



# Adjuvant hypofractionated stereotactic radiotherapy after resection of single large brain metastasis in patients with oligo-metastatic disease: a strategy finally validated?

Paul Lesueur<sup>1,2</sup>, William Kao<sup>1</sup>, Julien Geffrelot<sup>1</sup>, Dinu Stefan<sup>1,3</sup>

<sup>1</sup>Centre François Baclesse, Radiation Oncology Department, 14000 Caen, France; <sup>2</sup>Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy Group, GIP CYCERON, 14000 Caen, France; <sup>3</sup>Normandie Univ, UNICAEN, UNIROUEN, ABTE, 14000 Caen, France

Correspondence to: Paul Lesueur, MD, PhD Candidate. Département de Radiothérapie, 3 Avenue du General Harris, 14000 Caen, France.

Email: Paul.lesueur89@gmail.com.

*Provenance and Peer Review:* This article was commissioned and reviewed by the Section Editor Xian-Xin Qiu, MD, PhD [Shanghai Proton and Heavy Ion Center (SPHIC), a.k.a. the Proton and Heavy Ion Center of Fudan University Shanghai Cancer Center (FUSCC), Shanghai, China].

*Comment on:* Navarria P, Pessina F, Clerici E, *et al.* Surgery Followed by Hypofractionated Radiosurgery on the Tumor Bed in Oligometastatic Patients With Large Brain Metastases. Results of a Phase 2 Study. *Int J Radiat Oncol Biol Phys* 2019;105:1095-105.

Submitted Mar 25, 2020. Accepted for publication Apr 13, 2020.

doi: 10.21037/tcr.2020.04.15

View this article at: <http://dx.doi.org/10.21037/tcr.2020.04.15>

In 2019, Navarria *et al.*, published in *International Journal of Radiation Oncology, Biology, Physics*, a prospective phase II study evaluating safety and feasibility of neurosurgery followed by adjuvant hypofractionated stereotactic radiotherapy (HSRS) (1). In fact, in order to reduce the radionecrosis rate observed with Single fraction radiosurgery (SRS), radiation oncologists used to propose adjuvant HSRS in clinical practice for the treatment of large surgical cavities but without any robust prospective data. From June 2015 to May 2018, 101 patients with single large brain metastases, defined as a lesion  $\geq 2.1$  cm in maximum diameter or  $\leq 2$  cm with conditioning mass effect, neurologic deficit or massive oedema, and with an oligometastatic disease ( $\leq 5$  metastasis) were included. Patients underwent surgical resection followed by HSRS: 30 Gy, 10 Gy per fraction, with stereotactic volumetric modulated arc therapy administered within one month after surgery. Authors hypothesized that HSRS could increase the proportion of alive and free local progression patients from 75% to 90% at 6 months.

After a median follow up time of 26 months, authors reported excellent local control rate of 100%, 98.9%, and 85.9% at 6 months, 1 year and 2 years respectively. However an unexpected very high radionecrosis rate was recorded: G2-G3 radionecrosis occurred in 26% of treated patients, after a median time of 15 months. At 6 months,

no substantial cognitive changes were found excepted in long term verbal memory. Supra tentorial localization was associated with a higher local control rate ( $P=0.02$ ) and a longer brain distant progression (BDP) free survival rate ( $P=0.01$ ), while a shorter time between diagnosis and brain metastases occurrence ( $<21$  months,  $P<0.01$ ), and residual tumor volume  $>3$  cm<sup>3</sup> were predicted of shorted BDP free survival ( $P=0.01$ ).

Finally authors concluded that a combined treatment including neurosurgery followed by HSRS on the tumor bed lead to an excellent local control with “negligible toxicities” for patients with single large brain metastasis and oligo metastatic disease.

To date, only single fraction radiosurgery was prospectively validated in randomized phase III study, as post-operative irradiation, after brain metastases resection. Indeed in comparison with observation, in Mahajan study, SRS increase the 12-month local tumor recurrence-free rate from 43% (95% CI: 31–59%) to 72% (SRS) (95% CI: 60–87%) (HR 0.46, 95% CI: 0.24–0.88,  $P=0.015$ ) (2). Second, in Brown’s study, patients receiving SRS to the surgical cavity had improved cognitive function and quality of life compared with patients receiving WBRT, with no difference in overall survival (3). Since then, SRS became a standard. However in these studies, surgical cavities volumes remained very low with for example a median volume of

only 8.9 cc (range, 0.9–28.6 cc) in Mahajan's study. So far, progressively, based on literature dealing with large non-resected brain metastases (4,5), radiation oncologists used to propose HSRS to their patients with large surgical bed instead of SRS so as to reduce radionecrosis rate and to avoid them the need of a WBRT.

