

Optimising Brain Metastases Management in Resource-Limited Settings: Experience with Hypofractionated Stereotactic Radiotherapy at the Salah Azaiez Institute

Optimisation de la prise en charge des métastases cérébrales en contexte de ressources limitées : Expérience de la radiothérapie stéréotaxique hypofractionnée à l'Institut Salah Azaiez

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ABSTRACT

Introduction: Radiotherapy remains a cornerstone in the palliative management of brain metastases (BM), a highly technical and evolving field treatment is increasingly personalized. Stereotactic radiotherapy (SRT) has emerged as a precise and effective alternative to whole-brain radiotherapy (WBRT), offering better neurocognitive preservation and improved local control. This study aims to evaluate the efficacy and tolerance of SRT in the management of BM at the Salah Azaiez Institute.

Methodology: We conducted a single-center, retrospective, analytical study in the radiotherapy department of the Salah Azaiez Institute between 2015 and 2022. Treatment planning was performed using the iPlan (BrainLab) and Eclipse (Varian) systems, utilizing the Conical Cone and AAA 13.7 algorithms, respectively. Techniques such as Dynamic Conformal Arc (DCA) and Volumetric Modulated Arc Therapy (VMAT) were employed. The Clinac iX (Varian), equipped with a Multi-Leaf Collimator (MLC), enabled precise beam modulation. Hypofractionated SRT was administered in three fractions of 9 Gy or five fractions of 5–6 Gy at the 80% isodose line depending of the lesion volume and site.

Results: A total of 45 patients (25 men, 20 women; median age: 57 years) were included. The primary tumors were predominantly bronchopulmonary carcinoma (60%) and breast cancer (17.8%). Solitary BM was observed in 66.6% of cases, while 33.4% had 2–3 lesions. BM presented synchronously in 35.5% and metachronously in 64.5% of cases. Two patients (4.44%) had prior prophylactic cranial irradiation for small-cell lung cancer. BM were treated in situ in 66.7% of cases. In the remaining 33.3%, stereotactic radiotherapy was performed on the surgical cavity following tumor resection. No acute toxicities were reported during SRT. With a median follow-up of 23 months (range: 6–67 months), local control rates at 1 and 2 years were 87% IC 95% (73.9–94.5 %) and 75% IC 95% (59.8–85.8 %), respectively. Overall survival rates were 75% IC 95% (59.8–85.8 %) at 1 year and 50% IC 95% (35.2–64.8 %) at 2 years. Pseudoprogression occurred in 6.66% of patients, local recurrence in 15.55%, and radionecrosis in 6.66% (asymptomatic in two cases). Salvage WBRT was required in 35.5% of cases due to symptomatic cerebral relapse.

Conclusion: SRT appears to be a promising option in the management of BM, offering effective tumor control with reduced toxicity. However, careful patient selection remains essential for optimal outcomes. Our results are encouraging, but it would be preferable to expand our series and conduct a prospective trial to achieve better outcomes. Larger prospective studies and extended follow-up of our experience are needed to further validate these findings and refine treatment strategies.

Key words: Stereotactic, Whole brain radiation therapy, Brain metastases

RÉSUMÉ

Introduction : Évaluer l'efficacité et la tolérance de la radiothérapie stéréotaxique (SRT) pour les métastases cérébrales (MC).

Méthodologie : Nous avons mené une étude rétrospective monocentrique, au sein du service de radiothérapie de l'Institut Salah Azaiez, entre 2015 et 2022. La SRT hypofractionnée a été administrée en trois fractions de 9 Gy ou en cinq fractions de 5 à 6 Gy.

Résultats : Quarante-cinq patients (25 hommes, 20 femmes ; âge médian : 57 ans) ont été inclus. Les tumeurs primitives étaient majoritairement des cancers bronchopulmonaires (CBP) (60 %) et du sein (17,8 %). Les MC étaient synchrones dans 35,5 % des cas et métachrones dans 64,5 %. Deux patients avaient reçu une irradiation cérébrale (IC) prophylactique pour un CBP. Dans 33,3 % des cas, la SRT a été réalisée sur la cavité chirurgicale après exérèse tumorale. Aucune toxicité aiguë n'a été rapportée. Avec un suivi médian de 23 mois (intervalle : 6–67 mois), les taux de contrôle local à 1 an et 2 ans étaient de 87 % et 75 %, respectivement. Les taux de survie globale étaient de 75 % à 1 an et de 50 % à 2 ans. Une pseudoprogression est survenue chez 6,66 % des patients, une récurrence locale chez 15,55 %, et une radionécrose chez 6,66 % (asymptomatique dans deux cas). Une IC totale de rattrapage était nécessaire dans 35,5 % des cas pour une rechute cérébrale symptomatique.

