Contemporary practice patterns of stereotactic radiosurgery (SRS) for brain metastasis (BM) – a review of published Australian literature

Wee Loon Ong[1,2,3,4], Morikatsu Wada[1], Jeremy Ruben[5,6], Farshad Foroudi[1], Jeremy Millar[5,6]

[1]Department of Radiation Oncology, Olivia Newton-John Cancer Wellness and Research Centre, Austin Health, Heidelberg, Australia

[2]School of Clinical Medicine, University of Cambridge, UK

[3]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

[4]Health and Biomedical Informatics Centre, University of Melbourne, Melbourne, Australia

[5]Alfred Health Radiation Oncology Services, Melbourne, Australia

[6]Central Clinical School, Monash University, Melbourne, Australia

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Corresponding Author:

Wee Loon Ong

Department of Radiation Oncology

Olivia Newton-John Cancer Wellness and Research Centre

Austin Health

145 Studley Road

Heidelberg 3084 VIC Australia

E: weeloonong@cantab.net

P: 03 9496 2800

F: 03 9496 2826

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DR. WEE LOON ONG (Orcid ID : 0000-0001-6657-7193)
A/PROF. FARSHAD FOROUDI (Orcid ID : 0000-0001-8387-0965)

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ABSTRACT

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There has been a shift in the management of brain metastasis (BM), with increasing use of stereotactic radiosurgery (SRS), and delaying/ avoiding whole brain radiotherapy (WBRT), given the concern regarding the long-term neurocognitive effect and quality of life impact of WBRT. It is however unclear as to the contemporary practice pattern and outcomes of SRS in Australia. We conducted a literature search in PubMed and MEDLINE using a series of keywords: 'stereotactic', 'radiosurgery', and 'brain metastases', limiting to Australian studies, which report on clinical outcomes following SRS. Eight studies – one randomized trial and seven retrospective cohort studies – were identified and included in this review. A total of 856 patients were included, with the most common primary tumour types being melanoma, lung cancer and breast cancer. Approximately half of the patients had solitary BM, while 7% had ten or more BM lesions. SRS is not routinely given in combination with WBRT. The 6-month and 1-year intracranial control following SRS was reported in the range of 67-87% and 48-82% respectively, whereas the 1-year and 2-year overall survival was reported in the range of 37-60% and 20-36% respectively. There is limited data reported on SRS-related toxicities in all included studies. Overall, despite increasing use of SRS for BM, there is low number of published Australian series in the literature. There is potential role for establishing an Australian clinical quality registry or collaborative consortium for SRS in BM, to allow for systematic prospective data collection, and benchmarking of quality and outcomes of SRS.

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INTRODUCTION

More than one-third of cancer patients will develop brain metastasis (BM) (1), with lung cancer, breast cancer, melanoma, and renal cell carcinoma most commonly associated with BM development. The conventional treatment in patients with multiple BM has been whole brain radiotherapy (WBRT). However, over the past few years, there has been a change in the philosophy of radiotherapy for limited BM, favouring the use of stereotactic radiosurgery (SRS) and delaying or avoiding WBRT. This has been supported by a large body of evidence that has shown that while the use of WBRT in addition to SRS improves intracranial control compared to SRS alone, it does not improve overall survival (2-5), and is associated with worse neurocognitive function (6, 7) and quality of life (8).

In fact the RANZCR Faculty of Radiation Oncology Choosing Wisely recommendations advocate against routinely adding WBRT to SRS for patients with limited BM (9). A recent population-based study in Victoria has also shown increasing use of SRS for BM and that adjuvant WBRT is an uncommon practice (10). However such population-based study lacks the granularity on patient, tumour, and treatment details to evaluate the appropriate use of SRS for each individual patients. The aim of this paper is to systematically review the Australian literature on the use of SRS for management of BM.

