



Review Article



Research on Brain Metastasis in India: An Overview

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Citation: Surendran HP, et al. Research on Brain Metastasis in India: An Overview. J Neuro Onco Res. 2026;6(1):1-10.

<https://doi.org/10.46889/JNOR.2026.6108>

Received Date: 03-02-2026

Accepted Date: 04-03-2026

Published Date: 11-03-2026



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Abstract

Brain metastases are the most prevalent intracranial neoplasms, affecting 15-40% of systemic cancer patients. Despite advancements in detection and treatment, there is a dearth of epidemiological data on brain metastases from developing countries, particularly India, where disparities in healthcare and fragmented cancer registries complicate accurate incidence assessments. This study consolidates research on brain metastases in India, identifying trends and gaps in the literature. A systematic review identified 254 studies, yielding 26 pertinent articles, predominantly retrospective in nature. Notably, only one study provided Level 1 evidence, highlighting the efficacy of memantine in preserving neurocognitive function in brain metastases patients undergoing radiation therapy. Other significant findings included the feasibility of stereotactic radiosurgery as a treatment option and the effectiveness of hippocampal avoidance whole brain radiation therapy in preserving cognitive function and improving quality of life. The research underscores an increasing trend in stereotactic radiosurgery usage in India; however, challenges remain due to limited access to advanced treatment facilities, particularly in rural areas. The current literature reflects advancements but emphasizes the need for large-scale epidemiological studies and improved cancer registries. Addressing these gaps through collaborative efforts and increased funding is essential for enhancing patient outcomes and advancing treatment protocols in the Indian context. This overview serves as a call to action for further research and the establishment of standardized practices in managing brain metastases in India.

Keywords: Brain Metastases; Stereotactic Radiosurgery; Whole Brain Radiation Therapy; Neurocognitive Function; Memantine; Epidemiology; Indian-Origin-Research

Introduction

Brain Metastases (BM) are the most common intracranial neoplasms, occurring in 15-40% of patients with systemic cancers [1]. Over the past two decades, the incidence of BM has been on the rise, driven by increasing prevalence of primary malignancies such as lung and breast cancer, advancements in therapeutic modalities that prolong survival and early detection enabled by advanced imaging techniques [2]. These factors have contributed to a growing body of research on BM worldwide, aimed at improving treatment and patient outcomes. Despite increasing global awareness and research on BM, there remains a significant gap in data from developing countries, including India. India, with its large and diverse population, presents a unique set of challenges in cancer care. Disparities in healthcare access, regional variations in the quality of cancer care, poorly maintained and fragmented cancer registries together make it difficult to accurately assess the true incidence of BM in India. Nevertheless, the burden of BM is substantial, given the high incidence of lung, breast and colon cancers in India known to metastasize to the brain [3]. While there is a scarcity of large-scale epidemiological studies on BM in India, several primary and secondary research efforts have been undertaken at the state and institutional levels. This short communication aims to consolidate and present a

comprehensive overview of the available research data on BM conducted in India, followed by a critical analysis of the data and identifying gaps that warrant further investigation.

Research Methodology

A total of 254 studies were identified in PubMed using search terms: brain metastases, Indian patients, radiation, Stereotactic Radiosurgery (SRS), Whole Brain Radiotherapy (WBRT) and Hippocampal Avoidance WBRT (HA-WBRT). All the published articles from Indian origin were included and based on the level on evidence were segregated for analysis. In the Prisma flow chart, the number of articles included after duplication correction, then segregating based on level of evidences and quality of research work was done. Level of evidence and quality of work was considered by the research methodology, citations respectively. An additional 17 studies were identified through other resources such as hand-searching (Fig. 1).

