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Review Article

Stereotactic Radiosurgery for Operable Brain Metastases: A Literature Review

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Abstract

Brain metastases (BM) are a significant cause of morbidity and mortality in patients with metastatic cancer, with an incidence of up to 65% during the course of illness. Options for patients with BM had been limited for a long time to whole brain radiotherapy (WBRT) or supportive care. The development of treatment was viewed as an impressive oncologic event. While surgery remains the most important radical treatment, adjuvant radiotherapy is proven to be essential to prevent local and distant brain failure. Although, post-operative WBRT was associated to higher rate of intracranial control, there is no impact on overall survival (OS). The neurocognitive decline after WBRT, has led to the development of post-operative stereotactic radiotherapy (SRT) on the surgical bed. Randomized trials conclude to the safety of using hypo fractionated high doses with a BED10Gy > 40Gy for cavity volumes in order to sterilize residual tumor cells in the hypoxic surgical bed. In the other hand, preoperative SRT on BM is a promising alternative since it leads to less rate of radionecrosis (RN). In addition, it offers the same therapeutic results in term of local control with a lower rate of leptomeningeal dissemination comparing to post-operative SRT. Metanalalysis showed better compliance to the treatment for patients and less contouring variability and uncertainties for physiciens. This article is a brief summary of the most important trials about management of operable BM.

Keywords: Brain metastases; Stereotactic radiotherapy, Resection; Radionecrosis; Leptomeningieal; Relapse

Abbreviations

BM: Brain Metastases; WBRT: Whole Brain Radiotherapy; SRT: Stereotactic Radiotherapy; LMR: Leptomeningeal Relapse; RN: Radionecrosis; SRN: Symptomatic Radionecrosis; LR: Local Recurrence; LMD: Leptomeningeal Disease; DBM: Distant Brain Metastases; OS: Overall Survival; KPS: Karnofsky Performance Scale; DS-GPA: Diagnosis-Specific Graded Prognostic Assessment; NMDA: N-Methyl-D-Aspartate; IMRT: Intensity Modulated Radiotherapy; VMAT: Volumetric Modulated Arc Therapy; LC: Local Control; DBF: Distant Brain Failure; CT: Computed Tomography; HSRT: Hypofractionated Stereotactic Radiotherapy

Introduction

Brain metastases (BM) are the most frequent tumors of the central nervous system. Their incidence seems to be increasing due to better screening techniques to early identification of small BM [1,2]. As systemic therapies have become more efficacious in patients with metastatic disease, improved survival rates are now being observed. About 60% of patients with systemic disease have developed intracranial lesions. The most frequent primary tumor is lung and breast cancer followed by melanoma, renal and colorectal cancer. Most lesions are diagnosed when they become symptomatic.

Systematic imaging screening leads to early detection of 10% in asymptomatic patients. Surgery and whole brain radiotherapy (WBRT) have been the two main therapeutic options available until the initiation of stereotactic radiotherapy (SRT). SRT is a focused ablative radiation treatment delivered with sub-millimeter precision to the tumor localized in three- dimensions in 1-5 fractions leading to better neurocognitive results and quality of life for intact BM as well as post-operative lesion. Recently, preoperative SRT has become an interesting alternative demonstrated both retrospective and prospective trials with similar local control and less leptomeningeal relapses (LMR) comparing to post-operative SRT as well as better tolerance with less radionecrosis (RN) [3]. In this article, we aim to provide a clinical review on current status and recent advances in the management of resection cavity of BM. We also report the outcomes of pre-operative SRT on local control and radiation related toxicity for intact BM.

Brain Metastases Resection for Operable BM

The main purpose of surgery is to achieve a gross total resection while protecting the normal functioning brain tissue. The MD Anderson center recommend to perform an “en bloc” resection rather than a piecemeal resection, as it decreases the risk of tumor cells dissemination in the surgical tract as well as prevents from local recurrence (LR) as well as leptomeningeal disease (LMD) [4,5].

Histopathological proof may be necessary in situation of unknown primary tumor, so surgery may be mandatory to differentiate BM from primary brain tumor. Peritumoral edema or a large tumor causing a mass effect, may require an urgent surgical intervention to a rapid relief symptom for single or multiple BM up to 3 [6,7]. After surgery, Patel et al. identified the main two factors of LR: piecemeal

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resection and a large tumor volume higher than 9.7cm^3 [8]. Surgery of BM is an important radical treatment option, which improves OS when compared to WBRT alone [9]. However, the LR rate approaches 60–70%. Multiple randomized trials have concluded that adding post-operative radiotherapy (WBRT/SRT) is mandatory to provide satisfactory intracranial control and decrease the neurological death despite the improvements in neurosurgical techniques and cortical mapping [8-11].

