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Running title: Infratentorial brain mets in NSCLC: Outcome

The infratentorial localization of brain metastases in non-small cell lung cancer indicates poorer prognosis and distinct selection of radiotherapy

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Infratentorial brain metastases (BMs) are life-threatening because of the unique anatomical features and physiological functions of the posterior cranial fossa. However, the comparative prognosis of infratentorial BM and supratentorial BM remains poorly understood. We conducted a matching comparison of the prognosis between non-small cell lung cancer (NSCLC) patients with and without infratentorial BM and analyzed prognostic factors, including the radiotherapy (RT) method. 392 NSCLC patients who underwent brain RT from July 2010 until June 2023 were analyzed. After 1:1 propensity matching, we compared 115 patients with only supratentorial BMs (supraT-alone group) and 115 patients with infratentorial ± supratentorial BMs (infraT ± supraT group). We assessed intracranial control and overall survival (OS) using Kaplan-Meier and Cox regression. There was no statistical difference for extracranial progression-free survival (PFS), intracranial local PFS, or distant PFS. The supraT-alone group had significantly better OS (median: 35.3 vs. 24.2 months, $p = 0.021$). The supraT-alone group in the multivariate analysis had BM resection ($p = 0.031$), targeted therapy ($p < 0.001$), and immune therapy ($p = 0.006$) associated with improved OS. The infraT ± supraT group had RT method ($p = 0.002$), ≤ 60 years of age ($p = 0.002$), targeted therapy ($p = 0.017$), and number of extracranial metastases ($p < 0.001$) when reporting OS. We confirmed that WBRT+boost and SRT improved OS compared to WBRT alone. There was no statistical difference in OS for WBRT+boost and SRT. The overall grade 3-4 acute toxicities were similar for both groups.
Our study suggests that infratentorial BMs in NSCLC lead to worse OS. However, local high-dose RT strategies (SRT or WBRT+boost) may confer survival benefits to patients who present with infratentorial involvement.

Key words: brain metastases; infratentorial localization; whole-brain radiation therapy; stereotactic radiotherapy; prognosis

Brain metastases (BMs) are the most common type of tumor affecting the central nervous system, with an incidence of 30-50% among lung cancer patients. BM is one of the leading causes of cancer mortality, indicating a poor prognosis with a natural course lasting only 1-2 months. Moreover, with the extension of overall survival (OS) in cancer patients and the availability of advanced imaging techniques, the incidence of BM is increasing gradually [1-3].

Whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) have been applied to different cases of BM with concrete therapeutic effects [4]. The combination of WBRT and SRS may increase the intracranial control rate [5-7]. Hippocampal avoidance WBRT with simultaneous integrated boost (HA-WBRT-SIB) is efficient and cognitively conservative in treating BM. Especially for multiple BMs, several retrospective studies have shown that HA-WBRT-SIB can result in better OS and intracranial progression-free survival (iPFS) than WBRT alone [8-10]. The selection of local treatment methods depends on many factors, including the BM location, which determines the focal symptoms and signs. Consequently, different methods can influence the prognosis of patients [11-13].

The infratentorial region, situated within the posterior cranial fossa, is one of the region's most susceptible to nonuniform intracranial metastasis in patients with lung cancer [14-16]. The infratentorial BM is always considered more life-threatening than the supratentorial BM because of a greater risk of obstructive hydrocephalus, compression and injury of the brain stem, and transforaminal magna herniation [17]. In previous retrospective studies, infratentorial involvement of the BM was an independent risk factor for OS and the occurrence of adverse events in patients who underwent BM resection [16, 18-20]. A multicenter cohort study of preoperative SRS for BM revealed that the risk of meningeal disease was associated with the infratentorial location [21]. However, in multivariate analysis for patients without BM resection or total BM patients, the prognostic influence of the infratentorial location was inconsistent, and data from prospective randomized controlled studies are lacking [16, 22, 23].

The purpose of this study was to perform a matched comparative analysis with the retrospective data from two centers to identify prognostic differentials in patients with and without infratentorial brain metastases and to analyze prognostic indicators, such as strategies for radiotherapy intervention. While prior studies have demonstrated the prognostic significance of infratentorial brain metastases, there is still limited evidence around direct comparison of the impact of radiotherapy and the effect of dose escalation that is directed toward infratentorial lesions in non-

small cell lung cancer (NSCLC) [16].

Although the claim about radiation sensitivity in the infratentorial region is not well established in large clinical datasets, past anatomical and clinical radiotherapy studies indicate that this region, because of its relationship to the brainstem and cerebellum, is more sensitive to potential radiation toxicity [17]. As such, this study sought to determine whether local high-dose radiotherapy might improve survival in patients with infratentorial lesions within acceptable limits of toxicity. We hypothesized that infratentorial BMs in NSCLC are associated with poorer OS, but that local high-dose radiotherapy (RT) strategies, such as stereotactic radiotherapy (SRT) or WBRT with a local boost, may confer a survival benefit for these patients.

In conclusion, this study adds meaningful data to help clinicians with decision-making by clarifying prognostic differences and evaluating the role of radiotherapy in patients with infratentorial brain metastases.

Patients and methods

Patient source and data collection. A total of 392 patients with NSCLC and BM received WBRT alone, stereotactic radiotherapy (SRT), or WBRT with local dose boost (WBRT+boost) at Sun Yat-sen University Cancer Center or Yunnan Cancer Hospital from July 15, 2010, to June 2, 2023. Clinical and demographic data were obtained from hospital medical records on the following: age; sex; smoking history; date of BM diagnosis; primary tumor pathological type; number and location of brain metastases; maximum diameter of brain metastases; neurological symptoms; whether BM was surgically removed before brain RT; extracranial disease status; Karnofsky performance status (KPS) score; radiotherapy technique; dose prescribed; and treatment duration. Magnetic resonance imaging (MRI) and computed tomography (CT) scans before and after brain RT were examined. Systemic therapies (targeted therapy, chemotherapy, or immunotherapy) that were administered in the same period as the brain RT, and whether salvage RT or surgical resection of BM was performed after progression, were also collected.

However, given the retrospective nature of the study, several molecular markers (epidermal growth factor receptor (EGFR) / anaplastic lymphoma kinase (ALK) mutation status, programmed cell death-ligand 1 (PD-L1) expression, & volumetric burden of brain metastases) were not consistently measured and not included in matching or analysis.

Statement of ethics. The research proposal has been reviewed and approved by the Ethics

Committee of Yunnan Cancer Hospital (2024-11-18 KYLX2024-286) for the conduct of this research. The Declaration of Helsinki, Ethical Review of Biomedical Research involving Human Subjects, and other relevant international guidelines were strictly followed during the study. Due to the death or loss of follow-up of some patients, an application has been made to the Ethics Committee of Yunnan Cancer Hospital for exemption of some patients from signing the informed consent form. The rest of the patients have all signed the informed consent form.

