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Original article

Precision Medicine in Lung Cancer Brain Metastases: Integrating Novel Therapeutics and Radiotherapy for Optimal CNS Control

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ABSTRACT

Cerebral metastases develop in nearly half of patients with lung cancer, substantially impairing both survival and quality of life. Historically, poor blood–brain barrier penetration and modest intracranial activity of systemic agents limited treatment options. However, recent advances in immune checkpoint inhibitors and next-generation CNS-penetrant targeted therapies have reshaped the therapeutic landscape, achieving superior intracranial disease control and improved patient outcomes. Concurrently, stereotactic radiotherapy has emerged as a precise and effective local modality with a more favorable toxicity profile than whole-brain irradiation. The integration of systemic and local approaches, guided by molecular profiling and clinical risk stratification, offers new opportunities to optimize CNS disease management. Nevertheless, these advances raise key challenges regarding treatment sequencing, patient selection, and risk-adapted strategies. This review summarizes the contemporary management of lung cancer brain metastases and highlights future directions for clinical trial design, emphasizing the incorporation of multidimensional clinical, biological, and radiological tools to guide individualized treatment decisions.

Introduction

Brain metastases (BM) are a frequent complication of lung cancer and are present at diagnosis in ~15% of cases. During the course of disease, up to one-third of patients with non-small-cell lung cancer (NSCLC) and up to half of those with small-cell lung cancer (SCLC) will develop intracranial lesions. Their apparent incidence has increased with widespread use of high-definition brain magnetic resonance imaging (MRI) and with longer survival achieved through immune checkpoint blockade (ICB) and molecularly targeted therapies. BM substantially impairs quality of life (QoL). Median overall survival (OS) ranges widely, from 2 to 52 months according to the updated lung-specific graded prognostic assessment (DS-GPA), now incorporating PD-L1 expression, which underlines the need for individualized treatment strategies [1–4]. Although international guidelines provide a framework for BM management [5,6], the rapid development of central nervous system (CNS)-active systemic agents and advances in radiotherapy (RT) have challenged the historical opposition between local and systemic treatment. Instead, management increasingly relies on multidisciplinary integration of these modalities. This narrative review summarizes the evolving treatment landscape of lung cancer BM and proposes a framework for personalized, risk-adapted sequencing.

Methods

Search strategy and selection criteria

References were identified by systematic searches of PubMed and ClinicalTrials.gov for published articles and ongoing trials up to 29 March 2026. Only English-language publications were considered. Search terms included combinations of "non-small-cell lung cancer", "small-cell lung cancer", "brain metastases", "stereotactic radiotherapy", "stereotactic radiosurgery", "whole-brain radiotherapy", "chemo-immunotherapy" and "targeted therapy". Priority was given to prospective studies, practice-changing trials and evidence published over the last 10 years, with a focus on stage IV lung cancer.

Local radical approach for oligometastatic BM

Exclusive RT

In the context of BM, the definitions of oligometastatic and polymetastatic disease vary across clinical trials. Importantly, the concept of oligometastatic disease differs significantly between extracranial and intracranial compartments. Although extracranial oligometastatic disease is generally defined as <5 lesions, intracranial oligometastatic disease is not strictly defined by the absolute number of lesions, but rather by the proportion of lesions amenable to safe and radical local treatment [7]. Although historical trials often defined limited disease as 1–4 metastases, modern frameworks extend this to 10–20 lesions, provided the cumulative tumor volume is restricted [8,9]. In this setting, for patients with non-oncogene-addicted (non-OA) NSCLC lacking highly active targeted options, for whom immediate local control with neurosurgical resection is not essential, RT offers a critical non-invasive local treatment. Upfront RT can complement

