF TC count and minimum change in CSF TC after proton CSI, survival was poor (median CNS PFS of 4 months and OS of 5 months). In the previously mentioned phase 2 trial of proton CSI versus IFRT, patients who received proton CSI had decreasing CSF TC count after CSI while patients who received IFRT had increasing CSF TC count after IFRT, indicating that CSI is required to adequately address LMD disease burden in the CSF.

In addition to CSF TC, there is an increasing interest in the role of CSF circulating tumor DNA (ctDNA).[61,62] Given the increase in signal-to-noise ratio in CSF as a result of less circulating noncancerous genomic DNA, CSF ctDNA analysis has been shown to be a sensitive method to detect disease in the CNS.[61,62] Furthermore, CSF ctDNA also allows for an understanding of genomic and clonal differences between the primary cancer and the metastatic disease in the CNS.[61] In a recent paper, Wijetunga et al[60] demonstrated unique LMD evolution compared with systemic metastasis using matched plasma and CSF ctDNA in patients undergoing proton CSI for LMD. In addition, the authors observed unique selection pressure applied by CSI that was isolated to the CSF compartment, and that variant allele frequencies may be a biomarker of response to proton CSI.[63]

Guidelines for target volume delineation and dose constraints for proton CSI have been previously published.[14,64] Although proximal spinal nerve roots are generally part of the target for proton CSI, routine coverage of the optic nerves remains a topic of debate. Coverage of the optic nerves and retina may increase risk of toxicity in patients receiving what has historically been considered a palliative treatment, perhaps most notably elevating the risk of retinopathy in patients receiving

systemic therapies such as tyrosine kinase inhibitors (TKIs).[65-69] However, we have observed an anecdotal case of late (3 year) bilateral, retina-only relapse in a patient treated with optic-nerve sparing proton CSI, highlighting how changes in prognosis and treatments for these patients may increase the importance of comprehensive radiation coverage to at-risk structures in patients with disease that is otherwise well-controlled. The cribriform plate is often contoured as a separate target volume to ensure coverage.[70,71] Cranial foramina are generally also included in the clinical target volume as well as the spinal neural foramina, and sagittal T2 sequence on MRI spine helps to define the termination of the thecal sac. Before start of therapy, all patients should undergo a thorough neurologic examination, complete neuroaxis MRI imaging, and lumbar puncture. At the start of treatment, we generally prescribe memantine to reduce risks for neurocognitive deficits,[72] dexamethasone (typically 2 mg twice daily with adjustment as needed during CSI and taper after CSI) if not already on glucocorticoid steroids, proton pump inhibitor, and pneumocystis pneumonia prophylaxis. Systemic therapies are typically held during CSI. One should consider evaluating blood counts either in the last week or the week after CSI, and more frequently in patients with clinical need. After completion of RT, we repeat clinical examination, neuroaxis imaging, and lumbar puncture every 2 to 3 months.

Combined modality therapy

Intrathecal (IT) therapy, typically methotrexate (MTX), has been frequently studied in the treatment of LMD and has been nonrandomly combined with RT in multiple studies. A prospective randomized trial of IT MTX with or without cytosine arabinoside included the nonrandomized use of LMD-directed RT in half of the study participants.[73] This study found a significant improvement in response rate and survival when concurrent RT was used, but the decision to use RT was principally governed by prior irradiation of the cerebrospinal axis. An analysis of sequentially performed, single-arm prospective studies demonstrated no survival advantage for RT plus IT MTX, while documenting symptomatic delayed leukoencephalopathy in 20% compared with 0% treated with RT without IT MTX.[74] A prospective study of patients with LMD from breast cancer randomized treatment to IT MTX or non-IT treatment, while including nonrandomized use of LMD-direct RT in approximately half of the patients.[75] This study did not report on the relationship between use of RT and outcome but noted significantly higher rates of treatment-related neurologic complications in the IT treatment group. Another prospective trial randomized patients to IT MTX or IT thiotepa, showing similar efficacy and toxicity, but the study did not report on RT-related outcomes.[76] A recent randomized trial of IFRT given concurrently with IT MTX or IT cytarabine is listed as completed with 53 study participants, but no published results are available for review (National Clinical Trial [NCT] 03082144). Although patients who respond to treatment with RT and IT MTX survive longer than nonresponders,[73,77] treatment-related neurologic complications are a concern for patients treated with this combination.[74,75,78]