Inclusion and exclusion criteria. The inclusion criteria were as follows: 1) the primary tumor was NSCLC, and MRI or CT verified the presence of BM; 2) no prior brain RT; and 3) completion of WBRT alone, SRT, or WBRT+boost treatment. The exclusion criteria were as follows: 1) MRI or CT revealed leptomeningeal or skull metastasis; and 2) loss to follow-up within 3 months without cerebral imaging review after RT.

Radiotherapy. The WBRT-alone group received 3- Dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), or volume modulated arc therapy (VMAT). The X-knife or CyberKnife methods were used in the SRT group. The WBRT+boost group included the techniques of WBRT with simultaneous integrated boost (WBRT-SIB) or WBRT followed by local boost. WBRT-SIB adopted IMRT, VMAT, or TOMO, and “WBRT followed by local boost” adopted 3D-CRT or VMAT in WBRT, followed by X-knife or VMAT in boost.

The heads of patients in the supine position were immobilized via a thermoplastic mask. CT and MR simulations were conducted with contrast agents. The CT and MR images were fused in the treatment planning system to delineate the radiation target areas, including the clinical tumor target of the whole brain (CTV-brain) and gross tumor targets of intracranial metastases (GTV). If a patient underwent resection of the BM, the resection cavity was expanded by 3-5 mm to define the respective GTV. The CTV-brain and GTV were expanded by 3 mm to form the respective planning target volume (PTV)-brain and PTV-GTV.

The biological equivalent dose (BED) in this study was calculated via a universal survival curve, with an α/β of 8.6 according to the NSCLC [24]. The prescription dose for each group was as follows: 1) 28-40 Gy/2-5 fractions (BED=50.90 Gy-81.5 Gy) in the SRT group (n=151), among whom 73 patients received 30Gy/3F (BED=59.6 Gy), and 49 patients received 35Gy/5F (BED=63 Gy). 2) 40.47Gy~52.24Gy (BED) in the WBRT-alone group (n=132), among whom 62 patients received 30Gy/10F (BED=40.47Gy), and 44 patients received 40Gy/20F (BED=49.3Gy). 3) In the WBRT+boost (n=109) group, the dose of WBRT was 40.47 Gy~56.70 Gy (BED), among whom 60

patients received 30 Gy/10F (BED=40.47 Gy). There was no significant difference in the BED of WBRT between the WBRT-alone group and the WBRT+boost group (t test, mean values: 44.41 Gy vs. 44.7 Gy, p=0.646). In addition, the dose for metastases or resection cavities (GTV) was increased to 58.6~100.07 Gy (BED). The BED of the SRT group was significantly lower than the BED of the GTV in the WBRT+boost group (t test, mean values: 62.35 Gy vs. 72.22 Gy, $p < 0.001$). Twenty patients in the WBRT+boost group and 1 patient in the WBRT-alone group avoided the hippocampus during brain RT. The mean dose to the hippocampus was limited to 10-18 Gy, depending on the RT equipment used.

Follow-up. The cutoff date for follow-up was September 8, 2024. Patients underwent brain MR-enhanced/CT-enhanced review and physical examination routinely 1 month after treatment and every 2~3 months thereafter. The efficacy of treatment for intracranial metastases was evaluated according to the Response Assessment in Neuro-Oncology Brain Metastases criteria [25]. Acute radiation toxicities were assessed using the American Cancer Society Common Toxicity Criteria, Version 5 (CTC 5.0).

Observation endpoints. The primary endpoints included the following: 1) intracranial local progression-free survival (iLPFS) was defined as the time from the initiation of brain RT to local recurrence, death or last follow-up; 2) intracranial distant progression-free survival (iDPFS) was defined as the time from the initiation of brain RT to distant recurrence (i.e., any new brain metastasis), death or last follow-up; and 3) OS was calculated from the initiation of brain RT until death from any cause or the last follow-up. The secondary endpoints included: 1) intracranial progression-free survival (iPFS), defined as the time from the initiation of brain RT to recurrence, death, or the last follow-up; 2) incidence of acute radiation toxicity during brain RT.

Statistics. Logistic regression was used for 1:1 propensity score matching. The matching covariates included RT method, age, number of BMs, presence of extracranial metastases, resection of BMs before RT, and targeted therapy/chemotherapy/immunotherapy concurrent with and/or following brain RT. The caliper value was set to 0.06. The chi-square test was used to compare baseline characteristics and subsequent management between the InfraT±supraT group and the SupraT-alone group. The Kaplan−Meier method was employed to evaluate iLPFS, iDPFS, and OS. A log-rank test was used to compare the differences in prognosis. A Cox proportional hazard model was used to analyze the influencing factors of OS, iLPFS, and iDPFS. Baseline variables that were considered prognostically relevant or that showed a univariate relationship with outcome were entered into a

multivariate Cox proportional hazards regression model. Variables for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final model. The data were analyzed with SPSS 26.0 and R programming version 4.1.3.

Results

Baseline characteristics. Among the 392 patients who fulfilled the aforementioned criteria, the BM of 225 patients was located only in the supratentorial region, the BM of 144 patients was located in both the infratentorial and supratentorial regions, and the BM of 23 patients was located only in the infratentorial region. Among them, 151 patients received SRT, 132 patients received WBRT alone, and 109 patients received WBRT+boost (Table 1). A total of 109 patients received WBRT+boost, including 76 patients (69.7%) who received WBRT-SIB and 33 patients (30.3%) who received WBRT followed by local boost.

SRT patients completed brain RT within 2-14 days (median days: 3), and the majority of patients (88.7%) completed RT within 5 days. WBRT alone patients completed brain RT within 12-34 days (median days: 15). WBRT+boost patients completed brain RT within 12-42 days (median days: 24).

Before brain RT, 37 (9.4%) patients underwent surgical resection of the BM, including 14 SRT patients, 19 WBRT-alone patients, and 4 WBRT+boost patients. After brain RT, 101 (66.9%) SRT patients, 72 (54.5%) WBRT-alone patients, and 51 (47.79%) WBRT+boost patients developed intracranial progression, including local and distant progression. Subsequently, 52 (34.4%) SRT patients, 16 (12.1%) WBRT-alone patients, and 11 (10.1%) WBRT+boost patients received local salvage therapies (SRS or surgical resection).

The median follow-up time of the 392 patients was 21.4 months (range: 0.8-151.8 months).

The InfraT+supraT group vs. the SupraT-alone group. After 1:1 propensity score matching, there were 115 patients in the only supratentorial BM group (SupraT-alone group) and 115 patients in the infratentorial with/without supratentorial BM group (InfraT±supraT group) (Figure 1). The two groups were well balanced in terms of known prognostic covariates (Table 2). According to the score of Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) [26] for BM, there were no significant differences in DS-GPA between the two groups (p=0.135). In addition, the two groups did not significantly differ in extracranial progression-free survival (ePFS) time (21.9 months vs. 19.1 months, p=0.149).

