Case report

RADIOSURGERY FOR MULTIPLE BRAIN METASTASES IN NON-SMALL CELL LUNG CANCER – PARADIGM SHIFT

André LARANJA[1,*], Dora GOMES[1], Sofia CONDE[1], Artur AGUIAR[1], Luísa ROLIM[2], Luísa CARVALHO[1], Andreia PIRES[1]

[1] Department of External Radiotherapy, Instituto Português de Oncologia Francisco Gentil, Porto, Portugal

[2] Department of Radiotherapy, Instituto Português de Oncologia Francisco Gentil, Coimbra, Portugal

* Corresponding author: andrelaranja79@hotmail.com, andre.laranja@ipoporto.min-saude.pt

Received: 31. 5. 2021
Accepted: 8. 9. 2021
https://doi.org/10.47724/MIRTJ.2021.i01.a002

ABSTRACT

Purpose: The purpose of this paper is to present a case of multiple brain metastases treated with LINAC-based radiosurgery (SRS).

Materials and methods: Case report and a summary review of pertinent literature regarding SRS for multiple brain metastases.

Results / Case Study: This case presents a patient with non-small cell lung cancer diagnosed with nine brain metastases who was treated with SRS. During follow-up, all brain lesions showed complete response with minimal impact on the patient's quality of life.

Discussion and Conclusion: The role of SRS is expanding, and recent published trials have showed promising results supporting its use in patients with more than four brain metastases. As our case suggests, SRS can be an effective and safe treatment for these patients and should be considered by physicians when they are presented with a similar case.

Keywords: Stereotactic; Radiotherapy; Radiosurgery; Brain metastases

INTRODUCTION

Brain metastases (BM) from non-small cell lung cancer (NSCLC) occur in approximately 10% of patients at the time of diagnosis, and this proportion is even higher in patients with advanced-stage disease (approximately 30%) (1). BM can lead to serious complications related to neurological deterioration and a diminished quality of life (QoL).

Treatment options include surgical resection, radiotherapy (RT) (whole-brain radiotherapy (WBRT) and, in selected patients, stereotactic radiosurgery (SRS)) or a combination of both. Historically, SRS has been reserved for patients with one to four BMs. However, over the last decade, this treatment modality has become more widely available, and evidence from recent clinical investigations has shown promising results supporting the use of SRS in patients with more than four BM (2,3,4).

The authors present a clinical case report of a patient with NSCLC treated with SRS for nine BM, with a complete clinical response in all brain lesions.

MATERIALS AND METHODS

All the clinical information was based on medical records, imagiologic findings, patient interview and physical examination.

A Linear accelerator TrueBeam™ STx with 120 HD multileaf collimator was used for SRS delivery.

The authors conducted a brief search on Pubmed, SCOPUS and Clinical Key database, with MESH terms: "Stereotacic radiosurgery" and "multiple brain metastases". The authors reviewed publications since 2010.

CASE STUDY

A 62-year-old man with a Karnofsky Performance Status (KPS) score of 100% was diagnosed in September 2012 with lung adenocarcinoma stage III-B according to the TNM staging system, 7th edition (5). The patient underwent concomitant chemoradiotherapy until October 2012. The chemotherapy regimen consisted of paclitaxel and carboplatin, and radiation therapy was administered at a dose of 66 Gy for the primary tumour and regional lymph nodes. One month after RT, a follow-up CT showed disease progression in the lung, and the patient was treated with systemic chemotherapy with cisplatin and pemetrexed, followed by maintenance with pemetrexed until January 2014. Due to the local progression of the pulmonary lesions, pemetrexed was stopped and docetaxel was initiated until June 2014.

In December 2018, the patient developed neurological symptoms (syncope, tremor, and speech disorders). After admission to the emergency room, he underwent brain computed tomography (CT), which revealed two ring-enhancing lesions with surrounding oedema in the occipital and frontoparietal lobes.

An additional brain Magnetic Resonance Imaging (MRI) was performed that revealed nine suspected lesions (shown in Fig. 1, right column images): lesion 1 was 6 mm in the left side of the precentral gyrus; lesion 2 was 4 mm in the left side of the precentral gyrus; lesion 3 was 17.4 mm in the anterior left frontal lobe; lesion 4 was 20.8 mm in the left paramedian parietal-occipital region; lesion 5 was 5 mm in the right paramedian occipital region; lesion 6 was a millimetric lesion in the right cerebellar hemisphere; lesions 7, 8, and 9 were millimetric lesions in the left cerebellar hemisphere. Lesions 1 through 5 were associated with extensive surrounding oedema, causing a mass effect. MRI findings, along with patient clinical history, were considered highly suggestive of BM. Steroid therapy was immediately initiated, and the patient was scheduled for SRS.