Other therapeutics have been investigated for IT administration concurrently with RT. Before manufacturing discontinuation of liposomal cytarabine, 2 retrospective studies evaluated the safety profile of concurrent CNS-directed RT.[79,80] One study enrolled patients to receive IT liposomal cytarabine with concurrent or sequential WBRT (NCT00854867), although the results of this study have not been published. A phase 1/2 trial of IT pemetrexed and concurrent IFRT analyzed the safety profile of this combination,[81] which is being investigated in an ongoing randomized trial (NCT05305885) (Table 1). A phase 1/2 trial of IFRT followed by IT trastuzumab and pertuzumab is actively recruiting (NCT04588545). Given the lack of randomized studies examining benefit, as well as the potential for neurologic toxicity, IT therapy combined with RT is not recommended outside of clinical trials.

Limited work has been completed on the combination of novel systemic therapies and RT for LMD. In a retrospective study of patients with epidermal growth factor receptor mutant NSCLC, a combination of WBRT and TKI did not extend survival compared with TKI therapy alone.[28] Other retrospective studies of osimertinib combined with RT have not demonstrated a high likelihood of survival benefit.[82,83] The safety of combined WBRT and checkpoint inhibition with avelumab has been explored in an early-stage clinical trial that recently closed accrual and reported preliminary safety results (NCT03719768).[84] For patients with PI3K pathway alterations, an ongoing trial is evaluating safety of WBRT combined with paxalisib (NCT04192981). A single case report documents treatment with combined WBRT and trastuzumab emtansine for LMD, but this combination has not been evaluated prospectively or retrospectively.[85]

Radioisotopes

IT or intraventricular administration of radioisotopes has the theoretical benefit of a large therapeutic index from highly localized dose delivery.[86] Various radioisotopes have been explored in preclinical models, including auger electron, α-particle, and β-particle emitters, which primarily differ in their energy, linear energy transfer, range in tissue, half-life, and production process.[87-89] Delivery of radioisotopes can be facilitated through molecular targeting via conjugation to a monoclonal antibody or encapsulation, such as with a nanoliposome.[86,90-92] Clinical data on the use of radioisotopes in the treatment of LMD from non-

Table 1 Studies listed as active or recruiting on ClinicalTrials.gov, which relate to the use of RT in leptomeningeal disease from solid tumors originating outside of the CNS

Trial number	Study type	Status	Actual or estimated enrollment	Experimental arm	Comparator arm	Primary outcome
NCT03719768	Phase 1	Active, not recruiting	16	IV avelumab (fixed dose) concurrently with 30/10 Gy WBRT	N/A	Dose-limiting toxicities (3 mo)
NCT04192981	Phase 1	Recruiting	36	PO paxalisib (dose escalation) concurrently with 30/10 Gy WBRT	N/A	Maximal tolerated dose
NCT04343573	Phase 2	Active, not recruiting	102	30/10 Gy proton CSI	30 Gy/10 photon IFRT	CNS progression- free survival (2 y)
NCT04588545	Phase 1/2	Recruiting	39	20/5 or 30/10 Gy IFRT followed by IT trastuzumab (fixed dose) and pertuzumab (dose escalation)	N/A	Maximum tolerated dose of pertuzumab (phase 1); overall survival (1 y, phase 2)
NCT05034497	Phase 1	Recruiting	18	Intraventricular Rhenium-186 NanoLiposome (dose escalation)	N/A	Adverse events and dose-limiting toxicities (12 mo)
NCT05305885	Phase 2	Recruiting	100	IT/intraventricular pemetrexed (fixed dose) concurrently with 40 Gy/20 IFRT	IT/intraventricular pemetrexed (fixed dose)	Clinical response rate (up to 6 mo); adverse events (up to 6 mo)

Abbreviations: CNS = central nervous system; CSI = craniospinal irradiation; IFRT = involved-field RT; IT = intrathecal; IV = intravenous; NCT = National Clinical Trial; PO = by mouth; RT = radiation therapy; WBRT = whole brain RT.
RT prescriptions written as dose/fractions.