Intracranial progression-free survival outcomes. There were no significant differences in iLPFS or iDPFS between the SupraT-alone group and InfraT±supraT group, with rates of 80.8% vs. 76.1% at 1 year and 47.8% vs. 60.4% at 2 years for iLPFS (p=0.629, Figure 2A), as well as rates of 80.3% vs. 86.7% at 1 year and 53.6% vs. 72.2% at 2 years for iDPFS (p=0.183, Figure 2B), respectively. There was no significant difference in the median iPFS between the two groups (21.2 months vs. 26.2 months, p=0.913).

Overall survival outcomes. The median overall survival (OS) in the SupraT-alone group was 35.3 months (95% CI: 25.7-44.8), while the median OS in the InfraT±supraT groups was 24.2 months (95% CI: 20.1-28.2), p=0.021, Figure 2C). At one year, the one-year survival rates were 88.5% vs. 75.2%, and at two years, the two-year survival rates were 69.2% vs. 52.2%, respectively.

In looking at the individual subgroup analysis, in the WBRT-alone group, there was a significant difference in OS between the SupraT-alone and InfraT±supraT groups (35.3 months vs. 19.4 months, $p < 0.001$) (Figures 2D-2F). In the SRT group (54.0 months vs. 49.7 months, p=0.719) and WBRT+boost group (26.7 months vs. 26.2 months, p=0.759), there were no significant differences in OS between the groups.

Acute radiation toxicities. After matching, 21 patients from the SupraT alone group and 24 patients from the InfraT±supraT group experienced grade 3 acute radiation toxicity during radiotherapy. No grade 4 toxicity was observed. The incidence of grade 3–4 acute toxicity was 18.3% in the SupraT alone group and 20.9% in the InfraT±supraT group (p=0.766). Data on cognitive function deficit, late radiation toxicity, and quality-of-life outcomes were not available during follow-up.

Multivariate analysis. In the multivariate analysis of the SupraT-alone group (n=225) for OS (Table 3), surgical resection for BM before RT (HR=0.48995% CI, 95% CI 0.327-0.716, p=0.031), targeted therapy after RT initiation (HR=0.48495% CI, 95% CI 0.256-0.937, $p < 0.001$) and immunotherapy after RT initiation (HR=0.36495% CI, 95% CI 0.178-0.743, p=0.006) were independent influencing factors for better OS. However, the RT method (p=0.346) had no significant effect on OS.

In the multivariate analysis of OS in the InfraT+supraT group (n=167) (Table 3), the RT method (p=0.001) was an independent influencing factor for OS. The OS of the WBRT+boost RT group was better than that of the WBRT-alone group (WBRT+boost vs. WBRT-alone: HR=0.542, 95% CI 0.330-0.892, p=0.016), and the OS of the SRT group was better than that of the WBRT-alone group

(SRT vs. WBRT-alone: HR=0.309, 95% CI 0.159-0.603, p=0.001). However, there was no significant difference in OS between the SRT and WBRT+boost groups (SRT vs. WBRT+boost: HR=0.570, 95% CI 0.287-1.130, p=0.108). In addition, age ≤ 60 years (HR=0.471, 95% CI95% CI 0.295-0.751, p=0.002), the existence of extracranial metastases (HR=2.243, 95% CI95% CI 1.438-3.501, p < 0.001) and targeted therapy after RT initiation (HR=0.608, 95% CI95% CI 0.403-0.915, p=0.017) were also independent factors influencing OS.

According to the multivariate analysis of the InfraT±supraT group (n=167) for iLPFS, the RT method of WBRT+boost improved intracranial local BM control compared with that of WBRT alone (WBRT+boost vs. WBRT-alone: HR=0.449, 95% CI 0.228-0.882; p=0.020).

According to the multivariate analysis of the InfraT±supraT group (n=167) for iDPFS, the RT method of WBRT+boost improved iDPFS compared with that of WBRT alone and SRT (WBRT+boost vs. WBRT-alone: HR= 0.426, 95% CI95% CI 0.181-1.000, p=0.050; SRT vs. WBRT+boost: HR=2.580, 95% CI95% CI 1.032-6.451, p=0.042) (Table 4). In addition, the presence of extracranial metastases (HR=2.878, 95% CI 1.446-5.731, p=0.003) was an independent risk factor for iDPFS.

Discussion

In our study, the results revealed that infratentorial involvement of the BM in NSCLC was associated with inferior OS compared with only supratentorial BM (24.2 months vs. 35.3 months, p=0.021). Dou et al. [16] conducted a large retrospective study (n=1102) on BM without limitations for the primary type, and the results revealed that the OS in the InfraT±supraT group tended to worsen compared with that in the SupraT-alone group after approximately one year of follow-up (p=0.0673). A retrospective study on BM published by Cacho-Diaz et al. [11] reported that OS was similar among the following groups: the SupraT-alone group (n=282, median OS: 12 months [95% CI95% CI 8.9-15.1]), the InfraT-alone group (n=44, median OS: 12 months [95% CI95% CI 7.9-16.1]) and the InfraT+supraT group (n=158, median OS: 12 months [95% CI 9.7-14.3]). Nu et al. [27] reported a retrospective study of patients with BM, and the results revealed no significant difference in OS among the SupraT-alone group (n=140), InfraT-alone group (n=24), and InfraT+supraT group (n=106, median OS: 27 months vs. 18 months vs. 25.2 months, p=0.29).

Differences in patient selection, study design, and control of confounding variables may explain the differences between our results and existing literature. Key baseline factors, local treatment

methods, as well as systemic therapy methods, were balanced between groups in this study after propensity score matching, which may have explained differences in OS. However, it must be noted that this was a retrospective cohort study, so this observation should be interpreted with caution. In a retrospective study by Sperduto et al. [28] investigating BM from colorectal cancer, multivariable Cox regression analysis found infratentorial location to be an independent risk factor for OS (HR=1.77, 95% CI 1.31-2.39; $p < 0.001$). A similar finding has been reported in BM, where brainstem involvement was found to independently predict poorer survival [11, 12].

The mechanisms that lead to the association of infratentorial BM location with poorer outcomes remain unclear. In addition to the anatomical limitations of the posterior fossa and proximity of vital centers, there may be a difference in vascular density and perfusion, hemodynamics, and oxygenation in supratentorial and infratentorial areas that may affect metastatic behavior and treatment response [29, 30]. The study of Dou et al. [16] also implied associations between infratentorial metastases and clinical factors, including younger age, male sex, lung neuroendocrine and squamous histologies, and increased Ki-67 (proliferation) expression. Furthermore, infratentorial location often has an effect on the manner of treatment, particularly surgical resection procedures and the selection of dose with radiotherapy [31], which may also affect variability between outcomes. Though our multivariable analysis raises the plausible conclusion that local high-dose radiotherapy approaches, specifically either SRT or WBRT+boost, may be associated with improved survival in infratentorial BM patients, we present these results as hypothesis-forming rather than establishing causality. Previous retrospective analyses [9, 10] have posited similar benefits in intracranial control associated with WBRT+boost compared to WBRT alone, but differences in salvage treatment strategies between groups could also play a substantial role in influencing long-term outcomes. In our study, for example, a higher fraction of patients receiving SRT had access to salvage local therapies when compared to WBRT+boost (34.4% vs. 10.1%) in our cohort. Despite these limitations, differences in salvage SRS and surgery rates may influence the findings of that randomized clinical trial (RCT), which suggested that the addition of WBRT to SRS improved both iLPFS and iDPFS, without improving OS [6].