Role of WBRT in the Management of Post-Operative BM

Since 1990, adjuvant WBRT has been established as an effective therapeutic option after surgical resection with a benefit of median survival up to 9-10 months [9]. Patchell et al. compared surgery alone to surgery followed by WBRT for single lesion and demonstrated a significant reducing in LR of BM from 46% to 10 %. Time to LR was longer with combined treatment 52 weeks *vs.* 27 weeks [12].

The rate of distant brain metastases (DBM) and LMD was also significantly lower in the arm of WBRT 14% *vs.* 37%, with a rapid time to recurrence in the arm of surgery alone 220 weeks *vs.* 53 weeks. These results can be explained by the fact that microscopic undetectable tumor cells were better sterilized by adjuvant WBRT comparing to surgery alone, which lowers the rate of DBM. Post-operative WBRT had also improved the neurologic death rate 14% *vs.* 44% [12]. However, there is no difference in the overall survival (OS) between the two arms. These findings are also supported by McPherson et al., who concluded to a clear benefit of adjuvant WBRT for high risk group of patients: tumor size > 3 cm and with active systemic disease. WBRT is also a valid therapeutic option when there are multiple lesions, low KPS < 70% and specifically for short expected long-term survival defined as a low DSGPA score <2.5 [13]. However, WBRT impacts the neurocognitive functions in a biphasic pattern: a temporary subacute decline with a peak at four months, then a late delayed irreversible impairment after several months to one year [14]. Neurocognitive outcomes are highly correlated to the initial pre-treatment cognitive status which depends on the lesion volume and its location. The anatomopathological damages are demyelination, disruption of the blood-brain barrier, oxidative and pro-inflammatory stress and impairment of neurogenesis [15]. In this optic, a randomized trial by Brown et al. has evaluated the use of pharmacotherapy during and after RT and chose the N-methyl-D-aspartate NMDA antagonist « memantine », which is a valid neuroprotector [16]. It showed a considerable delay in the cognitive deterioration and a reduced decline rate of memory, processing speed and executive function. Hippocampal avoidance in WBRT using intensity modulated RT (IMRT/ VMAT) is an interesting modality for cognitive preservation, based on the theory that injury to the neural stem cell compartment of the hippocampal dentate gyrus represents an important mechanism of radiation-induced cognitive decline [15].

Role OF SRT in the Management of Post - Operative BM

The important neurocognitive decline in patients treated with WBRT has led to the introduction of SRT as an attempt to improve patients' life quality. A randomized phase III trial by Brown et al. showed no difference in OS between the two arms adjuvant WBRT or adjuvant SRT in a post-operative setting.

However, cognitive deterioration free survival was longer in the SRT arm and cognitive decline rate at 6 months was lower 52% *vs.* 85% [17]. Several retrospective studies reported local control (LC) and OS rates of 70% to 90% and of 50% to 70% at 12 months, respectively, following SRT [18].

Two recent randomized trials have established the efficacy of SRT in the post-operative setting. In the first study, Mahajan et al. compared observation to SRT after surgical resection of 1 to 3 lesions with a diameter < 4cm, and showed an increased rate of LC at 1 y of 72% *vs.* 43% in the observation group.

The efficiency of SRT in maintaining LC at 1y was correlated to tumor size, 74% for a diameter less than 3cm and 44% for 3cm or more, lesions with a diameter less than 2.5 cm had a LC rate of 91%. No difference in OS was observed between the two groups [19]. This article was especially interesting to show that large tumor needs to receive a dose superior to 14 Gy in a single fraction, which was corresponding to an insufficient biological effective dose (BED10Gy) < 33.6 Gy to control microscopic disease. The second prospective trial, NCCTG N107C/CEC.3 prospective randomized 194 patients with one resected BM to either SRT (12 to 20 Gy) to WBRT (30-37.5 Gy in 10-15 daily fractions), reported better preservation of neurocognitive function and quality of life in patients who received SRT with no negative impact on survival, although adjuvant WBRT was associated with better intracranial control compared to SRT. The negative impact of WBRT on cognitive function, quality of life and functional independence remained persistent over time [17].