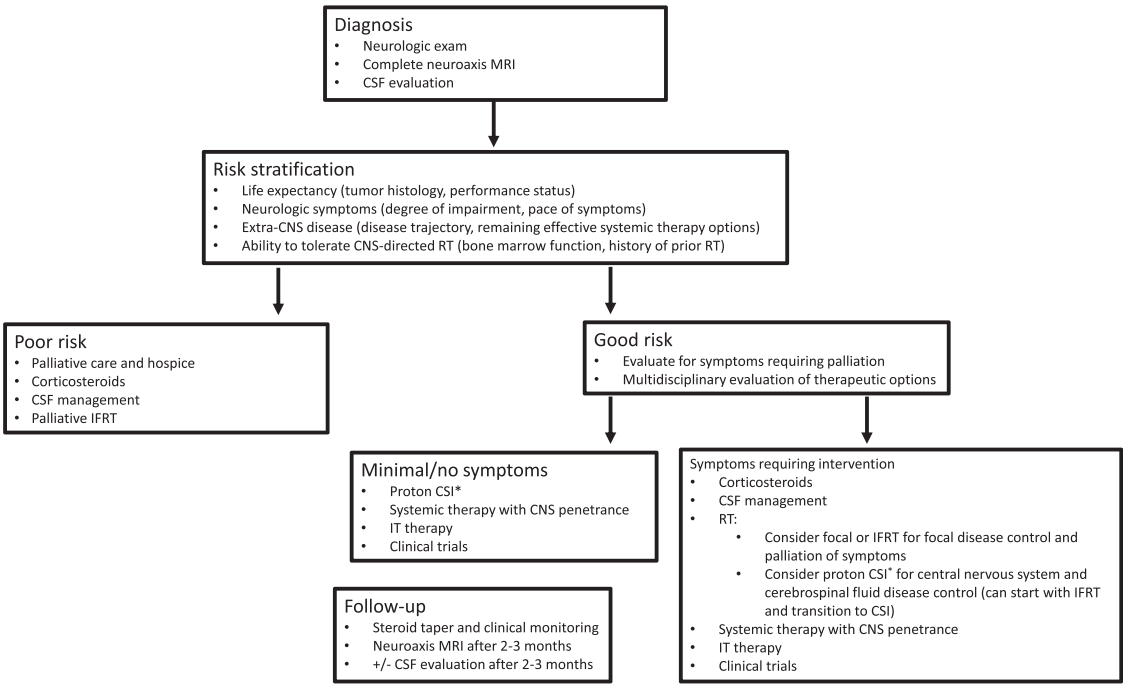

Figure 1 Algorithm for workup and management of leptomeningeal disease.
Abbreviations: CNS = central nervous system; CSF = cerebrospinal fluid; CSI = craniospinal irradiation; IFRT = involved-field RT; IMRT = intensity modulated RT; IT = intrathecal; MRI = magnetic resonance imaging; RT = radiation therapy; VMAT = volumetric-modulated arc therapy.
*Consider IMRT/VMAT vertebral-body sparing photon CSI where proton therapy is unavailable.

CNS, solid tumors are sparse and typically limited to case reports or studies of pharmacokinetics and dosimetry.[86,90,93,94] One of the largest series reporting clinical endpoints included 9 patients with lung, breast, melanoma, and ovarian primary tumors, finding a complete response in 3 patients and 1 treatment-related death.[95] Ongoing clinical trials include a study of a nanoliposome-encapsulated radioisotope that demonstrated reduction in CSF cell count in the first 2 study patients.[92] Given the paucity of research on radioisotopes, their use is limited to clinical trials, with a single active study recruiting patients (NCT05034497) (Table 1).

Conclusion

With only 1 randomized trial evaluating the role of RT for LMD, optimal management of LMD with RT remains reliant upon expert opinion. For patients with good performance status and extra-CNS disease that is absent, well-controlled, or has adequate remaining systemic therapy, CSI should be considered with the goal of comprehensive CNS and CSF disease control (Fig. 1), with a preference towardproton CSI where available, or conformal photon-based techniques/IMRT that maximizes bone marrow-sparing where proton CSI is not available. Further work on proton CSI is required to refine patient selection and to understand proper sequencing with systemic therapy. For patients with goals of symptom palliation/local CNS disease control or who are not appropriate for CSI, focal and IFRT remain essential palliative therapies. There is no strong evidence to support use of radioisotopes or combined modality treatment at this time, such as RT with IT or systemic therapy, but clinical trials are ongoing. Given the lack of prospective data on the treatment of LMD with RT, and a recent trial demonstrating a significant benefit of treatment with RT, this patient population presents a significant opportunity for future research. For standardization of radiographic response assessment in clinical trials, the use of Response Assessment in Neuro-Oncology group's revised criteria is recommended, which has been previously employed.[14,96]