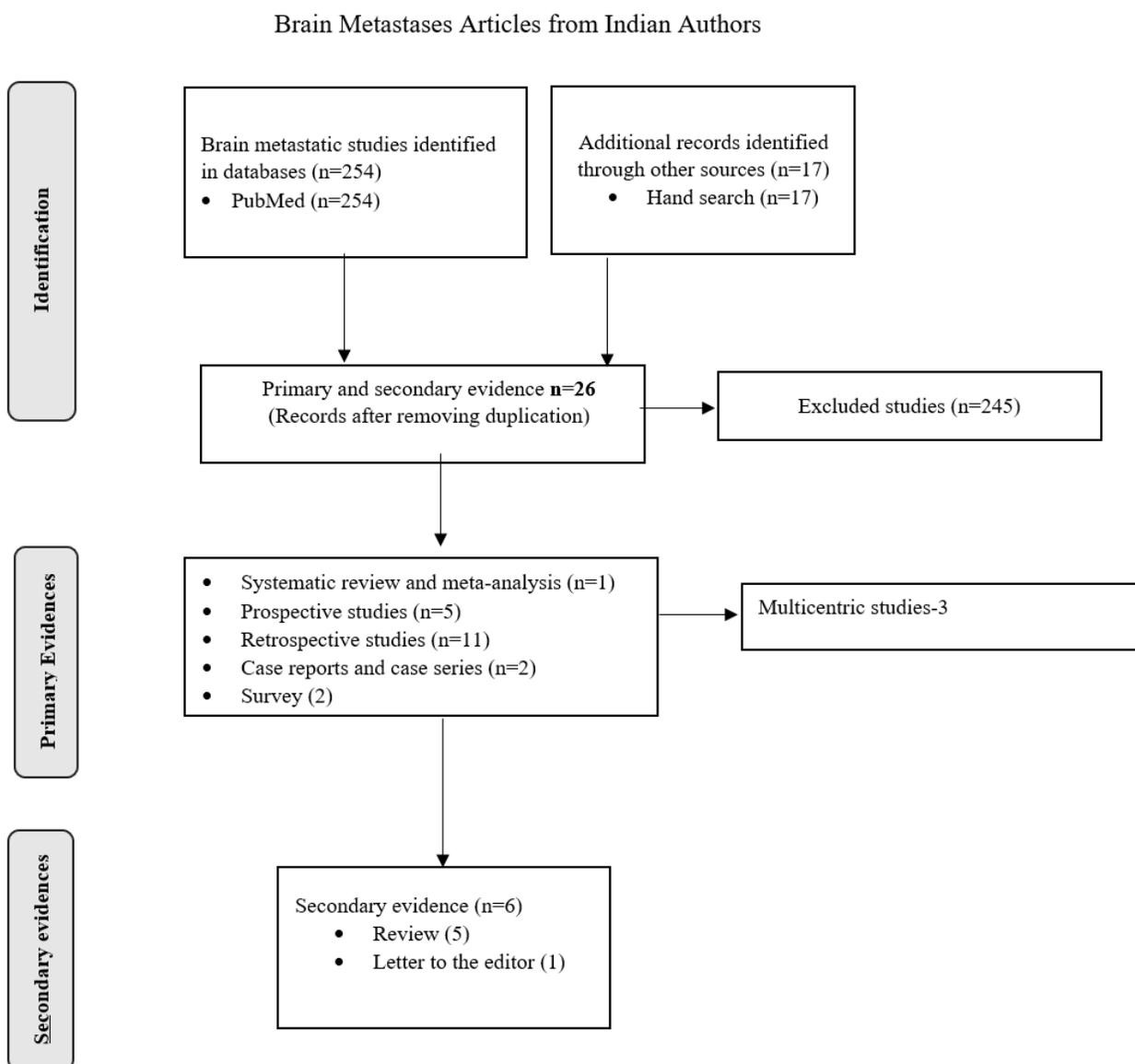


Figure 1: Prisma flow chart.

Research Trends in BM in Indian Patients From 1995 to 2024

We included 26 primary and secondary studies after removing duplicates and inappropriate articles. Among the primary studies, only one satisfied level 1 evidence (systematic review and meta-analysis). Five were prospective studies, while the majority were retrospective in nature [11]. Two were case series or case reports and two were surveys. Of the six secondary evidence, five were literature reviews and one was a letter to the editor. The published articles were described in details as per the level of evidence.

Level 1 Evidence

Dutta D, et al., conducted a systematic review (following PRISMA guidelines) of clinical trials to assess the efficacy of memantine in preventing cognitive dysfunction in BM subjected to radiation therapy [4]. The above meta-analysis included four studies published up to November 2021, enrolling 1,444 patients (729 in the intervention group and 715 in the control group). Three of four studies significantly (p 0.39 to <0.0001) improved neurocognitive functions such as recall, recognition and verbal fluency. Two studies also improved patients' quality of life, without any significant difference in toxicity between the memantine and control groups. Authors concluded that memantine has a modest but statistically significant positive effect on preserving neurocognitive function and improving quality of life in patients undergoing radiation for BM. This systematic review is one among the few Level 1 evidence sources addressing radiation-induced cognitive decline in BM patients in India [4].