METHODS

Search strategies and study criteria

This systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure-1). We conducted a literature search on PubMed and MEDLINE database for publications between 1 January 1995 and 31 March 2019, using a series of keywords: (‘stereotactic’ or ‘radiosurgery’), and (‘brain metastasis’ or ‘brain metastases’). Additional reference lists of related journal articles, were hand-searched for additional studies. The search was further narrowed down to studies conducted in Australia. This systematic review include randomised and non-randomised, prospective and retrospective, original studies of patients with BM treated with SRS. Reviews, editorial or commentary articles were excluded.

Data extraction and synthesis

Full text articles were retrieved and reviewed by the primary author (WLO). The primary outcomes of interest are intracranial control and overall survival following SRS – only studies reporting on at least one of these outcomes were included in this review. While SRS, strictly,

refers to large single fraction radiotherapy, studies reporting the use of fractionated stereotactic radiotherapy for BM were also included in this review. In the case of multiple reports on the same cohort of patients, only publications with the most updated data, or those with most detailed information on SRS techniques were included. Other relevant data extracted from the included studies are patient-, tumour-, and treatment-related (e.g. use of systemic therapy) variables. A narrative approach was adopted to synthesize the relevant findings of the studies, given the heterogeneity of the small number of studies identified, as well as the inconsistency in outcome definition and reporting. Pooling of the studies in the form of meta-analyses was not possible.

RESULTS

A total of eight Australian studies were identified and included in this review (Table-1) – one prospective randomized controlled trial (RCT) that was terminated before its accrual target was met (11), and seven retrospective single institutional studies from South Australia (12), Victoria (13), Queensland (14, 15) and New South Wales (16-18) respectively. The RCT randomised patients with solitary BM to either surgery plus WBRT, or SRS plus WBRT – only results from the SRS plus WBRT arm were included in this review.

Patient characteristics

A total of 856 patients with BM were included in this review (Table-1). Most patients were in their sixties. All studies, except one (18), reported on the sex of the cohort, with approximately equal distribution of men (51%) and women (49%). Five studies reported patients' performance status using either Karnofsky or ECOG performance status (12, 13, 15, 16), while performance status was not reported in the other studies.

Primary tumour type and systemic disease control

Most studies have a mix of different primary tumour types, while one study included patients with melanoma BM only (Table-1). The most common cancers reported include melanoma (n=293), lung cancer (n=238) and breast cancer (n=137). Two studies reported mutation status for melanoma patients, of which 69 (46%) were BRAF mutant, and 81 (54%) were BRAF wild-type (15, 16). The study by Nicholls et al also reported on mutation status for lung cancer (26% EGFR/ALK mutant, and 74% EGFR/ALK wild-type) and histological subtypes of breast cancer (41% Her2+ve, and 59% Her2-ve) (15). Five studies reported on the extra-cranial extent of cancer (13, 14, 16-18), with large majority of patients in most

studies reported to have extracranial disease, except the study by Izard et al whereby only about one-third of patients had extracranial disease (17).

Characteristics of brain lesions treated

Of the studies reporting the number of BM lesions per patient, 45% (323/710) had solitary brain BM. There were 51 (7%) patients with more than 10 BM lesions treated with SRS in three studies. Five studies reported the size of treated BM lesions in terms of diameter (12-14, 17) – with the treated lesions ranging from 3 to 70mm – while one reported the volume in cm^3 (16). One study reported the total volume of all treated BM lesions, with median size of $0.57cm^3$ (range: <0.005-$5.44cm^3$) (17).

Dose, fractionations, and techniques

Six studies reported the use of single fraction SRS, with doses ranging from 10Gy to 24Gy (Table-2). Two studies reported the prescribed dose based on the size of the lesions – 20Gy, 18Gy, and 15Gy to lesions with diameter of ≤20mm, 21-30mm, and 31-40mm in the study by Roos et al (11), and 20Gy and 16-18Gy for lesions <15mm and ≥15mm in the study by Izzard et al (17). In the study by Or et al, intact BM lesions were treated with single fraction SRS of 18-20Gy while all post-operative BM surgical cavity were treated with hypofractionated SRS to a dose of 25-30Gy in 5 fractions (18); whereas in the study by Croker et al, all patients were treated with hypofractionated SRS to a median dose of 24Gy in 3 fractions (range: 22-40Gy in 2-10 fractions) (14). The dose and fractionation were not reported in the study by Choong et al (16).