It is possible that improved local control partially explains how local high-dose radiotherapy impactful survival effect for infratentorial brain metastases (BM) patients; nevertheless, prospective studies need to confirm this. Prior studies [18-23] have demonstrated variability in the prognostic relevance of infratentorial BM location. Nevertheless, our intention with these prior studies was not

to highlight complexity, but rather to show that two different radiotherapy treatment modalities (i.e., WBRT versus SRS) may have different effects on overall survival (OS) in infratentorial cases. It adds further credence to the rationale that patients with infratentorial metastases require local dose escalation to achieve better local control [24].

Related to safety, the rates of acute radiation toxicity showed no statistical association with the location of the lesion (p=0.766). A limitation of this study was the inability to include any potential cognitive function outcomes, long-term radiation injury, or quality of life outcome measures, when relevant data were not available. Previous studies of SRS/SRT [33-36] have identified dose, target volume, and concurrent immunotherapy as factors associated with adverse radiation outcomes. Two randomized trials comparing SRS and WBRT have demonstrated superiority of SRS on neurocognitive outcomes and quality of life. [37, 38]. As for comparable data on WBRT+boost about WBRT alone, there is limited literature; in one paired retrospective analysis [9], there was no difference in neurocognitive decline between WBRT-SIB and WBRT alone.

The primary objective of this study was to compare the prognosis of NSCLC patients with infratentorial brain metastases to that of patients with supratentorial-only metastases, and to analyze the impact of different radiotherapy modalities on survival. As shown in the results, we found that patients with infratentorial metastases had a significantly worse overall survival, suggesting that anatomical location itself is a profound prognostic factor [39, 40]. Regarding radiotherapy techniques, multivariate analysis confirmed that for patients in the infratentorial±supratentorial group, local high-dose radiotherapy strategies such as WBRT+boost or SRT significantly improved survival compared to WBRT alone ($p = 0.002$) [41-43], with no statistically significant difference in survival benefit between the two intensified radiotherapy approaches. These findings are consistent with previous studies indicating that local dose escalation plays a critical role in the control of brain metastases [44, 45].

There are important limitations of this study. First, the retrospective or observational nature of analysis imposes selection bias in our data, even with propensity score matching. Second, the variability in radiotherapy techniques, dosing strategies, and differences in systemic treatments between groups are sources of heterogeneity that could also impact the observed outcomes. Third, important prognostic markers detected early on for biomarker-based targeted therapy, such as EGFR/ALK mutation status, PD-L1 expression, and brain metastasis volumetric burden, were not uniformly available in this analysis, which may restrict our ability to adjust for biological risk

factors. Further, the studies presented were conducted over a long period (2010-2023) during which time, there were substantial advances in imaging, systemic therapy, and improvements in radiotherapy technology that may limit their generalizability. Moreover, inherent biases may exist in neurosurgeons' decision-making regarding surgical management of infratentorial metastases. Future prospective studies are warranted to further validate these findings. Finally, we did not capture adequate data related to cognitively impaired patients who suffer from delayed neurotoxicity, and may suffer cognitive function outcomes and quality of their long-term lives, especially in early deceased patients.

Though our study has limitations, we provide preliminary evidence for the hypothesis that high-dose local radiotherapy approaches may confer potential survival benefits to NSCLC patients with infratentorial brain metastases. These results should be interpreted with caution and warrant further confirmation with rigorously designed prospective clinical trials.

In conclusion, our research indicates that infratentorial brain metastases confer worse overall survival as compared to patients who only have supratentorial brain metastases in NSCLC patients. Overall survival may be augmented through high-dose local radiotherapy (such as SRT or WBRT+boost) in NSCLC patients with infratentorial brain metastases. Interestingly, infratentorial involvement was not associated with an increased rate of acute radiation toxicity as observed in this cohort. However, due to the limitations of a retrospective study, small sample size, widely heterogeneous therapeutic options, and lack of molecular and long-term toxicity outcomes, results must be interpreted with caution. Prospective, controlled trials are needed to confirm these preliminary data and further explore therapeutic strategies for this specific patient population.

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References

[1] SIEGEL R, MA J, ZOU Z, JEMAL A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29. https://doi.org/10.3322/caac.21208

[2] VERGER E, GIL M, YAYA R, VIÑOLAS N, VILLÀ S et al. Temozolomide and concomitant whole brain radiotherapy in patients with brain metastases: a phase II randomized trial. Int J Radiat Oncol Biol Phys 2005; 61: 185-191. https://doi.org/10.1016/j.ijrobp.2004.04.061

[3] PREUSSER M, WINKLER F, VALIENTE M, MANEGOLD C, MOYAL E et al. Recent advances in the biology and treatment of brain metastases of non-small cell lung cancer: summary of a multidisciplinary roundtable discussion. ESMO Open 2018; 3: e000262. https://doi.org/10.1136/esmoopen-2017-000262

[4] SUH JH, KOTECHA R, CHAO ST, AHLUWALIA MS, SAHGAL A et al. Current approaches to the management of brain metastases. Nat Rev Clin Oncol 2020; 17: 279-299. https://doi.org/10.1038/s41571-019-0320-3

[5] AOYAMA H, TAGO M, SHIRATO H, JAPANESE RADIATION ONCOLOGY STUDY GROUP 99-1 (JROSG 99-1) INVESTIGATORS. Stereotactic Radiosurgery With or Without Whole-Brain Radiotherapy for Brain Metastases: Secondary Analysis of the JROSG 99-1 Randomized Clinical Trial. JAMA Oncol 2015; 1: 457-464. https://doi.org/10.1001/jamaoncol.2015.1145

[6] AOYAMA H, SHIRATO H, TAGO M, NAKAGAWA K, TOYODA T et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006; 295: 2483-2491. https://doi.org/10.1001/jama.295.21.2483

[7] RADES D, KUETER JD, HORNUNG D, VENINGA T, HANSSENS P et al. Comparison of stereotactic radiosurgery (SRS) alone and whole brain radiotherapy (WBRT) plus a stereotactic boost (WBRT+SRS) for one to three brain metastases. Strahlenther Onkol 2008; 184: 655-662. https://doi.org/10.1007/s00066-008-1946-8