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systemic therapies, particularly if they have limited intracranial activity and in patients with poor prognostic features, such as non-OA PD-L1-negative NSCLC. RT strategies should therefore be discussed in multidisciplinary tumor boards. In patients with multiple BM and poor performance status (PS), not eligible for aggressive local therapy, the seminal phase III QUARTZ trial demonstrated that best supportive care alone was comparable to whole-brain radiotherapy (WBRT) in terms of OS and QoL [10]. Stereotactic radiosurgery (SRS) and stereotactic RT (SRT) have gained prominence over WBRT due to shorter treatment times and fewer long-term neurological adverse events (AEs) [8,9,11–14]. The phase III trial by Aoyama et al. [11] comparing SRS alone versus WBRT+SRS in patients with ≤4 BM reported similar OS, with lower recurrence rates in the combined arm but preserved neurological outcomes in both. Other randomized phase III trials in patients with ≤3 BM found that SRS+WBRT improved intracranial control but caused greater neurocognitive decline than SRS alone [12,13]. The large prospective JLGK0901 study confirmed the safety and efficacy of SRS alone in patients with up to 10 BM, with OS and AE rates similar across subgroups, although new lesion rates increased with BM number [8,15]. These findings reinforce the role of SRS/SRT as frontline modalities in selected patients. Hippocampal avoidance (HA) has emerged as a strategy to limit neurocognitive decline in WBRT. The single-arm phase II RTOG 0933 trial showed lower mean relative neurocognitive decline compared with historical WBRT cohorts [16]. Pharmacologic protection with memantine has also shown benefit [17]. The phase III NRG CC001 trial evaluated HA WBRT with memantine compared with WBRT with memantine in patients with brain metastases and showed reduced risk of cognitive failure and less deterioration in executive functions, learning, and memory with HA [14] . A recent randomized phase III trial comparing SRS/SRT versus HA-WBRT in patients with 5–20 BM reported better QoL preservation over the first 6 months in the SRS/SRT arm, with no OS and grade 3+ AE difference [9]. Several ongoing trials are investigating the most suitable strategies for patients with 4–20 BM. Defining new neurological substructures potentially relevant to functional outcomes and studying brain radiosensitivity may further refine dose constraints [18]. Systematic neurocognitive and QoL assessments should be included during follow-up [19].

Surgery and Post-operative RT

Surgery is preferred in two main situations: first, when BM causes mass effect or intracranial hypertension requiring urgent decompression; second, for large (>3 cm) or cystic lesions. In these cases, resection reduces tumor volume, improves local control, and facilitates safer post-operative RT with lower risk of radiation necrosis (RN) [5,6]. Randomized trials have shown that post-operative RT reduces local recurrence compared with observation [20]. The phase III NCCTG N107C/CEC.3 trial compared post-operative SRS with WBRT in patients with ≤4 BM, including one resected lesion. SRS led to better cognitive-deterioration-free survival and fewer grade 3 AEs, despite shorter intracranial progression-free time SRS 6.4 months vs. WBRT 27.5 months (favouring WBRT for CNS control), and with no OS difference [21]. Long-term cognitive and QoL benefits were confirmed [22]. Similarly, the phase III JCOG0504 trial found worse CNS PFS but comparable OS and fewer cognitive side effects with salvage SRS versus WBRT [23]. The phase II ESTRON study reported no difference in local control, CNS PFS, or OS between post-operative SRT and WBRT, but less cognitive deterioration with SRT [24]. In a retrospective series of 558 patients, better PS, shorter delay to RT, and controlled primary tumor predicted longer OS; single BM, target volume ≤23 cm^3, and primary tumor control favored local control [25]. Overall, post-operative SRS/SRT provides survival comparable to WBRT while better preserving neurocognitive function and is therefore standard after BM resection. Fractionated SRT is increasingly preferred over single-fraction SRS for large cavities to reduce symptomatic RN risk [26]. As systemic therapies become more effective, some patients may safely defer local treatment, emphasizing the importance of individualized multidisciplinary decisions.

Improved CNS Response with Systemic Therapy Advances

The blood–brain barrier (BBB) has long limited drug delivery to the CNS [27]. Although macroscopic BM often disrupts the BBB, permeability is heterogeneous, resulting in uneven drug exposure [28]. The design of small molecules able to cross the BBB more effectively has therefore become essential [29]. In patients with multiple small, asymptomatic BM, deferring upfront local therapy may be reasonable in carefully selected cases, depending on the CNS activity of systemic treatment [5,6]. Comprehensive molecular profiling at diagnosis is crucial, with plasma liquid biopsy as a complementary option [30]. CSF liquid biopsy is a promising investigational tool [31]. Over the last decade, ICB and targeted therapies have transformed advanced NSCLC outcomes, including intracranial activity. In non-OA NSCLC, ~20% of patients treated with chemo-ICB and approximately one-third treated with ICB alone when PD-L1 ≥50% remain alive at 5 years [32]. In OA NSCLC, survival is even more favorable: ~75% of EGFR-mutated patients are alive at 2 years and up to two-thirds of ALK-rearranged patients at 4 years with next-generation TKIs [33,34]. By contrast, SCLC remains more aggressive, with earlier BM development and poorer prognosis; 5-year OS remains <10% [35]. ICB added to chemotherapy is now standard, but active or untreated BM was excluded from pivotal trials, leaving a significant evidence gap.