Level 2 Evidences

Dutta D, et al., conducted a prospective analysis of 138 patients with BM (251 brain lesions, median age: 59 years), primarily from lung (44%) and breast (30%) cancers (Table 1). The study evaluated outcomes after SRS for BM, without WBRT. With a median follow-up of 15 months, the results showed that SRS was feasible in India, producing survival outcomes and recurrence patterns comparable to the West. The mean actuarial overall survival was 23.7 months, with in-field recurrences in 11% of patients and out-of-field recurrences in 42%. Omission of WBRT was deemed safe in oligo-metastases and the study supported the application of Western prognostic models to Indian patients. Authors concluded that SRS alone is a viable treatment option for BM in India when patient selection and treatment protocols are properly standardized [5].

Goyal D, et al., explored the feasibility and benefits of Hippocampal Avoidance Whole Brain Radiation Therapy (HA-WBRT) in preserving neurocognitive function and quality of life in BM. The study involved 27 patients treated with LINAC-based IMRT using the VMAT technique (30 Gy in 10 fractions). Results indicated a significant reduction in cognitive decline over 12 months, along with improvements in social well-being, despite a decline in emotional well-being over 12 months. Overall, quality of life improved after nine months. The authors concluded that HA-WBRT is feasible and effective in preserving neurocognitive function without compromising therapy [6].

A 2021 prospective observational study examined the incidence of BM at diagnosis in 496 Non-Small Cell Lung Cancer (NSCLC) patients (median age: 57 years, predominantly male, 75% smokers). The study found that BM was present in 21% of patients, with 51% being asymptomatic. Factors associated with a higher incidence of BM included younger age (≤ 40 years), adenocarcinoma histology, poor performance status and an elevated Neutrophil-Lymphocyte Ratio (NLR). Brain imaging resulted in upstaging in 7% of cases. The study concluded that baseline brain imaging and the consideration of NLR are crucial in predicting BM and overall survival in NSCLC patients [7].

Agarwal, et al., assessed the quality of life in NSCLC patients with BM using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires. In a prospective cohort study ($n=140$) between 2012 and 2015, baseline quality of life was evaluated using the EORTC QLQ-C30 and lung cancer-specific LC13 modules. The study found significant differences in functional and symptom scores when compared to EORTC reference data and other studies, with notable variations in role and cognitive functioning, financial difficulties and peripheral neuropathy. The findings highlighted the need for region-specific baseline QoL scores for NSCLC patients in India, with implications for future studies employing QoL assessments in this patient population [8].

Author/year	Title	Journal	Pt No	Study site	Inclusion	Remarks
Dutta, et al.,	Efficacy of memantine in preventing neurocognitive dysfunction induced by radiation therapy in patients with brain metastases: A systematic review of clinical trials	Sem in Oncol	1444	AIMS, Kerala	All primary	<ul style="list-style-type: none"> • Memantine therapy provides modest but significant benefits for patients with BM. <ul style="list-style-type: none"> • It helps prevent radiation-induced neurocognitive dysfunction. • Improves quality of life and preserves some cognitive function. • No reported complications with its use. • Memantine is a reasonable treatment option during whole brain radiation therapy, pending further studies.
Dutta, et al.,	Prospective Evaluation of Response to Treatment, Survival Functions, Recurrence Pattern and Toxicity Profile in Indian Patients with Oligo-Brain Metastasis Treated with Only SRS	Neurol India	138	AIMS, Kerala	All primary	<ul style="list-style-type: none"> • SRS alone for BM is feasible in India, with outcomes similar to those of Western studies. <ul style="list-style-type: none"> • Survival, recurrence, and toxicity are comparable to Western data. • Standardization of patient selection, dose schedule, and planning is needed. • WBRT can be omitted in Indian patients with oligo-brain metastasis. • Western prognostication nomograms apply to Indian patients.
Goyal D, et al.,	Hippocampal avoidance whole brain radiotherapy in brain metastasis using volumetric modulated arc therapy: experience from a Regional Cancer Centre of Eastern India	Rep Pract Oncol Radiother	27	CNCI, Kolkata	Lung /Breast Ca	<ul style="list-style-type: none"> • HA-WBRT is feasible with LINAC-based IMRT using the VMAT technique. • Helps preserve neurocognitive function and quality of life. <ul style="list-style-type: none"> • Does not compromise disease control.
Naresh G, et al.,	Assessment of Brain Metastasis at Diagnosis in Non-Small-Cell	JCO Global Oncol	496	AIIMS, Delhi	NSCLC	<ul style="list-style-type: none"> • Prevalence of EGFR mutations: 33.4%; ALK fusions: 12%. <ul style="list-style-type: none"> • Brain imaging upstaged 7% of cases. • BM found in 21% of patients; 51% were asymptomatic.

