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An Update on Current and Emerging Therapies for Brain Metastases

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Abstract

Brain metastases (BMs) are the most common cause of brain malignancy, occurring 10 times more often than intracranial neoplasms. BMs most frequently arise from non-small cell lung cancer, melanoma, renal cell carcinoma and breast carcinoma. The overall survival after BM diagnosis remains poor, but depends on patient age, performance status, type of primary tumour, time of diagnosis from the primary, as well as many other factors.

The incidence of BMs may be due to the fact that some therapies control growth of the primary tumour, but such agents has a limited role in BM treatment, as they cannot or only partially penetrate the BBB. The brain therefore acts as a 'sanctuary site' for cancers which have successfully invaded the brain and escaped the effects of systemic cancer therapies. A reduced effect of classical systemic therapies on BMs can also be explained by other resistance mechanisms that only occur in the brain such as the astrocytic protection of extravagated cancer cells. Alternative approaches include surgery, stereotactic radiosurgery or whole brain radiotherapy. This review looks at the benefits and risks of different approaches to treatment of BMs and highlights areas of research in both current and prospective BM therapies.

Keywords: Brain Metastases; Stereotactic Radiosurgery; Whole brain radiotherapy; Stereotactic Radiosurgery, 3D conformal boost radiotherapy, Hippocampal Avoidance; Memantine; re-irradiation

Abbreviations: BMs: Brain Metastases; NICE: National Institute for Health and Care Excellence; SRS: Stereotactic Radiosurgery; SRT: Stereotactic Radiotherapy; PS: Performance Status; WBRT: Whole Brain Radiotherapy; NSCLC: Non-small Cell Lung Cancer; 3DCRT: 3DConformal Boost Radiotherapy; KPS: Karnofsky Performance Score.

Introduction

BMs are treated with the aim to increase local control and patient survival if possible, without affecting neurocognition [1-3]. The National Institute for Health and Care Excellence (NICE) recommends maximal local therapy using either surgery, stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) for patients with single BMs, and adjuvant SRS to the surgical cavities of people with 1 to 3 brain metastases post-resection [4].For patients with multiple brain metastases, SRS may be considered in those with controlled extracranial disease and Karnofsky performance status (PS) greater than 70.5. Another method of radiotherapy which can be used is whole brain radiotherapy (WBRT), which is however associated with a greater degree of neurocognitive deterioration compared with SRS [3]. Adjuvant WBRT is not offered to people with

a single brain metastasis following surgery or SRS [5], but may be discussed in some patients with multiple metastases, who meet criteria detailed in the annotation of Table 1. Management of BMs includes supportive treatments such as corticosteroids, antiepileptics (AEDs) and anticoagulants in addition to the definitive treatment of the tumour, to help with symptoms [6].

Number of Metastases	Treatment Options	
Single brain metastasis*	Consider surgery (higher risk that SRS/ SRT may be needed additionally)	Consider SRS/SRT (lower risk that surgery may be needed additionally)
Limited number of brain metastases (1-3)	Consider surgery +/- adjuvant SRS/SRT	
Multiple brain metastases**	Consider SRS/SRT	Discuss WBRT (with patient +/- relatives/ carers) & potential benefits and risks

Table 1: Summary of management options for BM patients with single, limited or multiple brain metastases [NICE Guidelines] [4]
*Based on co-morbidities, extent of oedema, location of metastasis, patient preference and tumour size [4].
**with controlled/controllable extracranial disease; Karnofsky PS of 70 or more; not received previous SRS or surgery [4].

Comparing Therapies

What is the Best Treatment Option

Multi-modality management of BMs is continually being researched and improved. *Table 2* illustrates recent clinical trials which have compared the success of different approaches to BM management.

Microscopic total resection remains a key treatment for single BMs [3]. Excision is especially indicated for larger brain lesions in non-eloquent areas [7]. Surgery provides immediate relief of neurological symptoms secondary to mass effect [5] and allows for histopathological diagnosis, which can be used to guide future treatment [4]. Surgical resection has also been shown to best improve intracranial hypertension and allows for more rapid tapering of corticosteroids [6]. The extent of the resection is a key factor for prognosis, with complete removal resulting in a significantly better prognosis than incomplete BM resection. Local recurrence of BMs after surgery can be as high as 67%, even after complete resection and post-operative radiotherapy [3].