Disclosures

Rupesh Kotecha reports honoraria, funding, and/or consulting fees from Accuray Inc, AstraZeneca, Blue Earth Diagnostics Ltd, Brainlab, Cantex Pharmaceuticals, Castle Biosciences, Elekta AB, Elsevier Inc, Exelixis, GT Medical Technologies, Kazia Therapeutics, Medtronic Inc, Novocure Inc, Peerview Institute for Medical Education, and ViewRay Inc. Joshua D. Palmer reports honoraria and/or funding from Genentech, ICOTEC,

Novocure, Varian Medical Systems, and NIH R702 and NIH R01 outside the submitted work.

References

1. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: Experience with 90 patients. *Cancer*. 1982;49:759-772.
2. Chamberlain MC. Leptomeningeal metastasis. *Curr Opin Oncol*. 2010;22:627-635.
3. Kaplan JG, DeSouza TG, Farkash A, et al. Leptomeningeal metastases: Comparison of clinical features and laboratory data of solid tumors, lymphomas and leukemias. *J Neurooncol*. 1990;9:225-229.
4. Beauchesne P. Intrathecal chemotherapy for treatment of leptomeningeal dissemination of metastatic tumours. *Lancet Oncol*. 2010;11:871-879.
5. Mack F, Baumert BG, Schafer N, et al. Therapy of leptomeningeal metastasis in solid tumors. *Cancer Treat Rev*. 2016;43:83-91.
6. Clarke JL, Perez HR, Jacks LM, Panageas KS, Deangelis LM. Leptomeningeal metastases in the MRI era. *Neurology*. 2010;74:1449-1454.
7. Kesari S, Batchelor TT. Leptomeningeal metastases. *Neurol Clin*. 2003;21:25-66.
8. Tincknell G, Naveed A, Nankervis J, et al. HER2-positive gastro-esophageal cancers are associated with a higher risk of brain metastasis. *Cancers (Basel)*. 2022;14:5754.
9. Mittica G, Senetta R, Richiardi L, et al. Meningeal carcinomatosis underdiagnosis and overestimation: Incidence in a large consecutive and unselected population of breast cancer patients. *BMC Cancer*. 2015;15:1021.
10. Lai R, Dang CT, Malkin MG, Abrey LE. The risk of central nervous system metastases after trastuzumab therapy in patients with breast carcinoma. *Cancer*. 2004;101:810-816.
11. Omuro AM, Kris MG, Miller VA, et al. High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib. *Cancer*. 2005;103:2344-2348.
12. Emoto S, Ishigami H, Yamaguchi H, Yamashita H, Kaisaki S, Kiutayama J. Frequent development of leptomeningeal carcinomatosis in patients with peritoneal dissemination of gastric cancer. *Gastric Cancer*. 2011;14:390-395.
13. Buszek SM, Chung C. Radiotherapy in leptomeningeal disease: A systematic review of randomized and non-randomized trials. *Front Oncol*. 2019;9:1224.
14. Yang JT, Wijetunga NA, Pentsova E, et al. Randomized phase II trial of proton craniospinal irradiation versus photon involved-field radiotherapy for patients with solid tumor leptomeningeal metastasis. *J Clin Oncol*. 2022;40:3858-3867.
15. NCCN: National Comprehensive Cancer Network. Central Nervous System Cancers. 2023. version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed August 21, 2023.
16. Le Rhun E, Preusser M, van den Bent M, Andratschke N, Weller M. How we treat patients with leptomeningeal metastases. *ESMO Open*. 2019;4: e000507.
17. Le Rhun E, Weller M, Brandsma D, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. *Ann Oncol*. 2017;28:iv84-iv99.
18. El Shafie RA, Bohm K, Weber D, et al. Outcome and prognostic factors following palliative craniospinal irradiation for leptomeningeal carcinomatosis. *Cancer Manag Res*. 2019;11:789-801.
19. Nguyen TK, Nguyen EK, Soliman H. An overview of leptomeningeal disease. *Ann Palliat Med*. 2021;10:909-922.
20. Pawlowska E, Romanowska A, Jassem J. Radiotherapy for leptomeningeal carcinomatosis in breast cancer patients: A narrative review. *Cancers (Basel)*. 2022;14:3899.