[8] LI Z, WANG J, DENG L, ZHAI Y, ZHANG T et al. Hippocampal avoidance whole-brain radiotherapy with simultaneous integrated boost in lung cancer brain metastases and utility of the Hopkins verbal learning test for testing cognitive impairment in Chinese patients: a prospective phase II study. BMC Cancer 2024; 24: 899. https://doi.org/10.1186/s12885-024-12559-1

[9] WANG X, CHEN J, LEI Z, CHEN H, ZHANG Y et al. Propensity score-matched analysis comparing hippocampus-avoidance whole-brain radiotherapy plus simultaneous integrated boost with hippocampus-avoidance whole-brain radiotherapy alone for multiple brain metastases-a retrospective study in multiple institutions. BMC Cancer 2023; 23: 796. https://doi.org/10.1186/s12885-023-11286-3

[10] POPP I, RAU S, HINTZ M, SCHNEIDER J, BILGER A et al. Hippocampus-avoidance whole-brain radiation therapy with a simultaneous integrated boost for multiple brain metastases. Cancer 2020; 126: 2694-2703. https://doi.org/10.1002/cncr.32787

[11] CACHO-DÍAZ B, LORENZANA-MENDOZA NA, CHÁVEZ-HERNANDEZ JD, GONZÁLEZ-AGUILAR A, REYES-SOTO G et al. Clinical manifestations and location of brain metastases as prognostic markers. Current problems in cancer. Curr Probl Cancer 2019; 43: 312-323. https://doi.org/10.1016/j.currproblcancer.2018.06.002

[12] EMERY A, TRIFILETTI DM, ROMANO KD, PATEL N, SMOLKIN ME et al. More than Just the Number of Brain Metastases: Evaluating the Impact of Brain Metastasis Location and Relative Volume on Overall Survival After Stereotactic Radiosurgery. World Neurosurg 2017; 99: 111-117. https://doi.org/10.1016/j.wneu.2016.11.119

[13] LE RHUN E, GUCKENBERGER M, SMITS M, DUMMER R, BACHELOT T et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol 2021; 32: 1332-1347. https://doi.org/10.1016/j.annonc.2021.07.016

[14] QUATTROCCHI CC, ERRANTE Y, GAUDINO C, MALLIO CA, GIONA A et al. Spatial brain distribution of intra-axial metastatic lesions in breast and lung cancer patients. J Neurooncol 2012; 110: 79-87. https://doi.org/10.1007/s11060-012-0937-x
[15] TAKANO K, KINOSHITA M, TAKAGAKI M, SAKAI M, TATEISHI S et al. Different spatial distributions of brain metastases from lung cancer by histological subtype and mutation status of epidermal growth factor receptor. Neuro Oncol 2016; 18: 716-724. https://doi.org/10.1093/neuonc/nov266
[16] DOU Z, WU J, WU H, YU Q, YAN F et al. The Infratentorial Localization of Brain Metastases May Correlate with Specific Clinical Characteristics and Portend Worse Outcomes Based on Voxel-Wise Mapping. Cancers (Basel) 2021; 13: 324. https://doi.org/10.3390/cancers13020324
[17] SUNDERLAND GJ, JENKINSON MD, ZAKARIA R. Surgical management of posterior fossa metastases. J Neurooncol 2016; 130: 535-542. https://doi.org/10.1007/s11060-016-2254-2
[18] ROGNE SG, HELSETH E, BRANDAL P, SCHEIE D, MELING TR. Are melanomas averse to cerebellum? Cerebellar metastases in a surgical series. Acta Neurol Scand 2014; 130: 1-10. https://doi.org/10.1111/ane.12206
[19] ENDERS F, GEISENBERGER C, JUNGK C, BERMEJO JL, WARTA R et al. Prognostic factors and long-term survival in surgically treated brain metastases from non-small cell lung cancer. Clin Neurol Neurosurg 2016; 142: 72-80. https://doi.org/10.1016/j.clineuro.2016.01.011
[20] VOGLIS S, PADEVIT L, VAN NIFTRIK CHB, KÄLIN V, BEYERSDORF B et al. Safety of microneurosurgical interventions for superficial and deep-seated brain metastases: single-center cohort study of 637 consecutive cases. J Neurooncol 2023; 165: 271-278. https://doi.org/10.1007/s11060-023-04478-1
[21] HEIMANN M, SCHÄFER N, BODE C, BORGER V, EICHHORN L et al. Outcome of Elderly Patients With Surgically Treated Brain Metastases. Front Oncol 2021; 11: 713965. https://doi.org/10.3389/fonc.2021.713965
[22] PRABHU RS, AKINYELU T, VASLOW ZK, MATSUI JK, HAGHIGHI N et al. Risk Factors for Progression and Toxic Effects After Preoperative Stereotactic Radiosurgery for Patients With Resected Brain Metastases. JAMA Oncol 2023; 9: 1066-1073. https://doi.org/10.1001/jamaoncol.2023.1629
[23] GRAHAM PH, BUCCI J, BROWNE L. Randomized comparison of whole brain radiotherapy, 20 Gy in four daily fractions versus 40 Gy in 20 twice-daily fractions, for brain metastases. Int J Radiat Oncol Biol Phys 2010; 77: 648-654. https://doi.org/10.1016/j.ijrobp.2009.05.032
[24] MAINWARING W, BOWERS J, PHAM N, PEZZI T, SHUKLA M et al. Stereotactic Radiosurgery Versus Whole Brain Radiation Therapy: A Propensity Score Analysis and Predictors of Care for Patients With Brain Metastases From Breast Cancer. Clin Breast Cancer 2019; 19: e343-e351. https://doi.org/10.1016/j.clbc.2018.11.001
[25] ROUTMAN DM, BIAN SX, DIAO K, LIU JL, YU C et al. The growing importance of lesion volume as a prognostic factor in patients with multiple brain metastases treated with stereotactic radiosurgery. Cancer Med 2018; 7: 757-764. https://doi.org/10.1002/cam4.1352
[26] PARK C, PAPIEZ L, ZHANG S, STORY M, TIMMERMAN RD. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative

radiotherapy. Int J Radiat Oncol Biol Phys 2008; 70: 847-852. https://doi.org/10.1016/j.ijrobp.2007.10.059

[27] LIN NU, LEE EQ, AOYAMA H, BARANI IJ, BARBORIAK DP et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol 2015; 16: e270-278. https://doi.org/10.1016/S1470-2045(15)70057-4

[28] SPERDUTO PW, CHAO ST, SNEED PK, LUO X, SUH J et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 2010; 77: 655-661. https://doi.org/10.1016/j.ijrobp.2009.08.025

[29] SAITO EY, VIANI GA, FERRIGNO R, NAKAMURA RA, NOVAES PE et al. Whole brain radiation therapy in management of brain metastasis: results and prognostic factors. Radiat Oncol 2006; 1: 20. https://doi.org/10.1186/1748-717X-1-20