	Lung Cancer: A Prospective Observational Study from North India					<ul style="list-style-type: none"> • Higher BM linked to young age (≤ 40), adenocarcinoma, poor ECOG status, and high NLR (> 2.5). • Median overall survival: 7.46 months with BM vs. 12.76 months without. • High NLR and molecular-graded prognostic assessment significantly impacted survival.
Agarwal J,	Reference Data for Standardized Quality of Life Questionnaires in Indian Patients with Brain Metastases from Non-small Cell Lung Cancer: Results from a Prospective Study	Cureus	140	TMH, Mumbai	NSCLC	<ul style="list-style-type: none"> • Functional and symptom scores in NSCLC patients differed significantly from EORTC reference data. • Study highlights the need for baseline reference scores specific to Indian patients. • Findings impact future QOL assessments in the Indian NSCLC population.
Niu X, et al.,	Brain Metastases in Women with Epithelial Ovarian Cancer: Multimodal Treatment Including Surgery or Gamma-Knife Radiation Is Associated with Prolonged Survival	J Obstet Gyn can	12	AIMS, Kerala / TMH, Mumbai	Ovary	<ul style="list-style-type: none"> • Twelve patients (mean age 56) from China, Canada, and India were included. • Median time from ovarian cancer diagnosis to BM: 19 months. • Overall median survival from ovarian cancer diagnosis: 38 months. • Median survival from BM diagnosis: 17 months. • Patients with multimodal treatment (including gamma-knife or surgery) had a median survival of 25.6 months, versus 6.0 months without these treatments ($P = 0.006$). • Multidisciplinary therapy, especially localized treatments, improves survival in ovarian cancer BM.

Table 1: Summary of Level 1 and 2 Evidence from India on brain metastases.

Level 3 Evidences

We identified 13 retrospective studies on BM from India, including one by Dhanawat A, et al., which reported no significant correlation between BM and cognitive impairment in older patients ($p = 0.086$) (Fig. 1) [9-19]. Further research is required to explore the impact of treatments on cognitive decline [9]. Most of the above studies, including those by Gosh S, et al., are clinical audits addressing the profile and incidence of BM. Gosh S, et al., found that 64.6% of BM patients were female, with lung cancer being the primary source in 50.8%. Survival improved for patients with solitary brain lesions and those undergoing surgical excision. However, many patients opted for WBRT because of the high cost of SRS. The majority had a poor prognosis, emphasizing the need for individualized treatment plans [10].

Another audit by Dutta D, et al., examined 778 Indian patients treated with radiation therapy for BM over 15 years. The study found an increase in BM incidence from 0.64% in 2007 to 1.24% in 2022. Lung and breast cancers were the most common primary sources of BM. Treatment modalities have changed with SRS usage increasing to 40% by 2022. The audit revealed a preference

for SRS in patients with oligo-brain metastases with better outcomes, reflecting changing treatment patterns and geographic variations in BM in India [19].

Patil V, et al., conducted a study on Leptomeningeal Metastasis (LMM) in NSCLC, highlighting the poor prognosis of this underdiagnosed condition in low- and middle-income countries. Of 1148 NSCLC patients, 36 (0.031%) developed LMM, with brain metastasis being the only significant risk factor ($p = 0.035$). The median Overall Survival (OS) after LMM diagnosis was 61 days. Patients treated with Osimertinib had a longer OS (245 days) compared to those without the drug (52 days). The study suggests that LMM incidence is low in India, but prognosis remains poor, especially where access to advanced therapies is limited [14].

Bhatt VR, et al., also explored the relationship between Epidermal Growth Factor Receptor (EGFR) mutations and BM in NSCLC, finding a nearly two-fold higher incidence of EGFR mutations in BM at diagnosis but did not predict outcomes [13]. Summary of level 3 evidences are presented in Table 2.