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Table 1. Summary Of Key Local Treatments

Trial / Study	Design	Population	Intervention	Key Clinical Outcomes
Historical Landmarks (Aoyama, Chang, ...)	Phase III	1–4 BM	SRS vs SRS + WBRT	WBRT reduces recurrence but causes cognitive decline
JLGK0901 (Yamamoto et al.)	Prospective Obs	Up to 10 BM	SRS alone	Safe and effective; new lesions ↑ with number; OS ≈ 10.8 mo
NRG-CC001 (Brown et al.)	Phase III	Any number BM	HA-WBRT + memantine vs WBRT	HA reduces cognitive failure risk (HR 0.74); OS ≈ 6–7 mo
Aizer et al. (2026)	Phase III	5–20 BM	SRS/SRT vs HA-WBRT	Better QOL at 6 mo with SRS/SRT; similar OS; higher new BM (45%)
NCCTG N107C (Brown et al.)	Phase III	≤4 BM (resected)	Post-op SRS vs Post-op WBRT	OS: SRS 6.4 mo vs WBRT 27.5 mo; better cognitive preservation with SRS
ESTRON (El Shafie et al.)	Phase II	Resected cavity	Post-op SRT vs WBRT	Investigates post-op stereotactic radiation vs WBRT

(Chemo)Immunotherapy

Despite the immunosuppressive CNS microenvironment and BBB, ICB can still be active in BM [36]. Chemotherapy may enhance immunogenicity and, when combined with ICB, provides moderate intracranial efficacy [37]. In a phase II study of 42 NSCLC patients with untreated or progressing BM, pembrolizumab monotherapy produced an intracranial response rate of 29.7% in PD-L1 ≥1% tumors, with median PFS, CNS PFS, and OS of 1.9, 2.3, and 9.9 months, respectively; no responses occurred in PD-L1 ≤1% disease [32]. Another phase II trial reported a 43% intracranial response rate in NSCLC, CNS PFS of 1.6 months, and OS of 8 months [39]. In CheckMate 817, first-line nivolumab plus ipilimumab in advanced non-OA NSCLC with untreated BM yielded median PFS of 2.8 months and OS of 12.8 months [40]. Chemoimmunotherapy combinations appear more active. In ATEZO-BRAIN, atezolizumab plus carboplatin–pemetrexed in 40 patients with untreated BM achieved an intracranial ORR of 42.7%, median PFS of 8.9 months, CNS PFS of 6.9 months, and OS of 11.8 months [41]. CAP-BRAIN reported an intracranial ORR of 52.5%, median PFS and CNS PFS of 7.4 and 7.6 months, and OS of 21 months [42]. NIVIPI-BRAIN also reported encouraging activity with dual ICB plus chemotherapy [43]. Antiangiogenic therapy may also contribute; bevacizumab has shown potential [44]. In SCLC, CASPIAN and IMpower133 improved survival with ICB plus chemotherapy, and exploratory analyses suggested intracranial benefit in patients with previously treated BM [45]. However, both trials excluded active BM. In the phase II LOGiK2001 study, durvalumab plus platinum–etoposide in untreated BM achieved an intracranial ORR of 66.7%, but median intracranial PFS was only 4.2 months, suggesting that immunotherapy alone is insufficient for durable CNS control [46].

Targeted Therapy

Earlier-generation EGFR and ALK inhibitors had limited CNS efficacy. Newer agents were designed to cross the BBB more effectively, resulting in better intracranial exposure [47,48]. In the phase III FLAURA trial, first-line osimertinib outperformed erlotinib–gefitinib in EGFR-mutant NSCLC, with longer PFS, higher intracranial response (66% versus 43%), longer CNS PFS (not reached versus 13.9 months), and improved OS [33]. FLAURA2 showed that adding platinum-based chemotherapy to osimertinib improved PFS and OS, with slightly better intracranial outcomes [49]. In MET-mediated resistance, osimertinib plus savolitinib improved CNS outcomes [50]. In ALK-rearranged disease, alectinib was superior to crizotinib, with greater intracranial efficacy [51]. In CROWN, lorlatinib showed markedly improved CNS control versus crizotinib, with a CNS PFS HR of 0.06 [34]. Newer highly brain-penetrant ALK inhibitors have also shown promising activity [52]. These advances challenge traditional treatment paradigms and raise the question of how best to integrate local and systemic approaches.