Based on this accumulated evidence, post-operative SRT has become the standard of care after surgery of BM. However, SRT treats only the resection cavity of the initial lesion which explains the high rate of intracranial recurrence. When compared to WBRT, which eradicates microscopic tumor cells anywhere in the brain, SRT has a higher risk of developing DBM. So, Surveillance imaging following SRT is mandatory to early detect distant brain failure DBF and to propose salvage therapy. Typically, magnetic resonance imaging was prescribed at a regular interval of 2-3 months after SRT.

The optimal management of resected BM remains challenging and several issues remain to be resolved, including the timing of postoperative SRT, optimal schedule (dose prescription / fractionation), and target delineation of the surgical bed [18]. In fact, the tumor bed can't be easily defined on MRI, specially that edema, hematoma or fibrosis can lead to uncertainties of the target volume. These dynamic volumetric changes are variable from patient to another, and may be change in the same patient between the planification CT scan and the day of treatment. There is a lack of consensus guidelines in delineation, most trials recommend a margin of 2 mm around the surgical cavity, but Soliman et al. published an experts' consensus concluding to more generous margins if the initial tumor was in contact with the dura meta or a venous sinus, along with the inclusion of the surgical tract seen on MRI [20]. For large volume, SRT with single fraction may be insufficient to cover the entire target volume. Hypo fractionated stereotactic radiotherapy (HSRT) is generally delivered in 2–5 fractions using frameless, mask-

based SRT systems with the same level of accuracy as radiosurgery. Most common schedules were 24–27 Gy in 3 fractions and 30–35 Gy in 5 fractions with a reported similar 1 year LC of 85–95%. However, lower doses (5 × 5 Gy or 3 × 7 Gy) were associated with lower LC rate. Therefore, the optimal dose that should be delivered to the resection cavity in order to achieve excellent control is BED10Gy > 40Gy [21]. It may offer the clinician the safety to use generous treatment volumes and allow a dose escalation without increasing the rate of RN [21]. The meta-analysis of 50 trials, published by Akanda et al. showed that HFSRT (2-5 fractions) offered better LC rates at 1year of 87.3% compared to 80% with single fractions [22]. Its recommended to use HFSRT at the dose of 27-35Gy in 3-5 fractions for lesions larger than 3cm, which increase LC rate to 81-93%, higher than the 44% observed in Mahajan's trial where SRT was delivered in a single fraction [19]. With the respect of healthy tissue constraints, radiation doses greater than 16 Gy in one fraction, 24 Gy in 3 fractions, and > 27.5 Gy in 5 fractions should be recommended to safely improve local cavity control 150 [18].

Interestingly, in the majority of retrospective and prospective series the rate of a symptomatic RN was about 5- 10 % [18]. In a systematic review and meta-analysis on postoperative SRT following excision of brain metastases, Akanda et al. observed a similar incidence of RN of less than 10% In 28 out of 36 studies using different imaging modalities [22]. HFSRT may represent a better approach for large cavities considering the low risk of RN after HSRT for volumes larger than 20-25 ml [22]. The risk of LMD after SRT of the tumor bed has been found to be around 8-25% [23]. Recent series reported an incidence of 6–15% at 1 year [18]. Its development is most likely due to iatrogenic dissemination of tumor viable cells into cerebrospinal fluid and meninges at the moment of resection. Different predictor factors were reported: tumor histology, tumor size and location (typically the posterior fossa), pial involvement and type of surgery especially with piecemeal instead of en bloc resection [16,24].

Pre-Operative Stereotactic Radiotherapy in the Management of Operable BM

Pre-operative SRT is an interesting new option for the management of BM to improve LC and potentially minimize the risk of LMD since it treats tumor cells prior to potential iatrogenic dissemination at the time of resection. It offers a high local rate while avoiding the neurocognitive decline and the contouring uncertainties due to a well limited lesion easily defined on the MRI.