For SRS treatment planning, a CT without contrast (slices of 1 mm thickness), along with a brain gadolinium-enhanced MRI (1 mm slice thickness) were requested. All lesions were treated with LINAC-based SRS using a commercial stereotactic mask fixation system in conjunction with the iPlan 4.1.1, Brainlab treatment planning system. Target volumes – Gross tumour volume (GTV), clinical target volume (CTV), planning target volume (PTV), and organs at risk were contoured on thin-slice (1 mm) gadolinium-enhanced T1-weighted axial MR imaging obtained 10 days prior to SRS and fused to the treatment planning CT. The GTVs were delineated as contrast-enhancing tumours demonstrated on MRI scans without CTV expansion. For all lesions, a 1 mm geometric expansion was created around the GTVs to generate the PTV. Linear accelerator TrueBeam^{TM} STx with 120 HD multileaf collimator was used for treatment delivery, and all the lesions were treated using flattening filter-free 6 MV photons (plan details are described

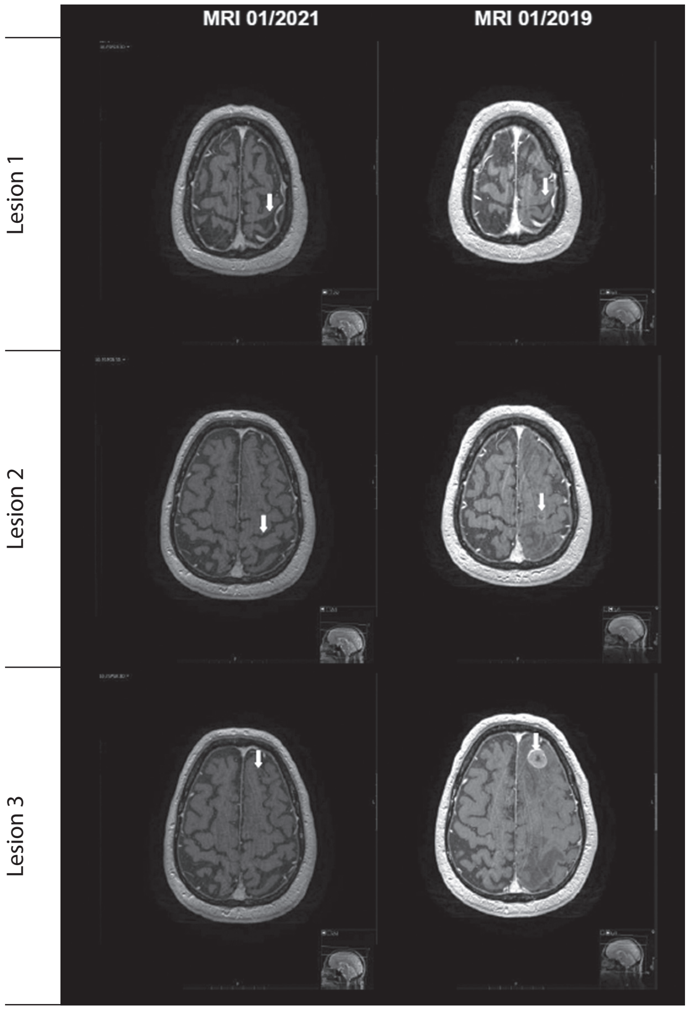

Figure 1: Brain MRI images - lesions 1, 2 and 3. On the left MRI from January 2019 (before radiotherapy treatment) and on right the MRI from January 2021 (last imagiologic follow-up)

Table 1 – Radiotherapy plan description

	Volume (cm^3)	***Total Dose / Fractions***	***Technique***	***$D_{98\%}$***	***CI***	***GI***	***Normal Brain***
PTV lesion 1 and 2	1,4	24Gy / 1fr	DA	23,3 Gy	1,35	5,36	V_{12Gy} = 5,6 cm^3
PTV lesion 3	5,82	27Gy /3 fr 1fr / day	VMAT	26,4 Gy	0,97	4,43	V_{18Gy} = 7,7 cm^3
PTV lesion 4	7,23	27Gy /3 fr 1fr / day	VMAT	26,3Gy	1,03	4,11	V_{18Gy} = 11,8 cm^3
PTV lesion 5	0,46	24Gy / 1fr	DA	21,7Gy	0,43	5,58	V_{12Gy} = 3,8 cm^3
PTV lesion 7	0,39	24Gy / 1fr	DA	22,8 Gy	0,77	5,9	
PTV lesion 6	0,41	24Gy / 1fr	DA	23,2 Gy	0,85	6,34	V_{12Gy} = 8,0 cm^3
PTV lesion 8	0,38	24Gy / 1fr	DA	23,4 Gy	1,00	7,89	
PTV lesion 9	0,36	24Gy / 1fr	DA	22,0 Gy	0,47	6,67	
	Total 16,45						

