



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

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In 2019, Navarra *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).

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