Five studies described the planning target volume (PTV) expansion for the SRS treatment. In the studies by Izard et al and Nicholls et al, all treatments were delivered with Gamma knife without GTV-PTV expansion (15, 17). In the study by Sia et al, 166 (52%) lesions were treated without GTV-PTV expansion, while 1mm and 2mm GTV-PTV expansions were used in 96 (30%) and 56 (18%) of the treated lesions respectively (13). Or et al reported a 1mm GTV-PTV expansion for single fraction SRS, and 3mm GTV-PTV expansion for multi-fraction SRS in their study (18). In the study by Croker et al whereby all patients were treated with hypofractionated SRS, the GTV-PTV expansion included a 2-3mm expansion from GTV to CTV, and a further 2-3mm expansion from CTV to PTV (14).

Addition of Surgery and/ or WBRT

There was large variation in surgical debulking reported prior to SRS, ranging from 0-52%. No patients in the RCT had surgical debulking (11). In the retrospective study by Roos et al, two (9%) patients had surgical debulking at 12 and 31 months prior to SRS (12). Croker et al reported that 32 (52%) of the 61 patients in their study had surgical debulking prior to SRS: 29 patients had their solitary lesions resected, while 3 patients had additional intracranial lesions left in situ (14). In the study by Izzard, one-third of the patients had surgical debulking prior to SRS (17). Sia et al reported that of the 318 SRS-treated BM lesions, 27 (8%) were surgically debulked prior to SRS (13), whereas in the study in Or et al, 74 (50%) BM lesions were surgically debulked prior to SRS (18).

All 10 patients in the RCT had adjuvant WBRT as part of the study protocol. Of the seven retrospective studies, three reported on the use of adjuvant WBRT in addition to SRS (Table-2) – 8 (36%) patients in the study by Roos et al and 42 (39%) patients in the study by Choong et al, while in the paper by Sia et al, 45 of the 318 (14%) BM lesions were treated with SRS and WBRT. None of the more contemporary studies reported the use of adjuvant WBRT (14, 15, 17, 18).

Use of systemic therapy

The studies included in this review span a period of more than two decades during which there was rapid development of novel systemic therapies, and some of the studies predated the era of systemic therapies. There is only one study which specifically reported the use of BRAF inhibitors and/ or immunotherapy along with SRS (16). Choong et al reported that 79 (73%) patients had systemic therapy within 6 weeks of SRS – 39 had immunotherapy (anti CTLA4 or anti-PD1), 40 had BRAF inhibitor/ MEK inhibitor (16). Croker et al reported 32 (52%) patients who had chemotherapy prior to SRS. The study by Nicholls et al reported that SRS was delivered at least 5 days from administration of cytotoxic chemotherapy, 0-3 days from targeted therapy, and immunotherapy was continued uninterrupted; however, the number of patients on each systemic therapy in the cohort was not reported (15).

Intracranial control

All patients in the studies were followed up with MRI surveillance imaging at least 2-3 monthly, with a median follow-up between 6.2 and 21 months (Table-3). The overall 6-month, 12-month, and 24-month intracranial control was reported to be between 67-87%, 48-82%, and 56% respectively. It is, however, important to note the varying definition for intracranial

control used in different studies. Sia et al only reported local intracranial control i.e. absence of recurrence of the SRS-treated lesion (13), whereas Choong et al reported intracranial control as absence of progression of the SRS-treated lesion, or any new intracranial lesions (16). Croker et al reported local and distant intracranial control separately, with local failure defined as increase in size of lesion in continuity or immediately adjacent to the irradiated lesion, and distant intracranial failure as new lesion outside the treated PTV (14).

Only two studies evaluated prognostic factors for intracranial control. Sia et al reported that greater GTV volume and melanoma histology were associated with worse intracranial control (13). Choong et al reported increasing age, performance status, lower Graded Prognostic Assessment (GPA) score, and symptomatic BM to be associated with worse intracranial control.