Conclusion : La SRT est une option prometteuse pour les MC, offrant un contrôle tumoral efficace.

Mots clés: Stéréotaxie, Radiothérapie cérébrale entière, Métastases cérébrales

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INTRODUCTION

Brain metastases (BM) represent a significant clinical challenge, occurring in approximately 20–40% of cancer patients during the course of their disease (1). This high incidence reflects both the increasing global cancer burden and advances in diagnostic imaging, which enable earlier and more accurate detection of metastatic spread (2). Historically, whole-brain radiotherapy (WBRT) has been the standard of care for BM, particularly in a palliative context. However, despite its effectiveness in disease control, WBRT is associated with significant neurocognitive decline, which can impair patients' autonomy, memory, and overall quality of life (3). Given the increasing number of long-term cancer survivors, there is a growing need for treatment strategies that balance disease control with the preservation of neurological function and quality of life (3). Stereotactic radiotherapy (SRT) has emerged as a highly precise and effective alternative to WBRT in the management of BM. This advanced radiotherapy technique allows for the targeted delivery of high radiation doses to metastatic lesions while minimizing exposure to surrounding healthy brain tissue. SRT has demonstrated superior outcomes in terms of local tumor control, reduced toxicity, and better preservation of neurocognitive function compared to WBRT, making it particularly beneficial for patients with limited brain metastases (typically ≤ 3 –4 lesions) (4,5).

In our institution, SRT has been an integral part of BM management since 2015. The aim of this study is to share our institution's experience with SRT in the treatment of BM, specifically evaluating local control, distant brain control, and treatment-related toxicity, with a particular focus on radiation-induced necrosis (RIN).

METHODS

Study Design and Population

This was a single-center retrospective study conducted in the radiotherapy department of the Salah Azaiez Institute between 2015 and 2022.

Indication for Stereotactic Radiotherapy (SRT)

Treatment decisions were made collaboratively during multidisciplinary meetings based on a thorough evaluation of clinical and paraclinical data. This assessment included disease extent and the most recent brain MRI findings. Patients were categorized using established prognostic scoring systems, including the Recursive Partitioning Analysis (RPA), the Graded Prognostic Assessment (GPA), and the Disease-Specific Graded Prognostic Assessment (DS-GPA) (6). SRT was considered appropriate for patients with an estimated survival of more than six months. However, surgery was prioritized as the first-line treatment for BM in cases of significant symptoms, such as intracranial hypertension, major neurological deficits, or large metastases (≥ 3 cm in maximum diameter). SRT was recommended as an adjuvant therapy for the tumor bed

following lesion removal. Candidates were selected based on criteria including a KPS score ≥ 70 , DS-GPA ≥ 2.5 , stable extracranial metastases, and no more than three brain metastases, regardless of resection quality.

In the postoperative setting, it was recommended to initiate stereotactic radiotherapy (SRT) within 6 to 8 weeks after surgery. This delay allowed the surgical cavity to shrink and decrease in volume, optimizing treatment accuracy. Conversely, whole-brain radiotherapy (WBRT) was preferred for patients with poor KPS less than 70, a life expectancy of less than six months, or multiple brain metastases (>3 lesions).

During the consultation, patients were systematically informed about the treatment protocol, including the sequence of procedures, techniques used, expected benefits, and potential side effects of SRT. Additionally, all patients received prophylactic corticosteroid therapy at least 48 hours before the initiation of SRT to reduce the risk of radiation-induced edema.

The technical platform

The technical platform for radiotherapy in our institution was equipped with state-of-the-art devices that ensured maximum precision and safety in patient treatments. The Philips Big Bore Scanner (CT sim) was used for CT simulation, delivering accurate imaging of the treatment area. To ensure rigorous patient immobilization, the Brain Lab Mask was utilized, with options for facial and buccal reinforcement, particularly for cranial treatments. Additionally, a non-invasive Brain Lab fixed frame was employed for imaging and positioning, ensuring precise alignment of the patient before each irradiation. The TPS iPlan (Brain Lab) used the Conical Cone algorithm for radiotherapy treatments, with cone sets ranging from 7.5 mm to 45 mm. The Eclipse (Varian) software, which employed the AAA 13.7 algorithm, allowed treatment planning using techniques such as DCA (Dynamic Conformal Arc) and VMAT (Volumetric Modulated Arc Therapy), optimizing dose distribution. Finally, the Winston-Lutz Kit and the Varian Cube were used to ensure precise quality control (QC), guaranteeing system performance and safety. The Clinac iX by VARIAN, fitted with 120/80 MLC (Multi-Leaf Collimator) with 5 mm leaves, enabled advanced beam modulation for targeted and optimal treatment. This system was enhanced by the integration of KV-OBI (KV/KV) and CBCT, which provided high-quality real-time imaging for patient monitoring during sessions.