Stereotactic radiosurgery (SRS) is image-guided and delivers a high dose of radiation to a specific target, minimising the dose to the surrounding brain tissue. It is an outpatient treatment, doesn't require general anaesthetic [4], and can be delivered in a single session [2]. SRS can target areas of the brain which cannot be easily accessed surgically, and therefore may be the only option for certain tumours [4]. SRS is the main alternative to surgical resection in patients with limited numbers of BMs, good Karnofsky performance score (KPS) and intracerebral tumour volume under 3cm [1,4,8]. There is however no clinically important difference in overall survival between these two management options [4]. However, first-line SRS has been shown to have a better local control than surgery and is less likely to need additional treatment than resection [4]. A side effect of radiotherapy is delayed radionecrosis of the brain tissue, which may require subsequent surgical resection (re-do surgery) [4]. This is more commonly seen in whole brain radiotherapy (WBRT) than SRS; however is still important to consider when selecting SRS as treatment of choice. For multiple brain metastases, SRS is commonly reserved for salvage therapy, or as consolidative boost therapy for larger lesions or radio-resistant histologic types e.g. melanoma or renal cell carcinoma [9].

WBRT delivers a relatively low dose of radiation to the entire cranium – destroying microscopic disease at the tumour site and at distant intracranial locations [10]. There are various WBRT fractionation schemes, the most common being 30Gy in 10 fractions, which requires 5-10 hospital visits [4]. WBRT involves the patient lying supine, with the head immobilised. The appointment takes approximately 15 minutes, but the actual 'beam-on time' is less than 5 minutes [4]. Possible acute toxicities of WBRT that can impact health-related quality of life (QOL) include: temporary hair loss, mild dermatitis, fatigue and decreased physical functioning [4,9,11]. Cognitive and neurologic deficits are more long-term toxicities associated with WBRT, which may occur secondary to transient oedema around the tumour site; which usually responds to initiation of corticosteroids, or a short-term increase in dose [4]. Cognitive decline associated with WBRT may manifest as loss of episodic memory, executive function, processing speed or fine motor control; however WBRT seems to have a particularly pronounced toxicity on episodic memory compared to other cognitive domains [4].

Optimizing BM control with adjuvant radiotherapy

contributes with a beneficial effect to survival. However the decision on modality requires a discussion of trade-offs with patients [4]. As the choice between SRS and WBRT involves trying to balance outcomes of both intracranial control and cognition [12]. SRS in the post-operative setting is a standard of care to improve surgical bed control relative to observation. Relative to WBRT, SRS is inferior in terms of surgical bed control and associated with a shorter time to intracranial failure; however, it is less toxic than WBRT and improves time to and incidence of cognitive decline [12]. Future research is needed to refine SRS technique in order to further improve outcomes such as surgical bed control [4]. Due to the recent understanding of the toxic effects of WBRT on cognition and health-related QOL, the use of WBRT should be limited, and other treatments such as SRS should be approached initially, delaying WBRT to later in a patient's disease course where appropriate [4].

Trial/Study	Comparison	Findings
NCT00960001	Surgery + adjuvant SRS vs.	Adjuvant SRS showed reduction in 12-month relapse rates.
	Surgery + observation	
107C/CEC.3	Surgery + adjuvant SRS vs.	Adjuvant SRS offered no difference in overall survival compared to WBRT, with the benefit of less neurotoxicity and cognitive decline.
	Surgery + adjuvant WBRT	Adjuvant WBRT has better local tumour control, but is more likely to result in cognitive decline, and at a faster rate than SRS.
EORTC 22952-26001	Surgery/SRS + adjuvant WBRT vs. Surgery/SRS + observation alone	Similar local control with surgical resection and SRS. SRS provided better local control, but the risk of recurrence over time was greater with SRS.
		Adjuvant WBRT reduced the risk of relapse at both initial and new intracranial sites in both groups. Patients who did not receive adjuvant WBRT often required salvage WBRT following tumour recurrence.
ID00-377	SRS + observation alone vs.	Adjuvant WBRT showed better local control than observation alone, but showed to cause deterioration in cognition.
	SRS + adjuvant WBRT	
JROSG 99-1	SRS + observation alone vs.	Adjuvant WBRT showed better local control than observation alone
	SRS + adjuvant WBRT	
QUARTZ	WBRT vs. SC in patients with NSCLC	No difference in quality-adjusted life years between the two treatment arms.
		No added benefit of WBRT particularly for NSCLC patients with poor prognosis.