[30] PIETRANTONIO F, APRILE G, RIMASSA L, FRANCO P, LONARDI S et al. A new nomogram for estimating survival in patients with brain metastases secondary to colorectal cancer. Radiother Oncol 2015; 117: 315-321. https://doi.org/10.1016/j.radonc.2015.08.023

[31] MAMPRE D, EHRESMAN J, ALVARADO-ESTRADA K, WIJESEKERA O, SARABIA-ESTRADA R et al. Propensity for different vascular distributions and cerebral edema of intraparenchymal brain metastases from different primary cancers. J Neurooncol 2019; 143: 115-122. https://doi.org/10.1007/s11060-019-03142-x

[32] SCHNEIDER T, KEMMLING A, SCHROEDER J, PANTEL K, GLATZEL M et al. Inverse Perfusion Requirements of Supra- and Infratentorial Brain Metastases Formation. Front Neurol 2018; 9: 391. https://doi.org/10.3389/fneur.2018.00391

[33] KANCHARLA P, IVANOV A, CHAN S, ASHAMALLA H, HUANG RY et al. The effect of brain metastasis location on clinical outcomes: A review of the literature. Neurooncol Adv 2019; 1: vdz017. https://doi.org/10.1093/noajnl/vdz017

[34] MILANO MT, GRIMM J, NIEMIERKO A, SOLTYS SG, MOISEENKO V et al. Single- and Multifraction Stereotactic Radiosurgery Dose/Volume Tolerances of the Brain. Int J Radiat Oncol Biol Phys 2021; 110: 68-86. https://doi.org/10.1016/j.ijrobp.2020.08.013

[35] ANDRUSKA N, KENNEDY WR, BONESTROO L, ANDERSON R, HUANG Y et al. Dosimetric predictors of symptomatic radiation necrosis after five-fraction radiosurgery for brain metastases. Radiother Oncol 2021; 156: 181-187. https://doi.org/10.1016/j.radonc.2020.12.011

[36] HELIS CA, HUGHES RT, GLENN CW, LANIER CM, MASTERS AH et al. Predictors of Adverse Radiation Effect in Brain Metastasis Patients Treated With Stereotactic Radiosurgery and Immune Checkpoint Inhibitor Therapy. Int J Radiat Oncol Biol Phys 2020; 108: 295-303. https://doi.org/10.1016/j.ijrobp.2020.06.057

[37] ZENG M, VERMA V, CHEN X, LI S, SUN Y et al. Stereotactic radiotherapy vs whole brain radiation therapy in EGFR mutated NSCLC: Results & reflections from the prematurely closed phase III HYBRID trial. Radiother Oncol 2024; 197: 110334. https://doi.org/10.1016/j.radonc.2024.110334

[38] BROWN PD, BALLMAN KV, CERHAN JH, ANDERSON SK, CARRERO XW et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 2017; 18: 1049-1060. https://doi.org/10.1016/S1470-2045(17)30441-2

[39] CACHO-DÍAZ B, ALVAREZ-ALVAREZ A, SALMERÓN-MORENO K, RODRÍGUEZ-MAYORAL O, SANTIAGO-CONCHA BG et al. Role of whole brain radiotherapy in the management of infratentorial metastases from lung and breast cancer. Rep Pract Oncol Radiother 2021; 26: 512-517. https://doi.org/10.5603/RPOR.a2021.0060

[40] KELLER A, DORÉ M, ANTONI D, MENOUX I, THILLAYS F et al. [Risk of radionecrosis after hypofractionated stereotactic radiotherapy targeting the postoperative resection cavity of brain metastases]. Cancer Radiother 2017; 21: 377-388. https://doi.org/10.1016/j.canrad.2017.01.017

[41] Chen Z, Zhou L, Zhao M, Cao K, Li Y et al. Real-world analysis of different intracranial radiation therapies in non-small cell lung cancer patients with 1-4 brain metastases. BMC Cancer 2022; 22: 1010. https://doi.org/10.1186/s12885-022-10083-8

[42] NI M, LIU W, JIANG A, WANG Y, SHENG Y et al. Whole Brain Radiation Therapy Plus Focal Radiation Boost May Generate Better Survival Benefit for Brain Metastases From Non-small Cell Lung Cancer. Front Oncol 2020; 10: 576700. https://doi.org/10.3389/fonc.2020.576700

[43] Karlsson AT, Hjermstad MJ, Omdahl T, Aass N, Skovlund E et al. Overall survival after initial radiotherapy for brain metastases; a population based study of 2140 patients with non-small cell lung cancer. Acta Oncol 2021; 60: 1054-1060. https://doi.org/10.1080/0284186X.2021.1924399

[44] Du TQ, Li X, Zhong WS, Tian JD, Zhao YX et al. Brain metastases of lung cancer: comparison of survival outcomes among whole brain radiotherapy, whole brain radiotherapy with consecutive boost, and simultaneous integrated boost. J Cancer Res Clin Oncol 2021; 147: 569-577. https://doi.org/10.1007/s00432-020-03359-8

[45] CHURILLA TM, WEISS SE. Emerging Trends in the Management of Brain Metastases from Non-small Cell Lung Cancer. Curr Oncol Rep 2018; 20: 54. https://doi.org/10.1007/s11912-018-0695-9

Figure Legends

Figure 1. Patient enrolment and propensity score matching flow diagram illustrating the inclusion of 392 NSCLC patients with brain metastases and the 1:1 propensity score matching process, resulting in 115 patients in each of the SupraT-alone and InfraT±supraT groups. [a]The patients in the group with brain metastases (BM) were located in only supratentorial region; [b]The patients in the group with BM located in the infratentorial region, with/without the supratentorial region; [c]The covariates 1:1 propensity score matching included radiotherapy (RT) method, age, number of BM, presence of extracranial metastases, resection of BM before RT, and targeted therapy/chemotherapy/immunotherapy following the initiation of RT. The calliper value was set to 0.06.

Figure 2. A) Intracranial local progression-free survival (iLPFS) comparison Kaplan-Meier curves

comparing iLPFS between the SupraT-alone group and the InfraT±supraT group after matching, showing no significant difference between groups (p=0.629). B) Intracranial distant progression-free survival (iDPFS) comparison Kaplan-Meier curves comparing iDPFS between the SupraT-alone group and the InfraT±supraT group, indicating no significant difference between groups (p=0.183). C) Overall survival (OS) comparison between groups Kaplan-Meier curves demonstrating significantly improved OS in the SupraT-alone group compared with the InfraT±supraT group (median OS: 35.3 vs. 24.2 months, p=0.021). D) Subgroup analysis of OS in WBRT-alone patients

Kaplan-Meier curves showing significantly longer OS in the SupraT-alone group compared to the InfraT±supraT group among patients receiving WBRT-alone ($p < 0.001$). E) Subgroup analysis of OS in SRT patients Kaplan-Meier curves comparing OS between groups among patients treated with SRT, showing no significant difference (p=0.719). F) Subgroup analysis of OS in WBRT+boost patients Kaplan-Meier curves comparing OS between groups among patients receiving WBRT+boost, showing no significant difference (p=0.759).