Radiotherapy Protocol

For lesions with a long axis ≤ 3 cm or located in eloquent brain regions, hypo-fractionated stereotactic radiotherapy (SRT) was administered in three fractions of 9 Gy at the 80% isodose line (7). When tumors were in proximity to radiosensitive structures, such as the optic chiasm, brainstem, hypo-fractionated SRT was delivered in five fractions of 5–5.7 to 6 Gy at the 80% isodose line, corresponding to a biologically effective dose (BED) of 43.3 Gy. In the postoperative setting, hypo-fractionated SRT was prescribed in three fractions of 7.7 to 9 Gy or five

fractions of 6 Gy at the 80% isodose line, particularly for large surgical cavities.

Target Volume Delineation and Treatment Planning

A neuronavigation MRI was performed within two weeks prior to CT simulation. For SRT planning, a 1.5 Tesla brain MRI with T1-weighted gadolinium-enhanced and T2 FLAIR sequences, acquired in millimetric slices, was required. MRI images were fused with CT data to ensure precise target delineation. The gross tumor volume (GTV) was defined using contrast-enhanced T1-weighted MRI and merged with CT images. The clinical target volume (CTV) included a 1 mm expansion around the GTV for intact tumors and a 2 mm expansion in the postoperative setting to account for potential microscopic infiltration, following the recommendations of the Consensus Contouring Guidelines for Postoperative Completely Resected Cavity Stereotactic Radiosurgery for Brain Metastases (8). The planning target volume (PTV) was generated by adding an additional 1–2 mm margin to the CTV to compensate for uncertainties related to patient positioning and equipment precision.

Ballistic Technique and Dosimetric Optimization

SRT was typically delivered using 5–6 non-coplanar arcs with 6 MeV photons, ensuring optimal target conformity while minimizing irradiation of surrounding healthy tissues. Treatment plan optimization was performed collaboratively by a physician-physicist team, refining parameters such as arc amplitude, couch positioning, collimator rotation, and multi-leaf collimator (MLC) apertures to achieve the prescribed dose distribution while respecting organ-at-risk constraints;

Follow up

Follow-up after treatment, the patients were followed-up with clinical examinations and MRI every 3-monthly during the first 18 months and 6-monthly for the next 30 months. LR was defined as the presence of any new progressive nodular enhancement involving the resection cavity on T1 gadolinium-enhanced MRI. In some cases, MR perfusion imaging was used, and an increased cerebral blood volume was considered suspect of LR. The differential diagnosis of RN was defined as the appearance of contrast enhancement on MRI with a T1-T2 mismatch (9). Addition functional imaging were used on physician request, such as perfusion MRI in some challenging cases. Stability or decrease of contrast enhancement on the close follow-up MRI under corticoids were suggestive of RIN. The diagnosis of RIN was finally established on a set of clinical and radiological arguments and validated by a multidisciplinary team board. Histological confirmation was in the case of persistent neurological symptoms despite corticosteroid. Distant brain relapse (DBR) was defined as the presence of any new enhancing BM or leptomeningeal disease outside the irradiated volume which was diagnosed based on MRI, clinical symptoms, and/or cerebrospinal fluid cytology.

Statistic methods

For the overall survival, the follow-up begins with the diagnostic and ends with the follow-up closure. For other censored variables involving relapses, the follow-up begins with the end of SRT and ends with the last MRI imaging. OS and PFS were computed with Kaplan-Meier method.

RESULTS

Patients' characteristics

Among the 55 patients treated with stereotactic radiotherapy (SRT) for brain metastases (BM), 45 were included in the analysis. Ten patients were excluded due to irregular follow-up imaging. A total of 45 patients were included in the study, comprising 25 men and 20 women, with a male-to-female ratio of 3:2. The median age at diagnosis was 57 years (range: 40–76 years). At the time of the initial consultation, the median Karnofsky Performance Status (KPS) score was 70, with values ranging from 70 to 100.

The primary tumor types were predominantly bronchopulmonary carcinoma (60%) and breast cancer (17.8%). Other primary cancer sites included the ovaries (2 cases), rectum (1 case), colon (2 cases), melanoma (3 cases), prostate (1 case), and one case of unknown origin. The median Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) score was 2.5 (range: 2–4), with 75% of patients having a DS-GPA score above 2.5. Molecular data for ALK and EGFR mutations were available for six lung cancer patients, with DS-GPA molecular scores ranging from 3 to 4.