Author	Title	Journal	Pt No	Study site	Primary Inclusion
Noronha, et al.,	KRAS in NCSLC with BM	ecancermedicalscience	133	TMH, Mumbai	NSCLC
Dutta, et al.,	Institutional audit of 788 BM	Neurol India	788	AIMS, Kerala	All primary
Dsouza H, et al.,	MCQ on Brain metasatsis	Ind J Cancer	-	Maharashtra	Lung /Breast Ca
Sammaddar D, et al.,	BM patient profile in Eastern India	Ind J Cancer	112	CNCI, Kolkata	NSCLC
Dhanawat A, et al.,	Cognitive function assessment in BM	ecancermedicalscience	597	TMH, Mumbai	All primary
Gupta S, et al.,	Review article on BM	J Egypt Natl Canc Inst	116	AIIMS, Rishikesh	All patients
Patil V, et al.,	Leptomeningeal metastasis in NSCLC	ecancermedicalscience	36	TMH, Mumbai	NSCLC
Bhatt VR, et al.,	EGFR in NSCLC with BM	Front Oncol	1522	TMH, Mumbai	NSCLC
Ghosh Laskar S, et al.,	Ca Nasopharynx with BM: Case series	JCRT	17	TMH, Mumbai	Nasopharynx
Ghosh S, et al.,	Audit of BM in South Indian pt	Asian Pac J Cancer Prev	130	Andhrapradesh	All patients
Gupta R, et al.,	Gall bladder Ca with BM: Case report	J Clin Diag Res	1	UP	Gallbladder
Amarnath S, et al.,	Review article on BM	J Thoracic Oncol	175	Delhi	NSCLC
Raina V, et al.,	Germ cell cancer with BM: Case report	Cancer	3	Delhi	Testicular tumour

Table 2: Summary of Level 3 Evidence from India on brain metastases.

Level 4 and 5 Evidence

E Razis, et al., conducted a global survey through the Breast International Group (BIG) Brain Metastasis Task Force to assess the management of Carcinomatous Meningitis (CM) resulting from breast cancer. The study involved a questionnaire distributed to 241 sites across Europe, North America, Central/South America, Asia and Australia/New Zealand. The findings revealed that most centers encounter fewer than five CM cases annually, with a significant proportion investigating only symptomatic patients. Diagnostic practices showed variability, with 71.8% relying on positive cerebrospinal fluid cytology for confirmation. Treatment approaches were also heterogeneous, with 97.1% of centers administering therapies, primarily intrathecal methotrexate. Notably,

only 20 centers reported having a national registry for CM patients, yet showed high interest in participating in future studies. This survey underscores the need for standardized guidelines in CM management and highlights a collective desire for further research to enhance patient care globally [20]. In parallel, Patwe PT, et al., conducted a nationwide survey assessing SRS practices and Quality Assurance (QA) in India. The study revealed extensive use of SRS in BM (99.3%) and highlighted the dominance of 6MV FFF photon energy and VMAT techniques. While pretreatment dose verification was common, there were inconsistencies in QA metrics, indicating a lack of standardization across centers. Patwe, et al., is the first to systematically evaluate SRS practices in India, emphasizing the need for postal dose audits for small static photon fields to improve treatment accuracy [21].

Furthermore, several review articles and level 5 evidence originating from India address various aspects of neurocognitive preservation in BM management, SRS for oligometastases and radiotherapy for BM from lung cancer. These contributions provide valuable insights into the management of BM and underscore the importance of ongoing research in this area, helping to inform clinical practices and improve patient outcomes [22-24].

Discussion

Role of SRS in brain metastasis was established with level I evidence in 2017. Brown, et al., published randomized studies with WBRT+SRS versus SRS alone [25]. There was difference in overall survival between these groups, however cognitive function preservation was better with SRS. Mahajan, et al., published randomized study surgery for brain metastasis with and without SRS. Post-operative cavity SRS also shown to improve local control. Post-operative WBRT did not have any additional benefits compared with cavity SRS [26]. In 1-4 BM with good performance status, SRS is the standard of care. Even in 4-10 BM, SRS is considered if there is targetable mutations (lung, breast, melanoma) and patient have good performance status. WBRT is 'oligo-brain metastasis' with good performance status (where patient is expected to be alive at 12 months follow up) reduces cognitive functions (in 82%), memory and hence impairs QOL. BM patients with limited survival, QOL is utmost important functions needs preservation. Treatment of BM is now mostly based on primary site, molecular markers, targetable mutations, volume of disease, performance status of patient and availability of facilities. Radiosurgery is considered the standard of care for BM patients with good performance status.