	SRT (%)	WBRT (%)	WBRT+boost (%)[b]	Total (%)	p value
Number of patients	151 (38.5)	132 (33.7)	109 (27.8)	392 (100)	
Sex					0.386
Male	94 (62.3)	73 (55.3)	60 (55.0)	227 (57.9)	
Female	57 (37.7)	59 (44.7)	49 (45.0)	165 (42.1)	
Age					0.024
≤ 60 years	98 (64.9)	105 (79.5)	78 (71.6)	298 (71.0)	
> 60 years	53 (35.1)	27 (20.5)	31 (28.4)	122 (29.0)	
Smoking history					0.053
Yes	75 (49.7)	48 (36.4)	42 (38.5)	165 (42.1)	
No	76 (50.3)	84 (63.6)	67 (61.5)	227 (57.9)	
Pathological type of primary tumor					0.004
Adenocarcinoma	121 (80.1)	121 (91.7)	100 (91.7)	342 (87.2)	
Squamous cell carcinoma	30 (19.9)	11 (8.3)	9 (8.3)	50 (12.8)	
No. of BM					< 0.001
≤ 3	131 (86.8)	35 (26.5)	31 (28.4)	197 (50.3)	
>3	20 (13.2)	97 (73.5)	78 (71.6)	195 (49.7)	
Location of BM					< 0.001
Only supratentorial	109 (72.2)	67 (50.8)	49 (45.0)	225 (57.4)	
Infratentorial[a]	42 (27.8)	65 (49.2)	60 (55.0)	167 (42.6)	
Largest diameter of BM					0.674
≤ 3cm	126 (83.4)	107 (81.1)	93 (85.3)	326 (83.2)	
> 3cm	25 (16.6)	25 (18.9)	16 (14.7)	66 (16.8)	
Resection of BM before RT					0.018
Yes	14 (9.3)	19 (14.4)	4 (3.7)	37 (9.4)	
No	137 (90.7)	113 (85.6)	105 (96.3)	355 (90.6)	
Existences of extracranial metastases					0.066
Yes	62 (41.1)	72 (54.5)	55 (50.5)	189 (48.2)	
No	89 (58.9)	60 (45.5)	54 (49.5)	203 (51.8)	
KPS					0.294
90-100	97 (64.2)	77 (58.3)	74 (67.9)	248 (63.3)	
≤ 80	54 (35.8)	55 (41.7)	35 (32.1)	144 (36.7)	
Systemic treatment after RT initiation	137 (90.7)	102 (77.3)	90 (82.6)	334 (85.2)	0.025
Targeted therapy	115 (76.2)	71 (53.8)	71 (65.1)	257 (65.6)	< 0.001
Immunotherapy	27 (17.9)	6 (4.5)	5 (4.6)	38 (9.0)	< 0.001

Table 1. Patient characteristics.

Abbreviations: SRT- stereotactic

radiotherapy; WBRT-whole-brain radiotherapy; WBRT+boost-WBRT with local boost; BM-brain metastasis; RT-radiotherapy; KPS-Karnofsky performance status; DS-GPA-Diagnosis-Specific Graded Prognostic Assessment

Notes: [a]147 patients with both infratentorial and supratentorial metastasis, 20 patients with infratentorial metastasis alone

[b]76 patients received WBRT with simultaneous integrated boost, 33 patients received WBRT followed by integrated boost

535 **Table 2.** Comparing the prognosis characteristics of SupraT-alone group and InfraT±supraT group before and after the 1:1 propensity score matching.

Factors	Before the 1:1 Propensity Score Match			After the 1:1 Propensity Score Match		
	SupraT-alone group (%)	**InfraT±supraT group (%)**	**p-value**	**SupraT-alone group (%)**	**InfraT±supraT group (%)**	**p-value**
Total	225 (57)	167 (43)		115 (50)	115 (50)	
RT method			< 0.001			0.793
SRT	109 (45)	42 (24)		33 (29)	35 (30)	
WBRT-alone	67 (30)	65 (39)		47 (41)	42 (37)	
WBRT + boost	49 (20)	60 (34)		35 (30)	38 (33)	
Sex: male	134 (60)	93 (56)	0.443	66 (58)	63 (56)	0.687
Age: ≤ 60	159 (71)	122 (73)	0.604	85 (75)	83 (74)	0.761
Smoking history yes	98 (44)	67 (40)	0.496	48 (43)	46 (41)	0.787
No. of BM: ≥ 4	74 (33)	121 (73)	< 0.001	68 (60)	68 (60)	1
Longest diameter of BM: ≥ 3cm	44 (20)	22 (13)	0.095	19 (17)	17 (15)	0.716
Intracranial Symptoms: yes	100 (44)	82 (49)	0.361	48 (43)	54 (48)	0.423
BM resection before the RT: yes	26 (12)	11 (7)	0.096	7 (6)	6 (5)	0.775
Existence of extracranial metastases: yes	98 (44)	91 (55)	0.032	50 (44)	58 (51)	0.287

KPS: ≤ 80	80 (36)	64 (38)	0.574	38 (34)	45 (40)	0.334
Targeted therapy after the initiation of RT: yes	148 (66)	109 (65)	0.917	72 (64)	74 (66)	0.781
Immunotherapy after the initiation of RT: yes	27 (12)	11 (7)	0.073	13 (12)	10 (9)	0.509
Chemotherapy after the initiation of RT: yes	122 (54)	66 (40)	0.004	55 (49)	60 (53)	0.506
Salvage radiotherapy/surgery after BM progression: yes	55 (24)	24 (14)	0.014	25 (22)	20 (18)	0.405
DS-GPA			< 0.001			0.135
3.0-4.0	90 (40)	37 (22)		36 (32)	33 (29)	
1.5-2.5	115 (51)	93 (56)		65 (58)	56 (50)	
0-1	20 (9)	37 (22)		12 (11)	24 (21)	