The BM were identified during the initial staging workup in 26.7% of cases, in asymptomatic patients. In contrast, 63.3% of cases presented with symptomatic BM, with clinical manifestations including headache, seizures, and neurological deficits (paresthesia, sensitive deficit...) (Table. 1).

BM were solitary in 66.6% of cases and multiple (2–3 lesions) in 33.4% of cases. BM presented synchronously in 16 cases (35.5%) and metachronous in 29 cases (64.5%), with a median time to appearance of 7.8 months. The brain metastases were located infratentorial in 40% of cases and supratentorial in 60%. The median initial lesion volume was 10 (2 to 16 cc). BM were treated in situ in 66.7% of cases. In the remaining 33.3%, stereotactic radiotherapy was performed on the surgical cavity following tumor resection.

Two patients had previously received prophylactic cranial irradiation (PCI) for small-cell lung cancer (4.44%). The median time from surgery to radiation was 35 days, with a range of 30 to 45 days. In 22.2% of cases, patients were oligometastatic, with other extracranial sites stabilized under systemic therapy, including chemotherapy, targeted therapy, and immunotherapy. We encountered two patients undergoing ALK-targeted therapy who required treatment interruption one week prior to the initiation of SRT for BM. Additionally, we managed three cases of patients on immune checkpoint inhibitors (one case on

nivolumab and two cases on pembrolizumab), whose treatments were paused one week before SRT.

Table 1. Patient Characteristics

Characteristics	N (%)
Sex (Male/Female)	Ratio = 3
Age (years)	Med = 57 (40-76)
Primary Histology	
NSCLC	60%
Breast cancer	17.8%
Others (ovaries/melanoma/kidney/prostate)	22.2%
KPS	Med = 80
GPA	Med = 2.5
DSGPA	Med = 2.5 (2-4)
[2.5-3,5]	75%
>= 3.5	15%
NA	10%
Asymptomatic	26.7%
Symptomatic	73.33%
Synchronous Metastasis (revealing)	35.5%
Metachronous Metastasis	64.5%
Number of Lesions	
1	66.6%
2-3	33.4%
Location of BM	
Infratentorial	40%
Supratentorial	60%

DS-GPA – Diagnosis-Specific Graded Prognostic Assessment, GPA – Graded Prognostic Assessment, KPS – Karnofsky Performance Status, Mediane – Median, NA – Not Applicable or Not Available, NSCLC – Non-Small Cell Lung Cancer

Treatment characteristics

The most commonly administered SRT protocol in our study consisted of 27 Gy delivered in three fractions, with occasional use of 30 Gy in five fractions for large lesions or cavities or organ at risk proximity. The median gross tumor volume (GTV) was 8 cc (range: 0.5–21 cc), while the median planning target volume (PTV) was 16 cc (range: 2.5–30 cc) for intact BM and 22 cc (range: 4.2–50.4 cc) in the postoperative setting. The median conformity index and heterogeneity index were 1.26 (range: 0.9–1.3) and 0.5 (range: 0.46–0.8), respectively. Dosimetric analysis of SRT for brain metastases demonstrated that the maximum dose (Dmax) was, on average, 125% of the prescribed dose (range: 120–128%), while the minimum dose (Dmin) was, on average, 90% of the prescribed dose (range: 85–92%). Among patients treated with SRT in three fractions, dose constraints for the healthy brain parenchyma included a mean V21 of 12 cc (range: 2.6–21 cc) and a mean V24 of 8 cc (range: 2.2–17 cc). In patients receiving five-fraction SRT, the mean V28 was 5 cc (range: 3–7 cc).

Outcomes

No acute toxicities were observed during the course of

SRT. However, one patient experienced an exacerbation of tonic-clonic seizures. Patient was already receiving valproate (Depakine), and a neurological consultation was obtained to adjust the valproate dosage and introduce corticosteroid therapy.

The median follow-up duration was 23 months (ranging from 6 to 67 months). A cerebral MRI was performed for monitoring, and comparative imaging studies showed a total lesion disappearance in 20% of cases. Three patients (6.66%) exhibited a pseudo progression, while 7 patients 15.55% experienced local recurrence. Stability was observed in 51.11% of cases. Additionally, there were 3 cases of RIN, accounting for 6.66% of the total which was asymptomatic in 2 cases. All 3 patients with DSGPA > 3 developed RIN, whereas none of the 37 patients with DSGPA < 3 experienced RN. The association between DSGPA > 3 and RN was statistically significant using Fisher's exact test (two-tailed $p \approx 0.001$). Regarding tumor location, 2 cases of RN occurred in infratentorial lesions ($n = 16$) and 1 case in a supratentorial lesion ($n = 24$). Fisher's exact test did not show a statistically significant association between tumor location and RN (two-tailed $p \approx 0.55$).