Table 2. Summary Of Key Systemic Therapies

Trial / Study	Cancer Population	Intervention	Intracranial ORR	Survival & CNS Outcomes	Key Toxicity / Notes
ATEZO-BRAIN (Nadal et al.)	Non-OA NSCLC	Chemo + Atezolizumab	42.7%	CNS PFS 6.9 mo; mOS 11.8 mo	12.5% G3+ neurotoxicity
CAP-BRAIN (Hou et al.)	Non-OA NSCLC	Chemo + Carrelizumab	52.5%	CNS PFS 7.6 mo; mOS 21 mo	No severe neurological AEs
FLAURA (Soria et al.)	EGFR-mut NSCLC	Osimertinib vs 1st-gen TKI	66% vs 43%	CNS PFS 13.9 mo; mOS 38.6 vs 31.8 mo	HR 0.80 for mOS
FLAURA2 (Planchard et al.)	EGFR-mut NSCLC	Osimertinib + Chemo vs Osimertinib	73% vs 69%	CNS PFS 30.2 vs 27.6 mo; mPFS 25.5 vs 16.7 mo	Overall survival benefit noted
CROWN (Shaw et al.)	ALK-fus NSCLC	Lorlatinib vs Crizotinib	76% vs 17% (no prior RT)	HR = 0.03 (BM subgroup)	G3 cognitive and mood AEs
LOGiK2001 (Shiraishi et al.)	ES-SCLC	Chemo + Durvalumab	66.7%	CNS PFS 4.2 mo; mOS 14.2 mo	ICB alone insufficient for durable CNS control

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Combined Multidisciplinary Strategies

The growing efficacy of systemic therapy and the precision of local RT increasingly support combined treatment strategies. In non-OA NSCLC, deferring local therapy is more controversial because intracranial efficacy remains modest and depends on PD-L1. In OA NSCLC, upfront SRS may often be avoided owing to the high CNS activity of next-generation TKIs. Nevertheless, RT can disrupt the BBB and modulate the immune microenvironment, potentially enhancing systemic treatment response [53]. SRS/SRT also provides excellent local control with limited toxicity. Some patients are likely to benefit from combined-modality approaches, although prior local treatment may compromise later systemic drug penetration [54]. Another concern is RN, especially in long survivors.

Integration of Radiotherapy with (Chemo)Immunotherapy

A retrospective study found that upfront RT improved OS, PFS, and CNS PFS in the ICB monotherapy cohort but not in the chemo-ICB cohort [55]. Prospective data are emerging. In the single-arm phase II C-BRAIN trial, upfront SRT or WBRT combined with platinum chemotherapy and camrelizumab in 65 patients achieved a 78.5% intracranial ORR, median PFS of 10.7 months, CNS PFS of 16.1 months, and OS of 20.9 months [56]. In the phase III CTONG 2003 study, camrelizumab plus chemotherapy improved CNS PFS versus chemotherapy alone [57]. Ongoing trials are expected to better define the role of RT with ICB. In SCLC, prophylactic cranial irradiation (PCI) historically reduced BM risk and modestly improved OS [58], although its role in extensive-stage disease is debated in the MRI and ICB era [59]. For SCLC BM, SRS is under study as a less toxic alternative to WBRT. In the FIRE-SCLC cohort, OS favored SRS, whereas CNS control favored WBRT [60]. CROSS-FIRE confirmed that although OS after SRS was worse in SCLC than NSCLC, CNS progression patterns were similar [61]. A prospective phase II study of SRS/SRT in extensive-stage SCLC with 1–10 BM found a median OS of 10.2 months [62]. Randomized trials such as NRG-CC009 and SHARP should clarify cognitive outcomes of SRS versus HA-WBRT in the ICB era.

Targeted Therapy: Should Radiotherapy Be Deferred?

As seen in FLAURA and CROWN, newer-generation TKIs substantially improve intracranial outcomes. However, evidence directly comparing CNS-active TKI alone versus TKI plus upfront RT remains limited. In the retrospective TURBO-NSCLC study of 317 patients treated with first-line next-generation TKI, upfront SRS did not improve OS but did improve local control and time to CNS progression [63]. Larger BM (≥1 cm) appeared more likely to benefit. Ongoing trials are expected to provide more definitive evidence. At present, CNS-active TKI with close MRI surveillance is reasonable for patients with small, asymptomatic BM, while early SRS should be considered for larger, symptomatic, or eloquent-location lesions [64].