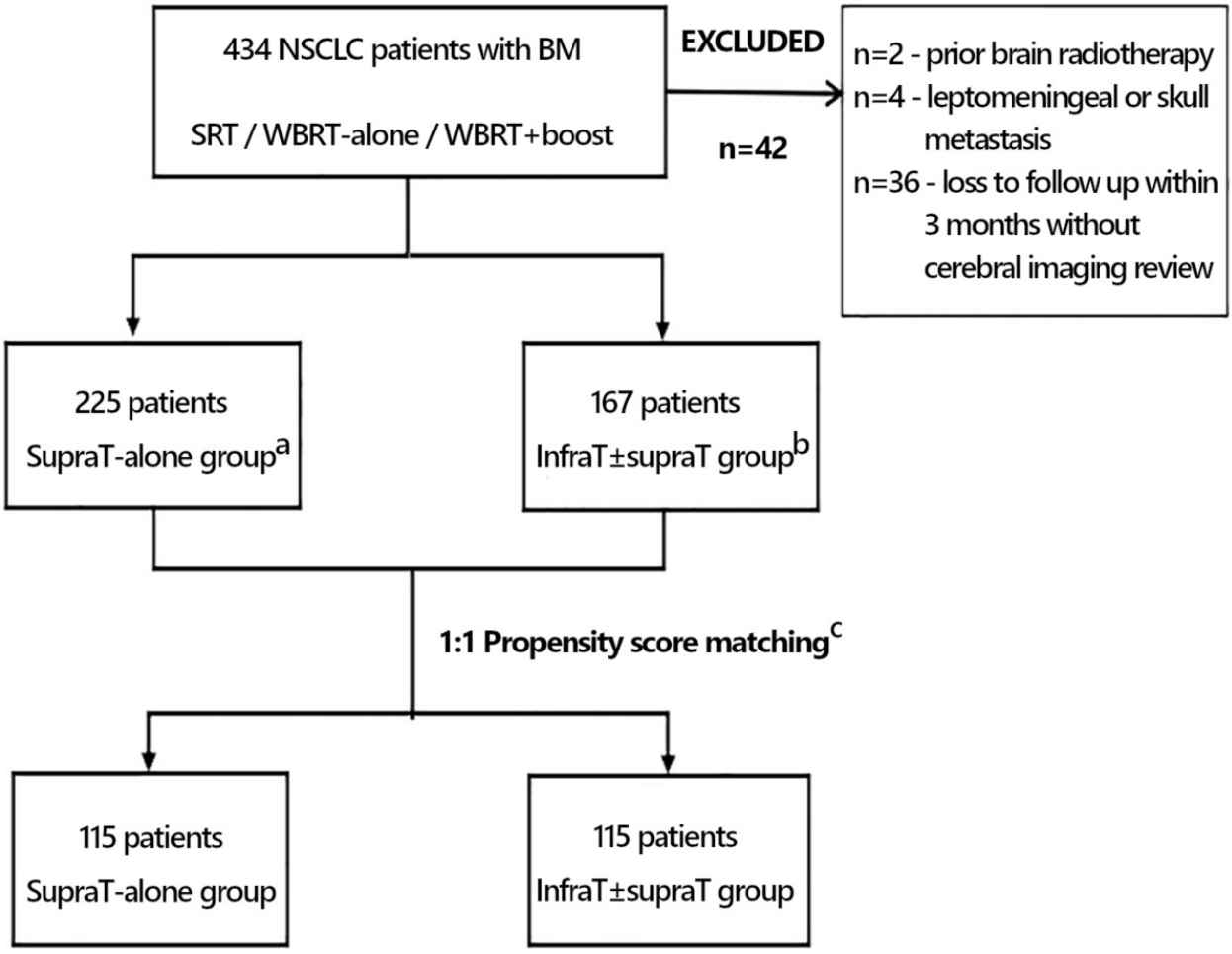
Table 3. The multivariable Cox proportional hazards regression for OS in SupraT-alone group and InfraT±supraT group respectively.

Factors	SupraT-alone group (n=225)		InfraT±supraT group (n=167)	
	p value	**HR (95% CI)**	**p-value**	**HR (95% CI)**
RT method	0.346		**0.001**	
SRT vs. WBRT+boost	0.425	0.802 (0.467-1.378)	0.108	0.570 (0.287-1.130)
WBRT+boost vs. WBRT-alone	0.149	1.421 (0.659-1.974)	**0.016**	0.542 (0.330-0.892)
SRT vs. WBRT-alone	0.639	1.140 (0.659-1.974)	**0.001**	0.309 (0.159-0.603)
Age: ≤ 60 vs. > 60 years	0.116	0.699 (0.461-1.061)	**0.002**	0.471 (0.295-0.751)
No. of BM: ≤ 3 vs.> 3	0.316	0.784 (0.487-1.262)	0.585	1.170 (0.667-2.051)
Existence of extracranial metastases: yes vs.no	0.380	1.182 (0.814-1.716)	< **0.001**	2.243 (1.438-3.501)
KPS: ≤ 80 vs. 90~100	0.826	0.957 (0.648-1.413)	0.999	1.001 (0.654-1.529)
BM resection before RT: yes vs.no	**0.031**	0.489 (0.327-0.716)	0.962	1.021 (0.427-2.443)
Targeted therapy after RT initiation: yes vs.no	< **0.001**	0.484 (0.256-0.937)	**0.017**	0.608 (0.403-0.915)
Immunotherapy after RT initiation: yes vs.no	**0.006**	0.364 (0.178-0.743)	0.082	0.389 (0.134-1.126)
Chemotherapy after RT initiation: yes vs.no	0.928	0.983 (0.671-1.439)	0.136	1.382 (0.903-2.115)
Salvage RT/surgery after BM progression: yes vs.no	0.359	0.800 (0.497-1.288)	0.896	1.039 (0.583-1.852)

Table 4. The multivariable Cox proportional hazards regression for intracranial local progression-free survival (iLPFS) and intracranial distant progression-free survival (iDPFS) in InfraT±supraT group respectively.

Factors	iLPFS (n=167)		iDPFS (n=167)	
	p-value	**HR (95% CI)**	**p-value**	**HR (95% CI)**
RT method	**0.048**		0.081	
SRT vs. WBRT+boost	0.071	2.004(0.943-4.261)	**0.042**	2.580 (1.032-6.451)
WBRT+boost vs. WBRT-alone	**0.020**	0.449 (0.228-0.882)	**0.050**	0.426 (0.181-1.000)
SRT vs. WBRT-alone	0.781	0.900 (0.427-1.894)	0.820	1.099 (0.489-2.468)
Age: ≤60 vs.>60 years	0.059	0.552 (0.298-1.022)	0.404	0.743 (0.370-1.493)
No. of BM: <4 vs.≥4	0.062	0.502 (0.244-1.035)	0.605	1.244 (0.544-2.843)
Longest diameter of BM: ≥3cm vs. <3cm	0.422	1.445 (0.589-3.545)	0.397	1.617 (0.531-4.918)
Existence of extracranial metastases: yes vs.no			**0.003**	2.878 (1.446-5.731)
BM resection before RT: yes vs.no	0.543	0.679 (0.195-2.369)	0.239	2.184 (0.594-8.021)
KPS: ≤80 vs. 90~100	0.924	0.981 (0.678-1.474)	0.621	0.854(0.457-1.597)
Concurrent systemic therapy: no vs. yes	0.558	0.852 (0.498-1.457)	0.320	1.361 (0.741-2.498)
Hippocampus protection □ no vs. yes	0.226	0.535 (0.194-1.473)	0.325	0.522(0.143-1.904)

Fig. 1 Download full resolution image



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