21. Zhen J, Wen L, Lai M, et al. Whole brain radiotherapy (WBRT) for leptomeningeal metastasis from NSCLC in the era of targeted therapy: A retrospective study. *Radiat Oncol*. 2020;15:185.
22. Prabhu RS, Turner BE, Asher AL, et al. A multi-institutional analysis of presentation and outcomes for leptomeningeal disease recurrence after surgical resection and radiosurgery for brain metastases. *Neuro Oncol*. 2019;21:1049-1059.
23. Nguyen TK, Sahgal A, Detsky J, et al. Predictors of leptomeningeal disease following hypofractionated stereotactic radiotherapy for intact and resected brain metastases. *Neuro Oncol*. 2020;22:84-93.
24. Le Rhun E, Devos P, Weller J, et al. Prognostic validation and clinical implications of the EANO ESMO classification of leptomeningeal metastasis from solid tumors. *Neuro Oncol*. 2021;23:1100-1112.
25. Le Rhun E, Ruda R, Devos P, et al. Diagnosis and treatment patterns for patients with leptomeningeal metastasis from solid tumors across Europe. *J Neurooncol*. 2017;133:419-427.
26. Okada Y, Abe T, Shinozaki M, et al. Evaluation of imaging findings and prognostic factors after whole-brain radiotherapy for carcinomatous meningitis from breast cancer: A retrospective analysis. *Medicine (Baltimore)*. 2020;99:e21333.
27. Morris PG, Reiner AS, Szenberg OR, et al. Leptomeningeal metastasis from non-small cell lung cancer: Survival and the impact of whole brain radiotherapy. *J Thorac Oncol*. 2012;7:382-385.
28. Li Y-S, Jiang B-Y, Yang J-J, et al. Leptomeningeal metastases in patients with NSCLC with EGFR mutations. *J Thorac Oncol*. 2016;11:1962-1969.
29. Yan W, Liu Y, Li J, et al. Whole brain radiation therapy does not improve the overall survival of EGFR-mutant NSCLC patients with leptomeningeal metastasis. *Radiat Oncol*. 2019;14:168.
30. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): Results from a phase 3, non-inferiority, randomised trial. *Lancet*. 2016;388:2004-2014.
31. El Shafie RA, Bohm K, Weber D, et al. Palliative radiotherapy for leptomeningeal carcinomatosis - analysis of outcome, prognostic factors, and symptom response. *Front Oncol*. 2019;8:641.
32. Niwinska A, Rudnicka H, Murawska M. Breast cancer leptomeningeal metastasis: The results of combined treatment and the comparison of methotrexate and liposomal cytarabine as intra-cerebrospinal fluid chemotherapy. *Clin Breast Cancer*. 2015;15:66-72.
33. Ozdemir Y, Yildirim BA, Topkan E. Whole brain radiotherapy in management of non-small-cell lung carcinoma associated leptomeningeal carcinomatosis: Evaluation of prognostic factors. *J Neurooncol*. 2016;129:329-335.
34. Gani C, Muller AC, Eckert F, et al. Outcome after whole brain radiotherapy alone in intracranial leptomeningeal carcinomatosis from solid tumors. *Strahlenther Onkol*. 2012;188:148-153.
35. Hirano Y, Konishi K, Ejima Y. Utility of whole brain radiation therapy for leptomeningeal carcinomatosis. *Int J Clin Oncol*. 2020;25:1432-1439.
36. Trifiletti DM, Ballman KV, Brown PD, et al. Optimizing whole brain radiation therapy dose and fractionation: Results from a prospective phase 3 trial (NCCTG N107C [Alliance]/CEC.3). *Int J Radiat Oncol Biol Phys*. 2020;106:255-260.
37. Chamberlain MC. Radioisotope CSF flow studies in leptomeningeal metastases. *J Neurooncol*. 1998;38:135-140.
38. Chamberlain MC, Kormanik PA. Prognostic significance of 111indium-DTPA CSF flow studies in leptomeningeal metastases. *Neurology*. 1996;46:1674-1677.
39. Grossman SA, Trump DL, Chen DC, Thompson G, Camargo EE. Cerebrospinal fluid flow abnormalities in patients with neoplastic meningitis. An evaluation using 111indium-DTPA ventriculography. *Am J Med*. 1982;73:641-647.