Table 3. Summary Of Combined Radiotherapy and Systemic Strategies

Trial / Study	Cancer Type	Patient Population	Treatment Strategy	Efficacy Outcomes	Safety / Toxicity
C-BRAIN (Xu et al.)	Non-OA NSCLC	Untreated BM	Upfront RT + Chemo + Camrelizumab	IC-ORR 78.5%; CNS PFS 16.1 mo; mOS 20.9 mo	RN 5%
CTONG 2003 (Li et al.)	Non-OA NSCLC	Non-OA NSCLC cohort	Chemo + Camrelizumab (± Upfront RT)	CNS PFS 12.7 vs 9.9 mo (RT favored)	Survival bias remains
TURBO-NSCLC (Pike et al.)	EGFR/ALK+ NSCLC	EGFR/ALK+ on TKI	TKI alone vs TKI + Upfront SRS	Upfront SRS improves local control; benefit for BM >1 cm	10% symptomatic RN
FIRE-SCLC (Rusthoven et al.)	ES-SCLC	ES-SCLC with BM	Upfront SRS vs WBRT	OS favors SRS (6.5 vs 5.2 mo); CNS control favors SRS	Neurological mortality 12.4% (SRS); RN 5%

Discussion and Perspectives

Future BM management will increasingly depend on emerging systemic agents, improved RT techniques and a better understanding of CNS-specific disease biology.

Next-generation Systemic Therapies

New therapeutic classes have shown promising activity in heavily pretreated patients. Early studies suggest activity in KRAS G12C-mutated disease [65], MET exon 14 skipping [66], RET [67], ROS1 [68], NTRK [69], and BRAF V600E-mutated NSCLC [70]. HER2-mutated NSCLC has also shown encouraging intracranial activity [71]. Antibody–drug conjugates (ADCs) and bispecific antibodies have generated substantial interest. TROP2-targeted ADCs have shown CNS activity [72,73], and HER2-targeted ADCs have done likewise [74]. However, combining ADCs with SRT may increase RN risk [75]. Bispecific antibodies may further improve control; in MARIPOSA, amivantamab plus lazertinib improved PFS versus osimertinib and showed better CNS outcomes [76]. In non-OA PD-L1-positive NSCLC, a PD-1–VEGF bispecific achieved superior PFS [77].

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In SCLC, the DLL3-targeting T-cell engager tarlatamab showed promising intracranial activity [78]. Other approaches include mRNA vaccines, CAR-T cells, tumor treating fields (TTFs), and focused ultrasound [79].

Table 4. Summary Of Emerging Agents

Agent & Class	Study Name	Target Population	CNS Activity	FDA Approved	Key Intracranial / Toxicity Findings
Trastuzumab Deruxtecan (ADC)	DESTINY–Breast12	HER2+ mBC with active/stable brain lesions	High	✓	Intracranial ORR ~79%; ILD/pneumonitis risk
Tucatinib + Trastuzumab (TKI+Ab)	HER2CLIMB	HER2+ metastatic breast cancer with CNS lesions	High	✓	Reduced intracranial progression; ALT/AST ↑; diarrhea
Osimertinib (EGFR TKI)	FLAURA	EGFR-mutated advanced NSCLC	High	✓	CNS ORR ~91% in pretreated lesions; low QT prolongation
Sacituzumab Govitecan (ADC)	ASCENT Sub-study	Pretreated metastatic TNBC	Moderate	✓	Prolonged intracranial PFS; neutropenia, diarrhea
Lorlatinib (ALK/ROS1 TKI)	CROWN	Untreated ALK+ advanced NSCLC	High	✓	Intracranial ORR ~82%; neurocognitive events, hyperlipidemia
Datopotamab Deruxtecan (ADC)	TROPION–Lung01	Advanced/metastatic non-squamous NSCLC	Moderate	☐	CNS stabilization; stomatitis, low-grade nausea