There was only 1 study reporting on leptomeningeal relapse following SRS (18). Leptomeningeal relapse was observed in 3 patients as first intracranial failure, and in 11 patients as subsequent failure among all 166 patients in the study – it is however unable to determine the proportion of patients who developed leptomeningeal disease after undergoing SRS alone.

Overall survival

The median OS was reported to be in the range of 6.2-21 months, with 1-year and 2-year OS of 37-60% and 20-36% respectively (Table-3). In the study by Sia et al, when stratified by primary tumour type, patients with melanoma BM had worse median OS of 5.1 months, compared to 12.2 months for patients with lung cancer BM and 14.7 months for breast cancer BM (13). The median OS for melanoma BM in this study appears to be significantly shorter compared to 14.2 month median OS reported in the study by Choong et al (16), likely reflecting that more than a third of patients in the study by Choong et al, which is a more contemporary series, were treated with BRAF inhibitors; the use of BRAF inhibitors is reported to be associated with improved OS. Other factors reported to be associated with OS were patients' age (17), sex (17), ECOG performance status (13, 16), extent of extracranial disease (13, 18), as well as early intracranial failure(18).

Salvage treatment for intracranial failure

Four studies reported on salvage treatments following intracranial failure. In the retrospective study by Roos et al, there were two patients who had WBRT for distant

intracranial failure and one patient had focal conventional radiotherapy for local intracranial failure (12). In the study by Croker et al, of the 14 patients who developed local intracranial failure, 2 had re-irradiation with SRS, three had WBRT, and four had salvage surgery, whereas of the 26 patients who had distant intracranial failure, seven had SRS, seven had WBRT, and three had surgery (14). In the study by Choong et al, 24 patients required salvage neurosurgery for progression of the SRS-treated lesions (16).

Toxicities

Only 3 studies reported toxicity data. CTCAE Grade 3 and above toxicities were reported to range between 0 and 30% (11, 14, 18). There were three studies that reported on the incidence of radionecrosis (16-18) – Choong et al reported surgically resected radionecrosis in 3 (3%) patients, while Izard et al and Or et al reported radiologically diagnosed radionecrosis in 22 (12%) and 2 (1.5%) patients respectively. Of the 22 patients with radionecrosis in the study by Izard et al, 21 were managed with steroids, and 1 underwent surgical resection. Of the 2 patients with radionecrosis in the study by Or et al, one was treated with bevacizumab, while the other was treated with a prolonged course of steroids of more than 6 months.

DISCUSSION

This review evaluated all published literature on the use of SRS for the management of BM in Australia. While our clinical experience and observations suggest an increasing trend in the use of SRS for BM in Australia, there is a surprisingly low number of published Australian studies on the outcomes of SRS for BM; they are mostly single institutional retrospective series. Of the few published Australian series, there is a varying degree in the quality of publications, with significant heterogeneity in terms of patient and tumour characteristics, number and sizes of BM lesions treated, and outcome definition. The overall outcomes, in terms of intracranial control and overall survival, nonetheless appears similar to other international series (19).

Addition of WBRT to SRS

Although the addition of WBRT to SRS improves intracranial control, it has not been reported to translate into overall survival benefits, and is associated with detrimental effects on neurocognitive function and a reduction in quality of life. One of the RANZCR Choosing Wisely recommendations advice against routinely adding WBRT to SRS for patients with

limited BM (9). Our review of the current Australian literature, reassuringly suggests that WBRT is not routinely given in conjunction with SRS. In the study by Sia et al, the data dated back to about a decade ago when WBRT was still part of standard of care, and even then only 14% of BM lesions were treated with adjuvant WBRT at an institution which had a strong stereotactic focus. In the more contemporary studies in this review, none of the patients were treated with adjuvant WBRT (15, 17, 18). A recently published Australian population-based study also showed significant drop in use of adjuvant WBRT following SRS from 4% in 2013 to 0.7% in 2017 (10).