In 2015, Gupta et al, in a letter to the editor emphasised the need to establish SRS facilities to treat the huge burden of brain metastasis in Indian patient population[24]. However, the nihilism regarding the BM prevailed and in 2022 in an editorial Agarwal, et al., admitted that in 'resource constraint' country like India, WBRT may be considered as the option in BM [27]. Although limited, studies originating from India have explored various aspects of BM. There are only a few prospective study in BM related to radiation therapy. Majority of the studies (level 3 and 4) are with WBRT and only one prospective study with SRS alone in BM. In India, at present there are 365 linear accelerator compatible with SRS facility for brain metastasis including eight Tomotherapy, seven CyberKnife and seven Gammaknife facilities. WHO recommendation for linear accelerator requirement for Indian patients population is one linear accelerator per million population [28]. However, present linear accelerator density in Indian is 0.4 per million population (ideal is 1.0 per million population). Hence, there are significant gaps in infrastructure. On top of it, majority of SRS compatible radiation facilities are concentrated in metro cities and still have not penetrated two-three tier cities. Still the number of documented SRS treatment in BM conducted in India is lesser than the capacity. It is the nihilism regarding brain metastasis treatment, cost factor as majority (85%) of SRS compatible facilities are in private sectors and lack of training among physicians that is major hinderance for providing SRS treatment in Indian patients with BM. Inadequate infrastructure for comprehensive data collection, lack of national cancer registries that accurately report the incidence of BM and insufficient research funding are key impediments to current research patterns. The existing literature highlights significant advancements in treatment modalities, such as SRS and HA-WBRT, but underscores the necessity for standardized practices and protocols across institutions. The findings from both primary and secondary studies indicate a growing awareness and interest in improving patient outcomes through innovative therapies. However, there remains a critical need for large-scale epidemiological studies and the establishment of registries to track treatment efficacy and patient demographics effectively. This will not only provide a clearer picture of the incidence of BM in the Indian population but also facilitate research into personalized treatment approaches and interventions tailored to unique challenges faced in the country. Further research efforts should focus on addressing these gaps, fostering collaborations among institutions and advocating increased funding and resources which would also be translated into better clinical practice, improved patient care and lower BM burden in India.

Ongoing Studies

Thirteen studies identified in the Clinical Trials Registry of India (CTRI) are actively investigating therapeutic strategies for managing BM, particularly focusing on radiation treatments and cognitive preservation. Key trials include CTRI/2024/04/066217, which explores Therapeutic Drug Monitoring (TDM) of memantine to optimize dosing and reduce toxicity (Phase 3) and CTRI/2022/01/039599, a randomized trial assessing memantine's role in preventing radiation-induced cognitive dysfunction (Phase 3)[29]. Other significant trials involve novel treatment combinations, such as CTRI/2022/01/039501, comparing Tyrosine Kinase Inhibitors (TKIs) with or without intrathecal methotrexate for leptomeningeal carcinomatosis in lung cancer patients (Phase 3) and CTRI/2020/09/027794, investigating WBRT plus Resveratrol-Copper in NSCLC patients (Phase 2). Radiotherapy advancements are also under examination, with studies like CTRI/2022/02/040576 on fractionated stereotactic radiotherapy for oligometastatic BM (Phase-2). Additionally, trials such as CTRI/2020/08/027279 evaluate cranial radiation in asymptomatic BM (Phase 3), while studies like NCT05144867 compare stereotactic radiosurgery and WBRT in breast cancer patients (Phase 2). These trials, alongside earlier research combining WBRT with agents like temozolomide or Nimotuzumab, collectively aim to enhance treatment efficacy, reduce toxicity and improve quality of life for patients with BM.

Conclusion

The present analysis was focused on the research on brain metastasis in Indian patient population regarding treatment with radiation therapy. Among the published 26 articles only a few are prospective randomized study, majority are observation or retrospective series. There are very few published literature with SRS in brain metastasis in Indian patient population. However, there are growing evidence and ongoing research regarding radiation therapy in BM in Indian patient population. SRS usage in BM have an increasing trend in Indian population. There is a need to overcome the nihilism regarding BM treatment and a need to fulfil the deficits with prospective studies having larger patient cohort and long-term follow up.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Acknowledgement

None

Data Availability Statement

Not applicable.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

All authors contributed equally to this paper.

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