40. Glantz MJ, Hall WA, Cole BF, et al. Diagnosis, management, and survival of patients with leptomeningeal cancer based on cerebrospinal fluid-flow status. *Cancer*. 1995;75:2919-2931.
41. Chamberlain MC, Kormanik P. Carcinoma meningitis secondary to non-small cell lung cancer: Combined modality therapy. *Arch Neurol*. 1998;55:506-512.
42. Wolf A, Donahue B, Silverman JS, Chachoua A, Lee JK, Kondziolka D. Stereotactic radiosurgery for focal leptomeningeal disease in patients with brain metastases. *J Neurooncol*. 2017;134:139-143.
43. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): Long-term results from a prospective, multicentre trial. *Lancet Oncol*. 2006;7:813-820.
44. Calaminus G, Kortmann R, Worch J, et al. SIOP CNS GCT 96: Final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. *Neuro Oncol*. 2013;15:788-796.
45. Pinnix CC, Yahalom J, Specht L, Dabaja BS. Radiation in central nervous system leukemia: Guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2018;102:53-58.
46. Devecka M, Duma MN, Wilkens JJ, et al. Craniospinal irradiation (CSI) in patients with leptomeningeal metastases: Risk-benefit-profile and development of a prognostic score for decision making in the palliative setting. *BMC Cancer*. 2020;20:501.
47. Harada H, Mitsuya K, Asakura H, et al. Cranio-spinal irradiation for leptomeningeal carcinomatosis: A pilot study. *Int J Radiat Oncol Biol Phys*. 2014;90. S310-S310.
48. Lee J, Kim E, Kim N, Suh C-O, Chung Y, Yoon HI. Pulmonary toxicity of craniospinal irradiation using helical tomotherapy. *Sci Rep*. 2022;12:3221.
49. Schiopu SR, Habl G, Hafner M, et al. Craniospinal irradiation using helical tomotherapy for central nervous system tumors. *J Radiat Res*. 2017;58:238-246.
50. Kwok JK, Yaraskavitch M, Henning JW, Graham D, Logie N. Craniospinal irradiation for leptomeningeal disease in recurrent breast cancer. *Appl Radiat Oncol*. 2021;10:42-47.
51. Seravalli E, Bosman M, Lassen-Ramshad Y, et al. Dosimetric comparison of five different techniques for craniospinal irradiation across 15 European centers: Analysis on behalf of the SIOP-E-BTG (radiotherapy working group). *Acta Oncol*. 2018;57:1240-1249.
52. Matsui J, Perlow H, Ewing A, et al. RADT-05. Volumetric modulated arc therapy craniospinal irradiation utilizing a vertebral body sparing approach: A dosimetric analysis. *Neuro Oncol*. 2022;24: vii49.
53. Brown AP, Barney CL, Grosshans DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2013;86:277-284.
54. Yang JT, Wijetunga NA, Yamada J, et al. Clinical trial of proton craniospinal irradiation for leptomeningeal metastases. *Neuro Oncol*. 2021;23:134-143.
55. Nayak L, Fleisher M, Gonzalez-Espinoza R, et al. Rare cell capture technology for the diagnosis of leptomeningeal metastasis in solid tumors. *Neurology*. 2013;80:1598-1605.
56. Lee JS, Melisko ME, Magbanua MJ, et al. Detection of cerebrospinal fluid tumor cells and its clinical relevance in leptomeningeal metastasis of breast cancer. *Breast Cancer Res Treat*. 2015;154:339-349.
57. Lin X, Fleisher M, Rosenblum M, et al. Cerebrospinal fluid circulating tumor cells: A novel tool to diagnose leptomeningeal metastases from epithelial tumors. *Neuro Oncol*. 2017;19:1248-1254.
58. van Bussel MTJ, Pluim D, Milojkovic Kerklaan B, et al. Circulating epithelial tumor cell analysis in CSF in patients with leptomeningeal metastases. *Neurology*. 2020;94:e521-e528.