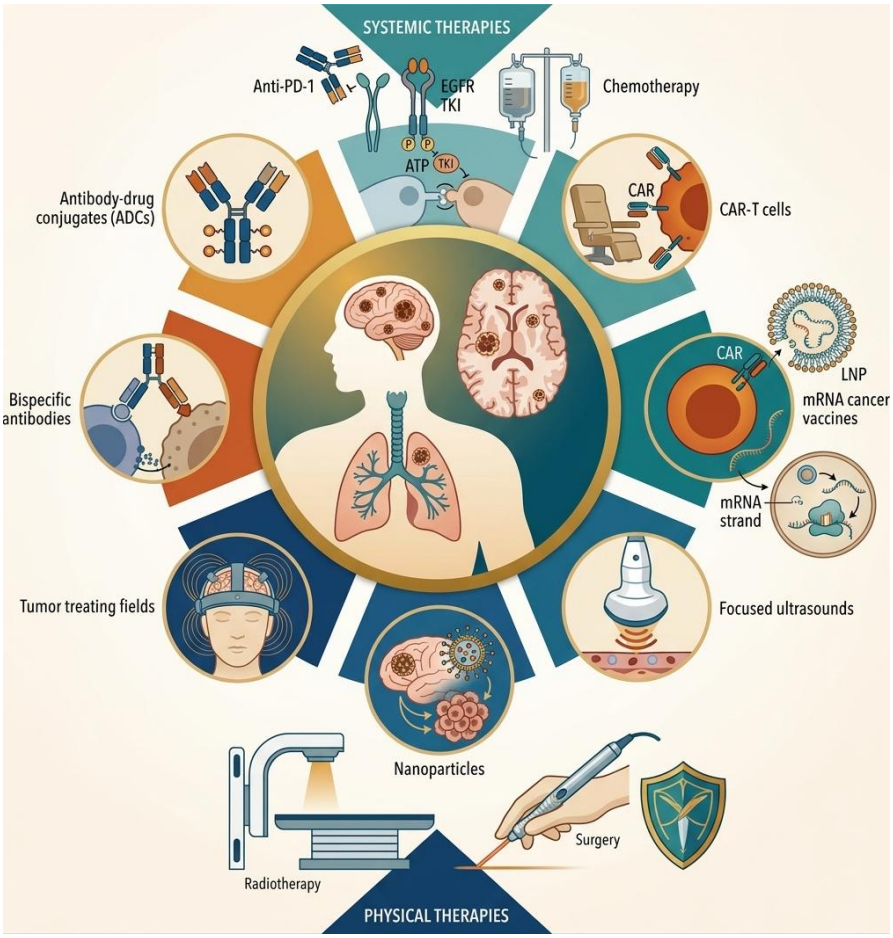

Figure 1. Emerging Treatments for Lung Cancer with Brain Metastasis

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Optimising RT to Limit Leptomeningeal Disease

Leptomeningeal disease (LMD) is increasingly recognized as survival improves. LMD appears more frequently in OA NSCLC [80]. Pre-operative SRS is emerging as a strategy to reduce LMD risk [81]. Preliminary results from an ongoing phase III trial showed shorter treatment completion with pre-operative SRT [82]. For established LMD, proton craniospinal irradiation improved CNS PFS and OS versus photon involved-field RT [83].

Refining Patient Selection: Treat Better, Harm Less

Both intracranial and extracranial tumor burden affect OS and CNS control [84]. Biological factors matter; low PD-L1 is associated with higher BM risk and reduced benefit from immunotherapy [85]. BM can differ genomically from primary tumors, which may explain discordant responses [86]. CSF ctDNA may become a more useful biomarker [87]. Advanced imaging and AI-based radiomics may further refine diagnosis [88]. Interpretation of intracranial efficacy remains limited by heterogeneous assessment methods; broader adoption of RANO-BM is needed [89]. Neurocognitive endpoints are inconsistent. Treatment toxicity, especially RN, must be integrated; reported rates are about 3–5% after exclusive SRT and up to 10% after post-operative SRT or in combination with EGFR/ALK TKIs [63]. Distinguishing RN from progression is difficult. Management includes corticosteroids, VEGF inhibitors, and surgery. Ultimately, treatment decisions should prioritise symptom burden, neurocognitive preservation and QoL. Multidisciplinary discussion and shared decision-making are essential [5,6].