When authors say that patients exhibited “negligible toxicities” while the reported symptomatic radionecrosis rate is about 26%, it could let us perplex. Indeed in retrospective studies exploring HSRS as adjuvant treatment after brain resection, 1 year local control rates were comprised between 75% and 93% and radionecrosis rates around 10% (6-10).

Three main factors could explain this unexpected radionecrosis rate: the surgical bed volume, the total dose delivered, and the PTV margin used.

First the median surgical cavity volume was much larger than all other reported series: 31.27 cm<sup>3</sup> (2.92–203 cm<sup>3</sup>) versus 17.5 cm<sup>3</sup> maximum in previous series. Though, we could wonder if investigators have really delivered a 3×10 Gy schedule for the 203 cm<sup>3</sup> surgical bed!

Second, a 3 mm PTV margin, which is quite large and unusual, has clearly increased the radionecrosis rate. A 1 or 2 mm margin is now preferred.

Finally, the total dose is much higher than other studies reporting lower radionecrosis rate. But this schedule led to excellent local control and thus, despite very large volume metastasis at diagnosis.

As usual, It's all about balancing benefits and risks!

We could regret that authors did not chose a statistical model such as the two-stage phase 2 design proposed by Bryant and Day for example, which allows to combine both safety and efficacy as primary endpoint (11).

In conclusion, considering this phase II, and retrospective studies, adjuvant hypofractionated stereotactic radiotherapy after resection of single large brain metastasis in patients with oligo metastatic disease can be considered as a validated strategy. However, radiation oncologist should pay attention to reduce radionecrosis rate by adapting their PTV margins, by following contouring guidelines or by reducing the dose per fraction or total dose (3×8 or 3×9 Gy for example) in case of very large volume. Otherwise, in the future all authors should report their dosimetry prescription according to ICRU91, so as, to make inter comparison easier (12).

## Acknowledgments

*Funding:* None.

## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.04.15>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. Navarra P, Pessina F, Clerici E, et al. Surgery Followed by Hypofractionated Radiosurgery on the Tumor Bed in Oligometastatic Patients With Large Brain Metastases. Results of a Phase 2 Study. *Int J Radiat Oncol Biol Phys* 2019;105:1095-105.
2. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:1040-8.
3. Brown PD, Ballman KV, Cerhan JH, 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;18:1049-60.
4. Lehrer EJ, Peterson JL, Zaorsky NG, et al. Single versus Multifraction Stereotactic Radiosurgery for Large Brain Metastases: An International Meta-analysis of 24 Trials. *Int J Radiat Oncol Biol Phys* 2019;103:618-30.
5. Blonigen BJ, Steinmetz RD, Levin L, et al. Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2010;77:996-1001.
6. Martinage G, Geffrelot J, Stefan D, 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.
7. Wang CC, Floyd SR, Chang CH, et al. Cyberknife hypofractionated stereotactic radiosurgery (HSRS) of resection cavity after excision of large cerebral metastasis: efficacy and safety of an 800 cGy × 3 daily fractions regimen. *J Neurooncol* 2012;106:601-10.
  8. Eaton BR, La Riviere MJ, Kim S, et al. Hypofractionated radiosurgery has a better safety profile than single fraction radiosurgery for large resected brain metastases. *J Neurooncol* 2015;123:103-11.
  9. Doré M, Martin S, Delpon G, et al. Stereotactic radiotherapy following surgery for brain metastasis: Predictive factors for local control and radionecrosis. *Cancer Radiother* 2017;21:4-9.
  10. Minniti G, Esposito V, Clarke E, et al. Multidose stereotactic radiosurgery (9 Gy × 3) of the postoperative resection cavity for treatment of large brain metastases. *Int J Radiat Oncol Biol Phys* 2013;86:623-9.
  11. Bryant J, Day R. Incorporating toxicity considerations into the design of two-stage phase II clinical trials. *Biometrics* 1995;51:1372-83.
  12. International Commission on Radiation Units and Measurements (ICRU) [Internet]. [cité 24 mars 2020]. Available online: <https://icru.org/content/reports/icru-report-91-prescribing-recording-and-reporting-of-stereotactic-treatments-with-small-photon-beams>

**Cite this article as:** Lesueur P, Kao W, Geffrelet J, Stefan D. Adjuvant hypofractionated stereotactic radiotherapy after resection of single large brain metastasis in patients with oligo-metastatic disease: a strategy finally validated? *Transl Cancer Res* 2020;9(5):3177-3179. doi: 10.21037/tcr.2020.04.15