59. Diaz M, Singh P, Kotchetkov IS, et al. Quantitative assessment of circulating tumor cells in cerebrospinal fluid as a clinical tool to predict survival in leptomeningeal metastases. *J Neurooncol*. 2022;157: 81-90.
60. Wijetunga NA, Boire A, Young RJ, et al. Quantitative cerebrospinal fluid circulating tumor cells are a potential biomarker of response for proton craniospinal irradiation for leptomeningeal metastasis. *Neurooncol Adv*. 2021;3:vdab181.
61. Figura NB, Rizk VT, Armaghani AJ, et al. Breast leptomeningeal disease: A review of current practices and updates on management. *Breast Cancer Res Treat*. 2019;177:277-294.
62. Pentsova EI, Shah RH, Tang J, et al. Evaluating cancer of the central nervous system through next-generation sequencing of cerebrospinal fluid. *J Clin Oncol*. 2016;34:2404-2415.
63. Freret ME, Wijetunga NA, Shamseddine AA, et al. Early detection of leptomeningeal metastases among patients undergoing spinal stereotactic radiosurgery. *Adv Radiat Oncol*. 2022;8: 101154.
64. Ajithkumar T, Horan G, Padovani L, et al. SIOPE - Brain tumor group consensus guideline on craniospinal target volume delineation for high-precision radiotherapy. *Radiother Oncol*. 2018;128: 192-197.
65. Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR. Radiation retinopathy after external-beam irradiation: Analysis of time-dose factors. *Int J Radiat Oncol Biol Phys*. 1994;30:765-773.
66. Durkin SR, Roos D, Higgs B, Casson RJ, Selva D. Ophthalmic and adnexal complications of radiotherapy. *Acta Ophthalmol Scand*. 2007;85:240-250.
67. Gupta A, Dhawahir-Scala F, Smith A, Young L, Charles S. Radiation retinopathy: Case report and review. *BMC Ophthalmol*. 2007;7:6.
68. Davis ME. Ocular toxicity of tyrosine kinase inhibitors. *Oncol Nurs Forum*. 2016;43:235-243.
69. Chan L, Sneed PK, Horton JC. Damage to the superior retinae after 30 Gy whole-brain radiation. *Adv Radiat Oncol*. 2021;6: 100706.
70. Schiff JP, Lee Y, Wang Y, et al. An analysis of major target deviations in craniospinal irradiation treatment plans for patients with intermediate-risk medulloblastoma within a phase 3 clinical trial (Children's Oncology Group Study ACNS0331). *Adv Radiat Oncol*. 2022;8: 101083.
71. Donahue B, Marymont MA, Kessel S, et al. Radiation therapy quality in CCG/POG intergroup 9961: Implications for craniospinal irradiation and the posterior fossa boost in future medulloblastoma trials. *Front Oncol*. 2012;2:185.
72. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: A randomized, double-blind, placebo-controlled trial. *Neuro Oncol*. 2013;15:1429-1437.
73. Hitchins RN, Bell DR, Woods RL, Levi JA. A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. *J Clin Oncol*. 1987;5:1655-1662.
74. Bokstein F, Lossos A, Siegal T. Leptomeningeal metastases from solid tumors: A comparison of two prospective series treated with and without intra-cerebrospinal fluid chemotherapy. *Cancer*. 1998;82:1756-1763.
75. Boogerd W, van den Bent MJ, Koehler PJ, et al. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: A randomised study. *Eur J Cancer*. 2004;40:2726-2733.
76. Grossman SA, Finkelstein DM, Ruckdeschel JC, Trump DL, Moynihan T, Ettinger DS. Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. *J Clin Oncol*. 1993;11:561-569.
77. Sause WT, Crowley J, Eyre HJ, et al. Whole brain irradiation and intrathecal methotrexate in the treatment of solid tumor leptomeningeal metastases—A Southwest Oncology Group study. *J Neurooncol*. 1988;6:107-112.