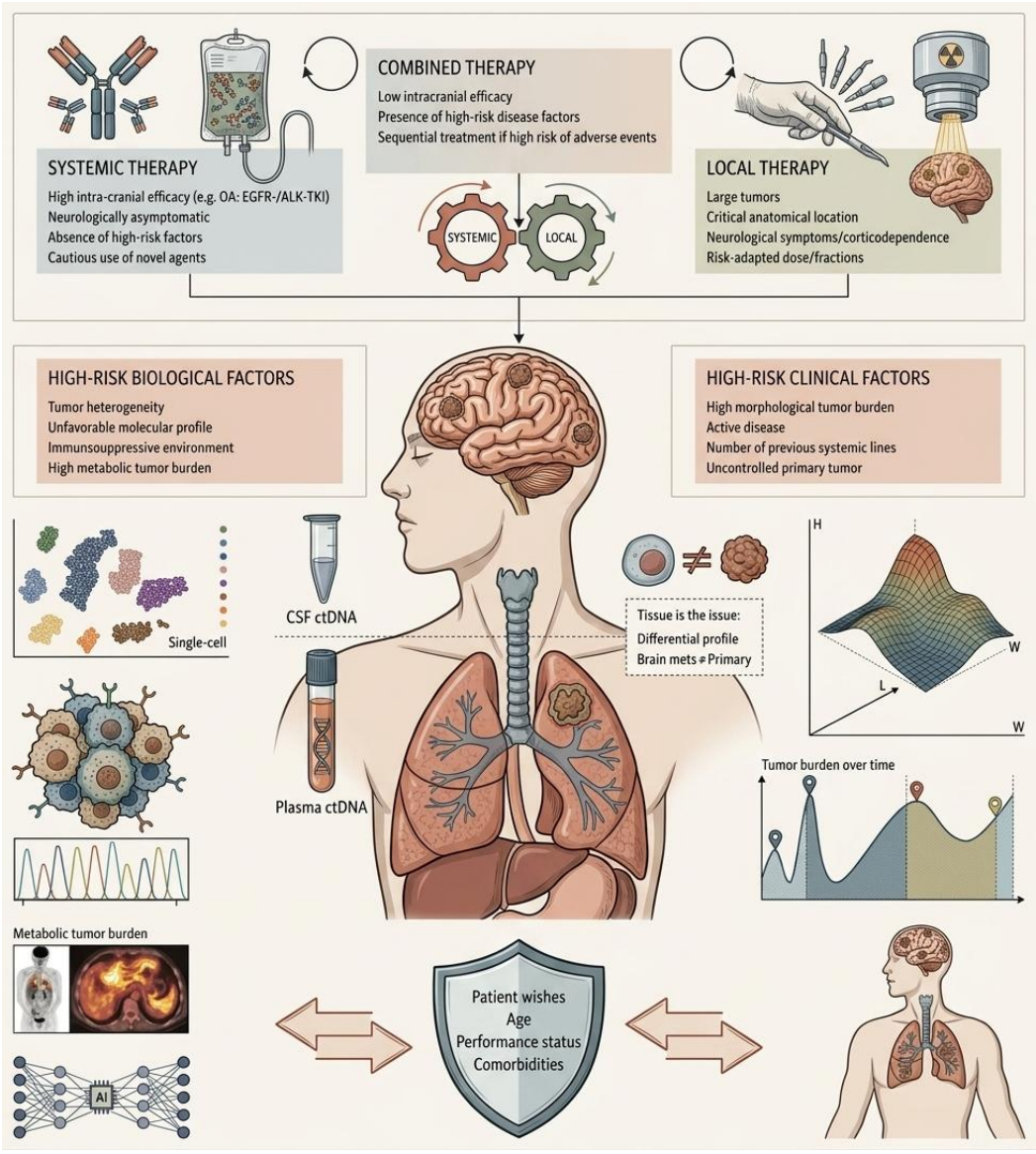

Figure 2. Brain Metastasis Management and Selection Strategy

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Conclusion

In the era of highly effective systemic therapies with growing intracranial activity, management of lung cancer BM is undergoing a major paradigm shift. SRT remains a cornerstone local modality because it offers precise, repeatable tumor control with limited toxicity. At the same time, the increasing efficacy of CNS-active systemic agents is redefining treatment sequencing and supporting more selective use of local therapy. Future trials should systematically incorporate brain MRI, standardized intracranial response criteria, and refined prognostic models integrating clinical, biological, and radiological features. A strategy centered on upfront CNS-active systemic therapy with selective integration of RT is increasingly plausible in well-chosen patients. Such individualized approaches will be critical to maximize survival while preserving neurocognitive function and QoL.

Conflict of interest. Nil

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