The Kaplan-Meier analysis for local control showed a rate of 87% IC95% (73,9–94,5 %) at 1 year and 75% IC 95% (59,8–85,8 %) at 2 years. For overall survival, the Kaplan-Meier analysis indicated a rate of 75% IC 95% (59,8–85,8 %) at 1 year and 50% IC 95% (35,2–64,8 %) at 2 years.

The rate of salvage WBRT was 35.5%, with 16 patients undergoing the procedure due to symptomatic cerebral relapse—8 cases of local recurrence and 8 of distant brain recurrence. The median interval before re-irradiation was 8 months (range: 3–15 months). For isolated BM recurrence outside the previously irradiated area, three patients experienced a second SRT, given their favorable DS-GPA scores and minimally symptomatic recurrence to postpone the cognitive side effects associated with salvage WBRT.

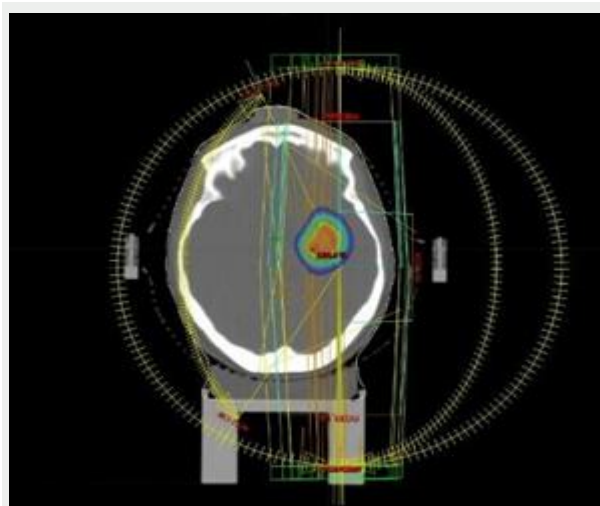


Figure 1. Axial View of Stereotactic Radiotherapy Treatment Planning with Dose Distribution

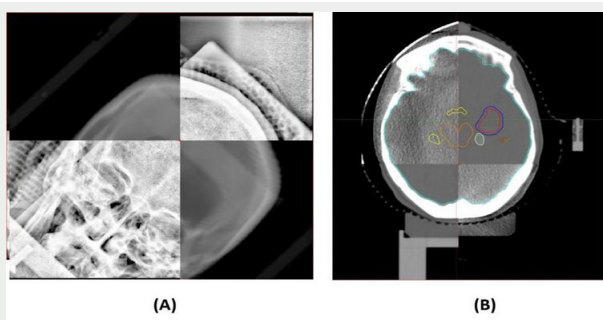


Figure 2. Control during treatment by the registration system of two orthogonal images (kV (A) and CBCT (B)) CBCT : Cone Beam Computed Tomography

DISCUSSION

This retrospective study of 45 patients treated with SRT for brain metastases showed good tolerance, with no significant acute toxicities apart from one case of seizure exacerbation managed medically. Local control rates were favorable, reaching 87% at 1 year and 75% at 2 years, with overall survival of 75% at 1 year and 50% at 2 years. Most patients achieved lesion stability, with 20% complete responses, 15.5% local recurrences, and a low rate of radionecrosis (6.6%). Salvage WBRT was required in one-third of cases, while selected patients with favorable profiles benefited from repeat SRT to delay cognitive toxicity.

Historically, WBRT was the standard technique for treating BM. However, SRT has gained prominence due to its superior local tumor control rates. The choice between WBRT and SRT is now guided by a collaborative evaluation to identify the most suitable approach for each patient. SRT is typically recommended for patients with a good life expectancy. In our study, we included only patients with a good DS-GPA score of 2.5 or higher. Regarding the number of BM, we limited our inclusion to patients with a maximum of three lesions, although the number of metastases is no longer considered the sole determinant factor. Current guidelines increasingly emphasize the concept of cumulative intracranial tumor volume (20–25 cm³) when planning radiotherapy instead of number (10,11). Indeed, for patients with large and/or multiple metastases, WBRT with or without a boost remains the preferred approach when the cumulative tumor volume exceeds 25 cm³ (11). In our study, the maximum volume of (GTV) was 21 cm³.