78. Pan Z, Yang G, He H, et al. Concurrent radiotherapy and intrathecal methotrexate for treating leptomeningeal metastasis from solid tumors with adverse prognostic factors: A prospective and single-arm study. *Int J Cancer*. 2016;139:1864-1872.
79. Chamberlain MC. Neurotoxicity of intra-CSF liposomal cytarabine (DepoCyt) administered for the treatment of leptomeningeal metastases: A retrospective case series. *J Neurooncol*. 2012;109:143-148.
80. Iglseder S, Nowosielski M, Bsteh G, et al. Whole brain radiotherapy combined with intrathecal liposomal cytarabine for leptomeningeal metastasis-a safety analysis and validation of the EANO-ESMO classification. *Strahlenther Onkol*. 2022;198:475-483.
81. Pan Z, Yang G, He H, et al. Intrathecal pemetrexed combined with involved-field radiotherapy as a first-line intra-CSF therapy for leptomeningeal metastases from solid tumors: A phase I/II study. *Ther Adv Med Oncol*. 2020;12: 1758835920937953.
82. Chiang CL, Ho HL, Yeh YC, et al. Prognosticators of osimertinib treatment outcomes in patients with EGFR-mutant non-small cell lung cancer and leptomeningeal metastasis. *J Cancer Res Clin Oncol*. 2023;149:5-14.
83. Piper-Vallillo AJ, Rotow JK, Aredo JV, et al. High-dose osimertinib for CNS progression in EGFR+ NSCLC: A multi-institutional experience. *JTO* Clin Res Rep. 2022;3: 100328.
84. Pina Y, Chen A, Arrington J, et al. Phase 1B study of avelumab and whole brain radiotherapy (WBRT) in patients with leptomeningeal disease (LMD): Preliminary results. *Neuro Oncol*. 2022;24:vii59.
85. Ricciardi GRR, Russo A, Franchina T, et al. Efficacy of T-DM1 for leptomeningeal and brain metastases in a HER2 positive metastatic breast cancer patient: New directions for systemic therapy - a case report and literature review. *BMC Cancer*. 2018;18:97.
86. Kramer K, Cheung NK, Humm JL, et al. Targeted radioimmunotherapy for leptomeningeal cancer using (131)I-3F8. *Med Pediatr Oncol*. 2000;35:716-718.
87. Mehta M, Bradley K. Radiation therapy for leptomeningeal cancer. *Cancer Treat Res*. 2005;125:147-158.
88. Zalutsky MR, Bigner DD. Radioimmunotherapy with alpha-particle emitting radioimmunoconjugates. *Acta Oncol*. 1996;35:373-379.
89. Aghevlian S, Boyle AJ, Reilly RM. Radioimmunotherapy of cancer with high linear energy transfer (LET) radiation delivered by radionuclides emitting alpha-particles or Auger electrons. *Adv Drug Deliv Rev*. 2017;109:102-118.
90. Pandit-Taskar N, Zanzonico PB, Kramer K, et al. Biodistribution and dosimetry of intraventricularly administered (124)I-omburtamab in patients with metastatic leptomeningeal tumors. *J Nucl Med*. 2019;60:1794-1801.
91. Häfeli UO, Sweeney SM, Beresford BA, Sim EH, Macklis RM. Magnetically directed poly(lactic acid) 90Y-microspheres: Novel agents for targeted intracavitary radiotherapy. *J Biomed Mater Res*. 1994;28:901-908.
92. Brenner A, Youssef M, LaFrance N, et al. CTNI-02. Preclinical data and initial clinical experience in the phase1/2A dose escalation trial of rhenium-186 nanoliposome (186RNL) in leptomeningeal metastases [LM]: The ReSPECT-LM trial. *Neuro Oncol*. 2022:24.
93. Yerrabelli RS, He P, Fung EK, et al. IntraOmmaya compartmental radioimmunotherapy using (131)I-omburtamab-pharmacokinetic modeling to optimize therapeutic index. *Eur J Nucl Med Mol Imaging*. 2021;48:1166-1177.
94. Cokgor I, Akabani G, Friedman HS, et al. Long term response in a patient with neoplastic meningitis secondary to melanoma treated with (131)I-radiolabeled antichondroitin proteoglycan sulfate Mel-14 F(ab')(2): A case study. *Cancer*. 2001;91:1809-1813.
95. Coakham HB, Kemshead JT. Treatment of neoplastic meningitis by targeted radiation using (131)I-radiolabelled monoclonal antibodies. Results of responses and long term follow-up in 40 patients. *J Neurooncol*. 1998;38:225-232.
96. Le Rhun E, Devos P, Boulanger T, et al. The RANO Leptomeningeal Metastasis Group proposal to assess response to treatment: Lack of feasibility and clinical utility and a revised proposal. *Neuro Oncol*. 2019;21:648-658.