PTV: Planning target volume; fr: fraction; DA: Dynamic arcs; VMAT: Volumetric modulated arc therapy; CI: Conformity index; GI: Gradient index in Table 1). This treatment ended in January 2019, was well tolerated, and the patient did not experience headaches nor did he have any other neurological complaints.

The patient was then followed-up with periodic physical examinations and MRI imaging according to the protocols of our institution (3-4 month intervals for the first year, 6 months for the second year, and then annually). At each visit, the neurological status and the severity of complications were scored according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.03 (6), and MRI scans were also performed and analysed by the same radiologist.

In April 2019, three months after SRS, all the cerebral lesions were smaller, as well as the surrounding oedema; however, there was disease progression in the lung and the patient began treatment. In September 2020, nine months after SRS, MRI showed complete radiologic response in all the nine brain lesions despite small residual gliosis.

As of January 2021 (24 months after SRS), the patient had remained with complete response on brain MRI (shown in Fig. 1-3, left images). At this time, the lung lesion had remained stable under pembrolizumab treatment, and the patient had remained highly functional (KPS 100%) without significant neurological symptoms or other treatment toxicities detected.

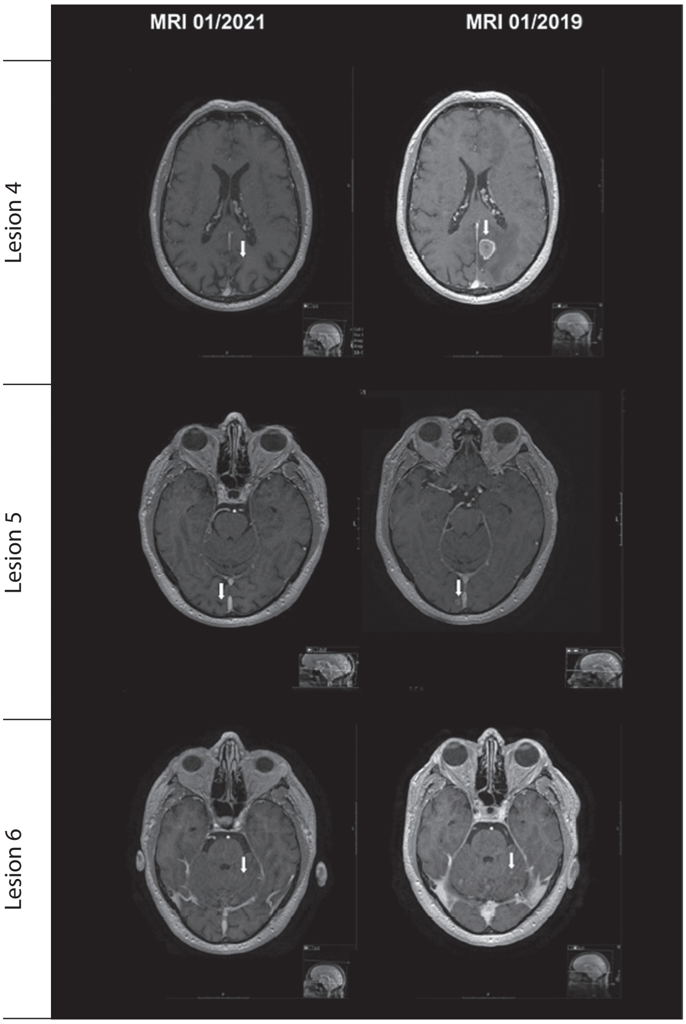

Figure 2: Brain MRI images - lesions 4, 5 and 6. On the left MRI from January 2019 (before radiotherapy treatment) and on right the MRI from January 2021 (last imagiologic follow)

DISCUSSION

The incidence of BM diagnosed in NSCLC patients has risen in recent years as a result of developments in imaging modalities, such as MRI, along with advances in systemic therapies, such as immunotherapy or targeted therapy (4). These refinements increased the sensitivity of detecting smaller lesions during screening examinations and improved survival rates. Locoregional treatment options for BM have never been as diverse as they are now (WBRT, surgical resection, SRS, or a combination of treatment modalities) (1).