Table 2: Overview and summary of the findings of studies comparing different therapeutic combinations of surgical resection, SRS and WBRT.

Up until recently, WBRT has been the standard treatment for patients with multiple BMs. However, due to the side effects and neurological dysfunction associated with WBRT, the use of SRS in patients with a small number of BMs has been investigated. A single-center retrospective study compared SRS to WBRT as the initial treatment for 10–20 BMs from NSCLC [13]. Patients in the WBRT group showed superior intracranial control and time-to-intracranial-progression, with a higher risk of intracranial recurrence seen in the SRS group. However, fewer adverse events were seen in the SRS group, and the study found no significant difference in overall survival between SRS and WBRT. Therefore, SRS may be a useful alternative up-front treatment for 10–20 BMs from NSCLC, prolonging the need for WBRT, and its associated adverse effects. Further prospective randomized studies analyzing neurocognitive complications are needed [13].

Advances in Whole Brain Radiotherapy (WBRT)

Suteu et al. looked at the impact of addition of 3D conformal boost radiotherapy (3DCRT) to WBRT in BM management. This technique is a similar alternative to SRS, as it is a localised treatment that can deliver a high radiation dose to the intracerebral tumour. The study concluded that WBRT+3DCRT did improve the QOL in patients with a limited number of brain metastases. Overall survival rates seemed to be better in patients with a single metastatic lesion and smaller intracranial tumour volumes, suggesting that these patients may benefit the most from WBRT+3DCRT [8].

Hippocampal neural stem-cell injury caused by WBRT may play a role in the memory deficit associated with WBRT [14]. As a result, recent clinical trials have looked at the potential cognitive preservation benefits of neuroprotective strategies during WBRT. *RTOG 0614*, a multi-institutional phase III trial, observed the administration of memantine (an agent originally used in Alzheimer's disease patients) during WBRT to reduce the probability of cognitive dysfunction at 6 months by 11%, and achieve better preservation of executive function and processing speed [15].

RTOG 0933, a single arm phase II trial found that hippocampal-sparing WBRT was associated with preservation of memory and health-related QOL [16]. By avoiding the hippocampus with intensity-modulated radiotherapy, the study found that the median decline in *Hopkins Verbal Learning Test-Revised Delayed Recall* from baseline to 4 months was 7%, compared to 30% seen in control patients who received conventional WBRT [16].

NRG-CC001 was a phase III trial analysing the effects of WBRT and memantine (M) with or without hippocampal avoidance (HA) in patients with BMs. Patients were randomised to WBRT+M or HA-WBRT+M, with WBRT given in 30Gy/10 fractions [17]. At 4 months, HA-WBRT+M was associated with a lower risk of deterioration in executive function. At 6 months, patients reported fatigue, difficulty speaking and problems with memory less frequently in the HA-WBRT+M arm. The results of patient-reported cognition and symptom interference also favoured HA-WBRT+M at 6 months [17]. The study concluded that hippocampal sparing reduces time to cognitive deterioration, while achieving similar intracranial control and survival to standard WBRT. The on-going clinical trial *NCT04277403* is randomizing patients to receive either hippocampal avoidance WBRT with integrated tumor boost (HA-WBRT+SIB) or SRS. It is hoped that the trial will answer whether HA-WBRT+SIB can offer better intracranial control than SRS, whilst both avoiding the neurocognitive side effects seen due to hippocampal neural stem-cell injury following standard WBRT, and delivering high intensity radiation in a more focused manner, similar to SRS.