The single-dose prescription is widely used, particularly following the RTOG 90-05 protocol for single-dose SRT, which recommends a minimum dose of 24 Gy to the encompassing isodose for metastases measuring less than 20 mm, 18 Gy for those between 20 and 30 mm, and 15 Gy for lesions larger than 30 mm (12). In our study, we exclusively used a hypofractionated regimen with either three or five fractions for two main reasons. First, due to our learning curve, we were initially unable to deliver high single doses, such as 20 Gy. For our earliest patients, we were particularly cautious about dose uncertainty. Second, hypofractionation is increasingly encouraged and has even demonstrated superiority over single-dose stereotactic radiosurgery (SRS) in some studies (13). Minniti et al analyzed

289 patients with BM > 2 cm treated with single-fraction (SF-SRS) or HFSRT at Sant'Andrea Hospital, University of Rome Sapienza. The 1-year local control rate was significantly higher in the HFSRT group (91% vs. 77%, $P = .01$), with fewer recurrences (11 vs. 25 patients, $P = .03$). RIN was also lower in the HFSRT group (8% vs. 20%, $P = .004$). After propensity score adjustment, these differences remained significant. The findings suggest that 27 Gy in 3 fractions is an effective approach for large brain metastases, offering improved local control and a lower risk of RIN compared to SF-SRS (14). In addition, the use of hypofractionation is increasingly favored in radiation oncology because it allows for the delivery of isocytotoxic doses to tumor tissues while minimizing side effects on surrounding healthy tissues, as described by the linear-quadratic model. This approach is particularly advantageous for large-volume lesions or in post-operative setting. By splitting the total dose into multiple intermediate-sized fractions, HFSRT optimizes tumor control while reducing toxicity risks (15). DSGPA is a well-established prognostic index correlated with longer survival, and by definition, patients with higher DSGPA scores are more likely to remain at risk of developing late toxicities such as radionecrosis (6). This observation is particularly relevant in the current context, as radionecrosis represents a severe late complication, and the risk may be further amplified in patients receiving concomitant immunotherapy (19). Regarding tumor location, deep lesions are generally considered more prone to radionecrosis; however, this association was not demonstrated in our series, most likely due to the limited sample size (16). Given the small number of events, these analyses should be interpreted with caution and regarded as preliminary and exploratory, warranting confirmation in larger prospective cohorts.

In SRT remains a controversial topic; however, it offers several advantages over single-session SRT. Fractionation allows dose escalation while preserving the tolerance of organs at risk (OARs) and is particularly well-suited for the post-operative context. In this setting, poorly oxygenated tissue can benefit from fractionation, which improves treatment adaptability and outcomes (14). Despite its theoretical and practical advantages, HFSRT has not yet been prospectively compared to SRS in a randomized trial. This lack of definitive validation leaves room for uncertainty regarding its relative effectiveness. In our experience, we exclusively used fractionated SRT, with an excellent clinical outcome, high local control rates of 87% at 1 year and 75% at 2 years, with 95% confidence intervals of 90–85% and 80–67%, respectively. Our findings support the effectiveness of our fractionation strategy.

In the postoperative setting, we rely on results from large prospective trials demonstrating that postoperative SRT provides local control equivalent to WBRT while offering superior quality of life and better functional autonomy (4,5). Postoperative SRT has been shown to enhance local control at the surgical cavity by targeting residual tumor cells and reducing the risk of recurrence (8). The integration of surgery with postoperative targeted therapies highlights the importance of a multimodal approach in optimizing treatment outcomes for patients with brain metastases. Despite following the recommended guidelines, our study

observed 8 local recurrences, 5 of which occurred within the postoperative cavity. The literature reports multiple controversies regarding key aspects of postoperative radiotherapy, including the optimal timing of irradiation, fractionation schedules, dose prescription, and target volume delineation, all of which remain unclear(16) . In our approach, we adhered to the guidelines, which recommend covering the entire surgical tract regardless of the preoperative tumor location (even for deep-seated lesions), extending up to 5 mm along the dura overlying the bone flap in cases of dural contact, and including the adjacent venous sinus when sinus contact is present (17). While these guidelines ensure comprehensive coverage, they also lead to larger target volumes, which may require a reduction in the prescribed dose to adhere to dose constraints. This, in turn, could potentially impact treatment efficacy(17) .