The first investigations evaluating SRS were performed in patients with single lesion metastatic disease, either in combination with WBRT or as an alternative therapy to surgical resection. These results showed a lasting response to BM local control with minimal impact on the patients' QoL (1,3). With recent awareness of the neurocognitive effects of WBRT, multiple studies have evaluated SRS combined with WBRT versus SRS alone for intracranial metastatic tumours. The results have been in favour of SRS as they have shown minimal neurocognitive decline and improved QoL, with no differences in overall survival (OS) (7). Current investigations confirmed previous results and showed several other advantages of SRS over WBRT, including sparing healthy brain tissue, decreased time of treatment, improved tolerance to treatment, and reduced acute treatment-related toxicity (8).

Traditionally, SRS was used for patients with up to four BM, each lesion smaller than 3-4 cm, and it was usually performed in a single session (up to a maximum of five sessions) under the guidance of real-time imaging (9). In fact, most of the previous studies used these values as reference cut-offs; however, current evidence in the literature has suggested a benefit for patients with five or more BM (4,10). A Japanese prospective study (11,12) included more than 1 000 patients

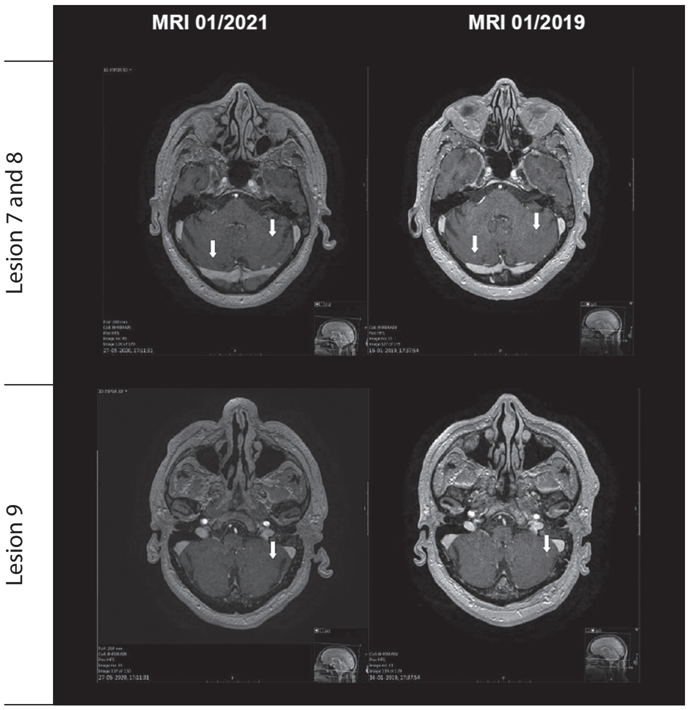

Figure 3: Brain MRI images - lesions 7, 8 and 39. On the left MRI from January 2019 (before radiotherapy treatment) and on right the MRI from January 2021 (last imagiologic follow-up)

divided into two groups of 2-4 and 5-10 brain metastases. Both groups were treated with SRS alone. In this non-inferiority study, overall survival, local failure, distant in-brain recurrences, neurological death, and toxicity were found to be similar in both arms. A retrospective cohort study showed no difference in survival between patients with > 10 and those with 2–9 brain metastases, all of whom underwent SRS monotherapy for all lesions (3).

Regarding the factors that influence survival, studies suggested that the rate of new BM development, total brain tumour volume, and the number of metastases should be considered as survival predictors in patients treated with SRS (13,14).

A multicenter retrospective study reported that patients treated with single-fraction SRS for > 4 BM, smaller total tumour volume, higher total dose, and lower volume of normal brain receiving >12 Gy were associated with increased survival (15). A single institutional retrospective study (16) included 1 017 patients with 1-10 BM treated with SRS and showed that tumour volume, KPS, and histology remained significant for OS on multivariate analysis, whereas lesion number did not. In this study, regarding histology, NSCLC and the group "Other" (including small-cell lung cancer, colorectal, ovarian, and prostate cancer) had a worse outcome than breast cancer, melanoma, and renal cell carcinoma. However, a clear definition of survival predictors in this setting must be supported by a stronger level of evidence (17).

Another significant issue that is related to survival rate is the cost at which the patient's survival is extended. One very recent study addressed this question by comparing health-related QoL between patients treated with SRS with 1-4 BM or 5-10 BM. Health-related QoL was assessed using the Functional Assessment of Cancer Therapy-Brain, a self-report questionnaire specific to patients with brain tumours. The results showed no statistical differences between the two groups, suggesting that SRS could be a useful tool for these patients when balancing disease control and QoL (18).