Therefore, there is no need to add margins of normal brain tissue because of fewer uncertainties of the dynamic volumetric changes of the cavity. Asher et al. gevaluated the clinical outcome of pre-operative SRT in 51 patients and concluded to an overall survival of 77.8%, 60% and 29.9% at 6, 12 and 24 months respectively [25]. LC rate was 97.8%, 85.6% and 71.8% at 6, 1 and 2 years respectively [25]. The DBF rate was 38.2% with a median time of appearance of 8 months. No LMD were observed and 6/8 of the failures were tumors either adherent to the dura mata or to the draining veins which make gross total resection very difficult. The LR was more likely with tumors > 10cc or >3.4cm. No increase in the surgical complications or perioperative mortality was observed [25]. These results are supported by the study of Prabhu et al. which enrolled 117 patients (125 lesions), pre-operative SRT was delivered in a single fraction at a median dose of 15 Gy and surgery was performed after 2 days. LR at 2 years was 25.1%, DBF 60.2%, LMD 4.3% [26]. In addition, contouring an intact tumor for pre-operative SRT is easier than tumor bed, so additional margins are no longer needed which results in a lower risk of RN. In the study of Prahbu et al., only 4.8 % developed symptomatic RN [26]. Patel et al. conducted a comparative study between pre and post-operative SRT among 180 patients (189 lesions) with a median follow up of 24.6 months. No margins were used in pre SRT *vs.* margins of 2 mm in the post SRT arm. The median dose delivered was 15Gy with pre SRT and 18Gy with post SRT [3]. The only predictor of OS, which was similar in the two arms, was the absence of active systemic disease. No difference in LR at 1 year was observed between the two groups: 15.9% with pre SRT *vs.* 12.6% in post SRT. DBF at 1 year was also similar. Pre SRT had significantly lower LMD rate at 1 y than post SRT, 3.2% and 8.3% respectively. The median time to the development of LMD was 14 months and the presence of multiple lesions was the significant predictive factor [3].

Many studies showed no complications of pre SRT, so surgery was always performed in time before the appearance of radiation induced inflammation. In a phase 2 trial, 20.4% of the enrolled patients did not undergo post SRT due to the post-operative morbidity [27]. In addition, the surgical cavity tissue is very hypoxic surgical bed evolving slowly to a fibrous scar, which requires high doses of RT in order to eradicate any residual tumor cells. The irradiation of a viable well oxygenated tumor with a functional vascularization in pre-operative SRT does not require the delivery of a high dose for cells' sterilization, so a dose reduction of 20% becomes possible for similar results [3]. The study of Patel et al. showed a significant difference in RN rate at 1-year between the two groups: 14.6% in post SRT *vs.*1.5% in pre SRT, and 2yrs rate of 16.4% and 4.9% respectively [3]. The conformity index, absence of active systemic disease and location of the BM are considered as predictive factors of symptomatic (RN). The pre-operative SRT decreases the risk of RN and therefore prevents the occurrence of neurological toxicities to the normal functioning organs.

The treatment of BM is an important step in oncology since it has a significant impact on the overall prognosis and on the pursuit of systemic treatment. Although SRT has helped preserve patients' cognitive functions, it needs to be further evaluated in order to standardize the dose to deliver, the fractionation and the radiation technique. Hippocampal avoidance and the use of neuro protectors in combination with RT are also promising options that need to be thoroughly tested. In this regard, two prospective trials randomizing patients undergoing pre-operative SRT versus post-operative SRT are currently recruiting patients (ClinicalTrials.gov, NCT03741673 and NCT03398694).

Conclusions

Preoperative SRT is a promising therapeutic option for brain metastases. It offers local control and overall survival rates similar to the current protocols while decreasing the risk of symptomatic RN and LMD seen with post SRS. Further studies need to be conducted in order to validate its feasibility and its safety. No available studies were found to evaluate its neurocognitive outcomes but the limited volume irradiated spares the cognitive parts of the brain. A coordination between radiotherapists and neurosurgeons is

necessary, and the decision to perform SRT always needs to be taken in a multidisciplinary board.

Authors' Contributions

Both authors contributed equally to the final version of the publication, have read, and approved the manuscript.

References

1. Kumar AMS, Miller J, Hoffer S, et al. Postoperative hypofractionated stereotactic brain radiation (HSRT) for resected brain metastases: improved local control with higher BED10. Journal of Neuro-Oncology. 2018; 139: 449-454.

2. Cagney DN, Martin AM, Catalano P, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. Neuro-Oncology. 2017; 19: 1511-1521.

3. Patel KR, Burri SH, Asher AL, et al. Comparing Preoperative With Postoperative Stereotactic Radiosurgery for Resectable Brain Metastases. Neurosurgery. 2016; 79: 279-285.

4. Suki D, Hatiboglu MA, Patel AJ, et al. Comparative risk of leptomeningeal dissemination of cancer after surgery or stereotactic radiosurgery for a single supratentorial solid tumor metastasis. Neurosurgery. 2009; 64: 664-676.