Approaches to Re-irradiation

Re-irradiation has shown success in the management of the primary brain tumour, Glioblastoma Multiform. High-dose salvage re-irradiation in patients with recurrent/progressive glioma is associated with: 1) improved or stable QOL (preserved functional domains and reduced symptom burden), 2) improvement in activities of daily living and 3) encouraging survival outcomes [18].

For BMs, the most useful indication for re-irradiation remains unknown. However patients may benefit under certain conditions (e.g. younger age, higher KPS, stable extracranial lesions and smaller tumour volume) whereas patients with peritumoral oedema, cystic BMs and low KPS might not be suitable. Zhou Huang et al. (2017) concluded that re-irradiation is an effective option for patients with BMs secondary to breast cancer [18]. Intracranial failure after re-irradiation may occur either due to the dose administered being too low, or due to radionecrosis. How to choose between SRS or WBRT for re-irradiation of recurrent BMs remains to be clarified. There is emerging evidence that SRS is a reasonable treatment for recurrent BMs, with the RTOG 90-05 protocol having already established the maximum tolerated dosage of SRS in re-irradiation after a course of WBRT. Data on using WBRT following SRS is limited. WBRT can reduce intracranial relapse, especially for distant BMs, and therefore can be considered as salvage therapy if BMs have disseminated recurrence and are thus not suitable for SRS. However, with WBRT come the risks of subacute leukoencephalopathy and neurocognitive dysfunction [19]. Nieder et al. (2018) compared the treatment of locally recurrent metastasis using A) WBRT and two courses of SRT, with B) two courses of WBRT and additional SRT. Usually this extent of re-irradiation is a last resort, with the patients being treatment-resistant and without other options, and thus the rate of adverse effects is not viewed to be as prohibitive. Patients must therefore decide and consent on an individual basis, with the clinician providing them with the best available clinical evidence. Current data is not sufficient to determine if there is a net benefit from re-irradiation (good rate of local control and/or symptomatic improvement without treatment-induced adverse events) [19].

Conclusion

Determining the best approach to the management of brain metastases is complex and requires taking into account factors which are patient-centred; such as KPS, co-morbidities, control of the primary tumour and the extent of intracranial disease. Surgical resection remains at the forefront of the management of most BM patients. It offers durable intracranial control and meaningful survival prolongation, but can also be optimized with adjuvant radiotherapy. The decision on modality is a trade-off between controls versus cognition - WBRT gives better intracranial control, but SRS has less toxic impact on cognition. Future EORTC trials comparing SRS vs WBRT will add to decision-making in the future, in addition to the observations described following EORTC 22952-26001 (Table 2). The choice of therapy given to patients should involve an informed discussion, taking into account the patient's own expectations, beliefs and values when selecting a treatment. Patients should be made aware of both the risks of the long-term impact on cognition associated with the treatment, versus the neurological

deficits associated with the tumour burden itself.

Up-front SRS is favourable to surgery in patients with three or less BMs, as there is less risk of requiring salvage surgical resection (compared to the risk of requiring salvage SRS following resection). Whole brain radiotherapy (WBRT) is currently the gold standard for patients with more than 3 BMs. SRS is also a promising treatment option for patients with four or more BMs and randomized trials are on-going to determine its value such as *NCT02353000* - a prospective randomized phase III trial comparing WBRT is to SRS for patients with between 4 to 10 BMs. For multiple BMs, up-front SRS has been shown to prolong the need for additional WBRT (compared to up-front WBRT requiring salvage SRS) - avoiding the associated neurocognitive effects, and poor QOL associated with WBRT. However, WBRT does have better intracranial control than SRS, and so is favourable in certain groups of patients, e.g. high KPS, controlled extracranial disease.

There is scope for development of both the techniques of radiotherapy available to BM patients, to improve local control in SRS and to improve health-related quality of life outcomes for WBRT. Research and development of different fractionation techniques and pre-operative options for SRS, and 3DCRT boost or using hippocampal-sparing techniques with WBRT, show promise. The analysis of HA-WBRT-SIB *NCT04277403* may help influence future decisions between using WBRT or SRS in the future. We must continue to trial the effects of both initial WBRT/SRS and re-irradiation for BMs to better understand the net benefit of using re-irradiation, and to help us identify patient groups in which this therapy is indicated or contra-indicated.