CONCLUSION

The present case describes a successful approach for a patient with multiple BMs treated with SRS. Patients with multiple lesions, but a low overall disease volume, might be suitable candidates for SRS. When presented with a similar clinical case, all treatment options should be considered by physicians and they should also be individually analysed considering numerous specific factors such as patient's performance status, comorbidities, lesion specificities (such as number and size of the BM), histopathologic features, and the extracranial tumour burden. Nevertheless, the authors believe that SRS should always be considered as a successful and effective approach with a few collateral effects.

REFERENCES

1. Suh JH1, Kotecha R, Chao ST, Ahluwalia MS, Sahgal A, Chang EL.. Current approaches to the management of brain metastases. Nat Rev Clin Oncol. 2020 May;17(5):279-299. doi: 10.1038/s41571-019-0320-3.

2. Yang I, Udawatta M, Prashant GN, Lagman C, Bloch O, Jensen R, et al. Stereotactic Radiosurgery for Neurosurgical Patients: A Historical Review and Current Perspectives. World Neurosurg. 2019 Feb; 122:522-531. doi:10.1016/j.wneu.2018.10.193.

3. Yamamoto M, Kawabe T, Sato Y, Higuchi Y, Nariai T, Watanabe S, et al. Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2-9 versus 10 or more tumors. J Neurosurg. 2014 Dec;121 Suppl:16-25.

4. Yamamoto M, Kawabe T, Sato Y, Higuchi Y, Nariai T, Barfod BE, et al. A case-matched study of stereotactic radiosurgery for patients with multiple brain metastases: comparing treatment results for 1-4 vs ≥ 5 tumors: clinical article. J Neurosurg. 2013 Jun;118(6):1258-68.

5. Amin MB. American Joint Committee on Cancer and American Cancer Society AJCC cancer staging manual. 8th Ed. Chicago IL: American Joint Committee on Cancer, Springer, 2017.

6. National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services. [last accessed July 14, 2020] Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. NIH publication # 09-7473. Published May 28, 2009; Revised Version 4.03 June 14, 2010.

7. Fuentes R, Osorio D, Expósito Hernandez J, Simancas-Racines D, Martinez-Zapata MJ, Bonfill Cosp X. Surgery versus stereotactic radiotherapy for people with single or solitary brain metastasis. Cochrane Database Syst Rev. 2018 Aug 20;8.

8. J.N. Greenspoon, MSc MD, P.M. Ellis, MD PhD, G. Pond, PhD, S. Caetano, MSc, J. Broomfield, MD and A. Swaminath, MD. Comparative survival in patients with brain metastases from non-small-cell lung cancer treated before and after implementation of radiosurgery. Curr Oncol. 2017 Apr; 24(2): e146–e151.

9. Knisely JPS, Apuzzo MLJ. Historical Aspects of Stereotactic Radiosurgery: Concepts, People, and Devices. World Neurosurg. 2019 Oct;130:593-607.

10. Yoshihisa Kida, Yoshimasa Mori. Radiosurgeryfor Patients with More Than Ten Brain Metastases. Cureus. 2020 Jan; 12(1)

11. Shuto T, Akabane A, Yamamoto M, Serizawa T, Higuchi Y, Sato Y et al. Multiinstitutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases from non-small cell lung cancer (JLGK0901 study-NSCLC). J Neurosurg. 2018 Dec 1;129(Suppl1):86-94.

12. Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, Yamanaka K, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol. 2014 Apr;15(4):387-95.

13. 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. 2017 May 1;98(1):131-141.

14. Andrew M Baschnagel, Kurt D Meyer, Peter Y Chen, Daniel J Krauss, Rick E Olson, Daniel R Pieper et al. Tumor volume as a predictor of survival and local control in patients with brain metastases treated with Gamma Knife surgery. J Neurosurg. 2013 Nov;119(5):1139-44.

15. Limon D., McSherry F., Herndon J. Single fraction stereotactic radiosurgery for multiple brain metastases. Adv Radiat Oncol. 2017;2:555–563.

16. Routman DM, Bian SX, Diao K, 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(3):757–764.

17. May N. Tsao, Dirk Rades, Andrew Wirth, Simon S. Lo, Brita L. Danielson, Laurie E. Gaspar, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol. 2012 Jul; 2(3): 210–225.

18. Eline Verhaak, Wietske C. M. Schimmel, Karin Gehring, Wilco H. M. Emons, Patrick E. J. Hanssens, Margriet M. Sitskoorn, Health-related quality of life after Gamma Knife radiosurgery in patients with 1–10 brain metastases. J Cancer Res Clin Oncol. 2020 Oct 6.