The management of recurrent BM is increasingly informed by Brain Metastasis Velocity (BMV), a predictive index for survival following single-dose stereotactic radiotherapy (SRT). BMV stratifies patients based on the number of new metastases post-treatment into three categories: low velocity (<4 metastases; average survival 12.4 months), intermediate velocity (4–13 metastases; average survival 7 months), and high velocity (>13 metastases; average survival 4.3 months). This classification is pivotal in guiding treatment decisions, such as selecting between WBRT and additional SRT in cases of relapse (18). In our study, distant brain recurrence (DBR) occurred in 28.9% of patients, with a median time to recurrence of 8 months, or approximately one in three patients. This rate is lower than those reported in the literature, such as the 49% recurrence rate in a meta-analysis and the 40.7% DBR rate observed in the SRS group of the randomized NCCTG study, where the median time to recurrence was 6.4 months (5). Several factors may explain this discrepancy, including a shorter follow-up period and the small sample size in our study, which may not be representative. Additionally, limited access to targeted therapies and immunotherapies in our cohort may have contributed to a shorter overall survival, reducing the number of patients who experienced recurrence. These findings emphasize the importance of maintaining regular clinical and imaging follow-up, especially for patients who do not undergo WBRT.

In our study, salvage treatment was predominantly WBRT. Re-irradiation using SRT was performed in only three patients who developed distant recurrences, as our center had limited experience with stereotactic re-irradiation at the time. This highlights the importance of institutional expertise and the learning curve associated with implementing advanced re-irradiation techniques in clinical practice.

There is currently no consensus on the optimal treatment strategy for managing DBR. However, recent studies have explored ways to reduce the occurrence of new BM, emphasizing the potential synergy between SRS and systemic therapies. Immunomodulatory and targeted agents, particularly those with improved blood-brain barrier penetration, are emerging as promising options, especially for patients with targetable genetic mutations (19). The optimal treatment of recurrent or new BM

remains unclear due to the lack of high-level evidence. Common salvage treatments include WBRT, repeated SRS/SRT, or surgery. Repeated SRS/SRT appears to be a viable alternative, as it is less invasive than surgery and helps mitigate neurocognitive decline and quality-of-life deterioration compared to WBRT (5). Several small retrospective cohort studies suggest that multiple courses of SRT may be a safe and effective approach following SRT failure. Since the primary goal of first-line or repeated SRT is to delay or avoid WBRT and its cognitive side effects, selecting the right treatment approach for each patient is crucial (20). A nomogram predicting WBRT-free survival (WFS) has been developed based on a retrospective cohort of 895 patients with good performance status (0–1) who were treated with SRS for up to five newly diagnosed BM (< 4 cm) in two academic centers (21). Overall, our results underscore the need for a personalized approach to treatment selection, considering tumor characteristics (e.g., volume, location) and patient-specific factors. Further research is essential to identify optimal strategies for managing various clinical scenarios and to further validate the role of HFSRT in these settings.

This retrospective study has several limitations, including the small sample size and the retrospective design. Accordingly, the findings should be regarded as preliminary and exploratory. Confirmation will require a prospective study with adequate statistical power. Furthermore, no correlation analyses were performed to investigate potential associations between clinical or treatment parameters and outcomes. Furthermore, the study did not include an evaluation of patient quality of life or recognized memory assessment tools from the literature, such as the Mini-Mental State Examination (MMSE) score, which could have provided deeper insights into the cognitive and functional impact of treatments.

CONCLUSION

In conclusion, diagnostic and therapeutic advances in the management of BM have led to a paradigm shift in treatment approaches. With a focus on individualized care and improved quality of life, the integration of SRT, has enabled precise and effective treatment delivery. However, to strengthen the current evidence and optimize treatment strategies, it is crucial to expand our series by conducting studies on larger cohorts in our institution. Moreover, encouraging prospective clinical trials is essential to generate high-level evidence, reduce biases inherent to retrospective analyses. Another key aspect is the importance of rigorous post-treatment follow-up. Systematic and long-term monitoring is crucial for accurately assessing treatment efficacy, detecting distant intracranial recurrences at an early stage, and ensuring timely therapeutic salvage intervention. Early identification of progression or recurrence can significantly impact patient prognosis by enabling prompt adaptations in treatment strategy. Ultimately, a multidisciplinary and personalized approach, supported by robust clinical evidence and vigilant post-treatment surveillance, will be fundamental in refining BM management and improving

patient survival and quality of life.