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References

1. Lehrer EJ, Peterson J, Brown PD, Sheehan JP, Quiñones-Hinojosa A, et al. (2019) Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data. Radiother Oncol 130: 104-12.

2. Lehrer EJ, McGee HM, Peterson JL, Laura Vallow, Henry Ruiz-Garcia, et al. (2018) Stereotactic Radiosurgery and Immune Checkpoint Inhibitors in the Management of Brain Metastases. Int J Mol Sci 19(10): 3054.

3. Preusser M, Winkler F, Valiente M, Manegold C, Moyal E, et al. (2018) Recent advances in the biology and treatment of brain metastases of non-small cell lung cancer: summary of a multidisciplinary roundtable discussion. ESMO Open 3(1): e000262.

4. NICE Guidelines (2020) Brain tumours (primary) and brain metastases in adults.

5. Lin X, DeAngelis LM (2015) Treatment of Brain Metastases. J Clin Oncol 33(30): 3475-3484.

6. Arvold ND, Lee EQ, Mehta MP, Kim Margolin, Kim Margolin, et al. (2016) Updates in the management of brain metastases. Neuro Oncol 18(8): 1043-1065.

7. Kleinberg LR (2009) Brain Metastasis: A Multidisciplinary Approach. Demos Medical Publishing, New York, NY.

8. Suteu P, Fekete Z, Todor N, Nagy V (2019) Survival and quality of life after whole brain radiotherapy with 3D conformal boost in the treatment of brain metastases. Med Pharm Rep 92(1): 43-51.

9. Brown PD, Ahluwalia MS, Khan OH, Asher AL, Wefel JS (2017) Whole-Brain Radiotherapy for Brain Metastases: Evolution or Revolution? J Clin Oncol 36(5): 483-491.

10. Kocher M, Soffietti R, Abacioglu U, Salvador Villà, Francois Fauchon, et al. (2011) 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 29(2): 134-141.

11. Nieder C, Guckenberger M, Gaspar LE, Chad G Rusthoven, Dirk De Ruysscher, et al. (2019) Management of patients with brain metastases from non-small cell lung cancer and adverse prognostic features: multi-national radiation treatment recommendations are heterogeneous. Radiat Oncol 14(1): 33.

12. Gondi V, Mehta MP (2018) Control versus cognition: the changing paradigm of adjuvant therapy for resected brain metastasis. Neuro Oncol 20(1): 2–3.

13. Mizuno T, Takada K, Hasegawa T, Yoshida T, Murotani K, et al. (2019) Comparison between stereotactic radiosurgery and whole-brain radiotherapy for 10-20 brain metastases from non-small cell lung cancer. Mol Clin Oncol 10(5): 560-566.

14. Maitre P, Gupta T, Maitre M, Goda J, Krishnatry R, et al. (2020) Prospective Longitudinal Assessment of Quality of Life and Activities of Daily Living as Patient-Reported Outcome Measures in Recurrent/Progressive Glioma Treated with High-dose Salvage Re-irradiation. Clinical

Oncology

15. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, et al. (2014) Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial. J Clin Oncol 32(34): 3810-3816.

16. Brown PD, Pugh S, Laack NN, Jeffrey S Wefel, Deepak Khuntia, et al. (2013) Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 15(10): 1429-1437.

17. Gondi V, Deshmukh S, Brown PD, Wefel JS, Tome W, et al. (2019) NRG Oncology CC001: A phase III trial of hippocampal avoidance (HA) in addition to whole-brain radiotherapy (WBRT) plus memantine to preserve neurocognitive function (NCF) in patients with brain metastases (BM). J Clin Oncol 37(S15): 2009.

18. Huang Z, Sun B, Shen G, Cha L, Meng X, et al. (2017) Brain metastasis reirradiation in patients with advanced breast cancer. J Radiat Res 58(1): 142-148.

19. Nieder C, Yobuta R, Mannsaker B (2018) Second Re-irradiation of Brain Metastases: A Review of Studies Involving Stereotactic Radiosurgery. Cureus 10(12): e3712-e3712.