5. Suki D, Abouassi H, Patel AJ, et al. Comparative risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa. Journal of Neurosurgery. 2008; 108: 248-257.

6. Paek SH, Audu PB, Sperling MR, Cho J and Andrews DW. Reevaluation of surgery for the treatment of brain metastases: review of 208 patients with single or multiple brain metastases treated at one institution with modern neurosurgical techniques. Neurosurgery. 2005; 56: 1021-1034.

7. Aziz Hatiboglu, David M Wildrick, Raymond Sawaya. The role of surgical resection in patients with brain metastases Mustafa. E cancer medical science. 2013; 7: 308.

8. Patel AJ, Suki D, Hatiboglu MA, Abouassi H, et al. Factors influencing the risk of local recurrence after resection of a single brain metastasis. Journal of Neurosurgery. 2010; 113: 181-189.

9. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A Randomized Trial of Surgery in the Treatment of Single Metastases to the Brain. New England Journal of Medicine. 1990; 322: 494-500.

10. Aoyama H, et al. 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.

11. Kocher M, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J. Clin. Oncol. 2011; 29: 134-141.

12. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative Radiotherapy in the Treatment of Single Metastases to the Brain. JAMA. 1998; 280.

13. McPherson CM, Suki D, Feiz-Erfan I, Mahajan A, Chang E, Sawaya R, et al. Adjuvant whole-brain radiation therapy after surgical resection of single brain metastases. Neuro-Oncology. 2010; 12: 711-719.

14. Tallet AV, Azria D, Barlesi F, Spano J-P, Carpentier AF, Gonçalves A, et al. Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. Radiation Oncology. 2012; 7: 77.

15. Robin TP & Rusthoven CG. Strategies to Preserve Cognition in Patients With Brain Metastases: A Review. Frontiers in Oncology. 2018: 8.

16. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro-Oncology. 2013; 15: 1429-1437.

17. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton A, 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. The Lancet Oncology. 2017; 18: 1049-1060.

18. Minniti G, Niyazi M, Andratschke N, Guckenberger M, Palmer JD, Shih H, et al. Current status and recent advances in resection cavity irradiation of brain metastases. Radiation Oncology. 2021; 16.

19. 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. The Lancet Oncology. 2017; 18: 1040-1048.

20. 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. International Journal of Radiation Oncology*Biology*Physics. 2018; 100: 436-442.

21. Vellayappan BA, McGranahan T, Graber J, Taylor L, Venur V, Ellenbogen R, et al. Radiation Necrosis from Stereotactic Radiosurgery—How Do We Mitigate? Current Treatment Options in Oncology. 2021; 22.

22. Akanda ZZ, Hong W, Nahavandi S, Haghighi N, Phillips C, Kok DL. Post-operative stereotactic radiosurgery following excision of brain metastases: A systematic review and meta-analysis. Radiotherapy and Oncology. 2019.

23. Atalar B, Modlin LA, Choi CY, et al. Risk of leptomeningeal disease in patients treated with stereotactic radiosurgery targeting the postoperative resection cavity for brain metastases. Int J Radiat Oncol Biol Phys. 2013; 87: 713-718.

24. Ojerholm E, Lee JYK, Thawani JP, Miller D, O'Rourke DM, Dorsey JF, et al. Stereotactic radiosurgery to the resection bed for intracranial metastases and risk of leptomeningeal carcinomatosis. Journal of Neurosurgery. 2014; 75-83.

25. Asher AL, Burri SH, Wiggins WF, Kelly RP, Boltes MO, Mehrlich M, et al. A New Treatment Paradigm: Neoadjuvant Radiosurgery Before Surgical Resection of Brain Metastases With Analysis of Local Tumor Recurrence. International Journal of Radiation Oncology*Biology*Physics. 2014; 88: 899-906.

26. Roshan S Prabhu, Katherine R Miller, Anthony L Asher. Preoperative stereotactic radiosurgery before planned resection of brain metastases: updated analysis of efficacy and toxicity of a novel treatment paradigm. J Neurosurg. 2018; 1-8.

27. Brennan C, Yang TJ, Hilden P, et al. A phase 2 trial of stereotactic radiosurgery boost after surgical resection for brain metastases. Int J Radiat Oncol Biol Phys. 2014; 88: 130-136.