REFERENCES

- Sacks P, Rahman M. Epidemiology of Brain Metastases. *Neurosurg Clin N Am.* oct 2020;31(4):481-8.
- Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep.* févr 2012;14(1):48-54.
- Hügel M, Stöhr J, Kuhnt T, Nögler F, Papsdorf K, Klagges S, et al. Long-term survival in patients with brain metastases-clinical characterization of a rare scenario. *Strahlenther Onkol Organ Dtsch Röntgengesellschaft Al.* avr 2024;200(4):335-45.
- Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol.* août 2017;18(8):1040-8.
- Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, 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.* août 2017;18(8):1049-60.
- Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, et al. Estimating Survival in Patients With Lung Cancer and Brain Metastases: An Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA). *JAMA Oncol.* 1 juin 2017;3(6):827-31.
- Minniti G, D'Angelillo RM, Scaringi C, Trodella LE, Clarke E, Matteucci P, et al. Fractionated stereotactic radiosurgery for patients with brain metastases. *J Neurooncol.* avr 2014;117(2):295-301.
- Soltys SG, Adler JR, Lipani JD, Jackson PS, Choi CYH, Puataweepong P, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys.* 1 janv 2008;70(1):187-93.
- Kano H, Kondziolka D, Lobato-Polo J, Zorro O, Flickinger JC, Lunsford LD. T1/T2 matching to differentiate tumor growth from radiation effects after stereotactic radiosurgery. *Neurosurgery.* mars 2010;66(3):486-91; discussion 491-492.
- Ali MA, Hirshman BR, Wilson B, Schupper AJ, Joshi R, Proudfoot JA, et al. Improving the Prognostic Value of Disease-Specific Graded Prognostic Assessment Model for Renal Cell Carcinoma by Incorporation of Cumulative Intracranial Tumor Volume. *World Neurosurg.* déc 2017;108:151-6.
- Hirshman BR, Wilson BR, Ali MA, Schupper AJ, Proudfoot JA, Goetsch SJ, et al. Cumulative Intracranial Tumor Volume Augments the Prognostic Value of Diagnosis-Specific Graded Prognostic Assessment Model for Survival in Patients with Melanoma Cerebral Metastases. *Neurosurgery.* 1 août 2018;83(2):237-44.
- Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys.* 1 mai 2000;47(2):291-8.
- Minniti G, Scaringi C, Paolini S, Lanzetta G, Romano A, Cicone F, et al. Single-Fraction Versus Multifraction (3 × 9 Gy) Stereotactic Radiosurgery for Large (>2 cm) Brain Metastases: A Comparative Analysis of Local Control and Risk of Radiation-Induced Brain Necrosis. *Int J Radiat Oncol Biol Phys.* 15 juill 2016;95(4):1142-8.
- Mousli A, Bihin B, Gustin T, Koerts G, Mouchamps M, Daisne JF. Surgical bed stereotactic radiotherapy of brain metastases: Clinical outcome and predictors of local and distant brain failure. *Cancer Radiother J Soc Francaise Radiother Oncol.* juill 2020;24(4):298-305.
- Martinage G, Geffrelet J, Stefan D, Bogart E, Rault E, Reyns N, et al. Efficacy and Tolerance of Post-operative Hypo-Fractionated Stereotactic Radiotherapy in a Large Series of Patients With Brain Metastases. *Front Oncol.* 2019;9:184.
- Noel G, Keller A, Antoni D. [Stereotactic radiotherapy of brain metastases in complex situations]. *Cancer Radiother J Soc Francaise Radiother Oncol.* oct 2019;23(6-7):708-15.
- Soliman H, Ruschin M, Angelov L, Brown PD, Chiang VLS, Kirkpatrick JP, et al. Consensus Contouring Guidelines for Postoperative Completely Resected Cavity Stereotactic Radiosurgery for Brain Metastases. *Int J Radiat Oncol Biol Phys.* 1 févr 2018;100(2):436-42.
- Farris M, McTyre ER, Cramer CK, Hughes R, Randolph DM, Ayala-Peacock DN, et al. Brain Metastasis Velocity: A Novel Prognostic Metric Predictive of Overall Survival and Freedom From Whole-Brain Radiation Therapy After Distant Brain Failure Following Upfront Radiosurgery Alone. *Int J Radiat Oncol Biol Phys.* 1 mai 2017;98(1):131-41.
- Tallet AV, Dhermain F, Le Rhun E, Noël G, Kirova YM. Combined irradiation and targeted therapy or immune checkpoint blockade in brain metastases: toxicities and efficacy. *Ann Oncol Off J Eur Soc Med Oncol.* 1 déc 2017;28(12):2962-76.
- Mousli A, Bihin B, Gustin T, Koerts G, Mouchamps M, Daisne JF. Application of a multi-institutional nomogram predicting salvage whole brain radiation-free survival to patients treated with postoperative stereotactic radiotherapy for brain metastases. *Cancer Radiother J Soc Francaise Radiother Oncol.* avr 2021;25(2):141-6.
- Gorovets D, Ayala-Peacock D, Tybor DJ, Rava P, Ebner D, Cielo D, et al. Multi-institutional Nomogram Predicting Survival Free From Salvage Whole Brain Radiation After Radiosurgery in Patients With Brain Metastases. *Int J Radiat Oncol Biol Phys.* 1 févr 2017;97(2):246-53.