While the use of adjuvant WBRT following SRS in the study by Choong et al is slightly higher at 40%, the study comprised patients with melanoma BM only. This subgroup of patients is known to have high rates of intracranial failure (20, 21). An Australian-led international (ANZMTG-01.07 WBRTMel) trial specifically investigated the role of adjuvant WBRT in this group of patients (22). Findings from this single-histology BM trial has recently been reported to show no improvement in intracranial control with adjuvant WBRT – 12-month cumulative incidence of intracranial failure was 42% in patients who underwent adjuvant WBRT vs. 51% in patients who did not (P=0.16) (23).

Combination of SRS and systemic therapy

With increasing systemic therapy options available to patients with BM, such as EGFR/ ALK inhibitors in lung cancers and BRAF/ MEK inhibitors in melanoma, as well as immunotherapies, the outcomes of patients with BM continue to improve following SRS (24, 25). This is evident in the current review of Australian literature with worse outcomes of melanoma BM reported in the study by Sia et al in the pre-targeted therapy era (median OS of 5.1 months) compared to the study by Choong et al whereby a large proportion of patients received targeted therapy or immunotherapy (median OS of 14.2 months). However, there are still many unanswered questions regarding the combination of SRS and systemic therapy, for example the best sequencing of systemic therapy and SRS (26), and the potential toxicities with concurrent use of systemic therapy with SRS (27), amongst others. Hence, it is important for any future studies reporting on the outcomes of SRS to include details on systemic therapy received by the patients.

Pre-operative vs. post-operative SRS

An evolving area in SRS for BM is the use of pre-operative SRS (28). One of the concerns with surgical resection of BM is the risk of tumour seeding leading to increased risk of

leptomeningeal disease (29). Only one study in this review reported on the risk of leptomeningeal disease. The rationale for pre-operative SRS is that it not only allows for contouring of intact BM lesions instead of irregularly shaped surgical cavities, but importantly it is postulated to reduce the risk of intra-operative seeding of viable tumours, thus reducing the risk of leptomeningeal disease, and may also reduce the rate of symptomatic radionecrosis (28). While anecdotally, pre-operative SRS is offered in several Australian institutions, there has been no published Australian studies in the literature.

Future direction

Given the limited number of published Australasian data on SRS, we would encourage publications of SRS outcomes by Australian institutions, especially by centres with high-volume SRS practice, in order to allow for evaluation of contemporary SRS practice and outcomes. Also, as evident in this review, there is variation in the quality of reporting of study cohort characteristics, and outcome definition, which hinder meaningful direct comparison of the outcomes. There is hence a potential role for the establishment of a clinical quality registry to prospectively capture information on SRS performed across all Australian institutions, or a collaborative consortium such as the International Radiosurgery Oncology Consortium of Kidney (IROCK) (30) to pool data using standardized definitions and methodologies. It is important for such efforts to have buy-in from the radiation oncologists across all sites, and this can potentially be coordinated through collaborative trial groups such as the Cooperative Trials Group for Neuro-Oncology (COGNO), or by the RANZCR Quality Improvement Committee. By employing the 'measure to improve' philosophy and learning from 'positive deviance', this benchmarking process will allow institutions to learn from each other to achieve the best outcomes for our patients.

CONCLUSION

With increasing evidence supporting the use of SRS for limited BM, and the detrimental effects of WBRT, we expect that there will be continual increase in the use of SRS. The large body of evidence to date discourages routinely adding WBRT to SRS, and the limited Australian data in the literature suggests that Australian radiation oncologists are indeed 'choosing wisely' in not doing so. We would strongly encourage most Australasian institutions to publish on their experience and outcomes of SRS for BM. There is potential role for establishing a clinical quality registry to prospectively capture all SRS performed in Australia in a systematic manner, thus allowing for benchmarking and improvement of SRS practice and outcomes.

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Figure -1 | Flow diagram of search strategies adapted from PRISMA

REFERENCES

1. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G. Epidemiology of metastatic brain tumors. Neurosurg Clin N Am. 2011;22(1):1-6, v.

2. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(2):134-41.

3. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA : the journal of the American Medical Association. 2006;295(21):2483-91.

4. Kayama T, Sato S, Sakurada K, Mizusawa J, Nishikawa R, Narita Y, et al. Effects of Surgery With Salvage Stereotactic Radiosurgery Versus Surgery With Whole-Brain Radiation Therapy in Patients With One to Four Brain Metastases (JCOG0504): A Phase III, Noninferiority, Randomized Controlled Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018:JCO2018786186.

5. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, 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(8):1049-60.

6. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA : the journal of the American Medical Association. 2016;316(4):401-9.

7. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. The lancet oncology. 2009;10(11):1037-44.

8. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(1):65-72.

9. Royal Australia and New Zealand College of Radiologists. Five Things Clinicians and Consumers Should Question [Available from: http://www.choosingwisely.org.au/getmedia/041eb540-e46d-434a-87c4-640991c7dd87/CW_Recommendations_RANZCR_combined_20170410.pdf.aspx.

10. Ong WL, Foroudi F, Milne RL, Millar JL. Are We Choosing Wisely in Radiation Oncology Practice-Findings From an Australian Population-Based Study. International journal of radiation oncology, biology, physics. 2019.

11. Roos DE, Smith JG, Stephens SW. Radiosurgery versus surgery, both with adjuvant whole brain radiotherapy, for solitary brain metastases: a randomised controlled trial. Clin Oncol (R Coll Radiol). 2011;23(9):646-51.

12. Roos DE, Brophy BP, Bhat MK, Katsilis ES. Update of radiosurgery at the Royal Adelaide Hospital. Australasian radiology. 2006;50(2):158-67.

13. Sia J, Paul E, Dally M, Ruben J. Stereotactic radiosurgery for 318 brain metastases in a single Australian centre: the impact of histology and other factors. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2015;22(2):303-7.

14. Croker J, Chua B, Bernard A, Allon M, Foote M. Treatment of brain oligometastases with hypofractionated stereotactic radiotherapy utilising volumetric modulated arc therapy. Clin Exp Metastasis. 2016;33(2):125-32.

15. Nicholls LW, Pinkham MB, Bernard A, Lusk R, Watkins T, Hall B, et al. Radiological Kinetics of Brain Metastases and Clinical Implications for Patients Treated With Stereotactic Radiosurgery. Clin Oncol (R Coll Radiol). 2019;31(1):34-40.

16. Choong ES, Lo S, Drummond M, Fogarty GB, Menzies AM, Guminski A, et al. Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies. European journal of cancer. 2017;75:169-78.

17. Izard MA, Moutrie V, Rogers JM, Beath K, Grace M, Karle B, et al. Volume not number of metastases: Gamma Knife radiosurgery management of intracranial lesions from

an Australian perspective. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2019;133:43-9.

18. Or M, Jayamanne D, Guo L, Stevens M, Parkinson J, Cook R, et al. Focal radiation therapy for limited brain metastases is associated with high rates of local control and low subsequent whole brain radiation therapy. ANZ journal of surgery. 2019;89(4):418-22.

19. McTyre E, Ayala-Peacock D, Contessa J, Corso C, Chiang V, Chung C, et al. Multi-institutional competing risks analysis of distant brain failure and salvage patterns after upfront radiosurgery without whole brain radiotherapy for brain metastasis. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2018;29(2):497-503.

20. Farris M, McTyre ER, Cramer CK, Hughes R, Randolph DM, 2nd, 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. International journal of radiation oncology, biology, physics. 2017;98(1):131-41.

21. Ayala-Peacock DN, Peiffer AM, Lucas JT, Isom S, Kuremsky JG, Urbanic JJ, et al. A nomogram for predicting distant brain failure in patients treated with gamma knife stereotactic radiosurgery without whole brain radiotherapy. Neuro Oncol. 2014;16(9):1283-8.

22. Fogarty G, Morton RL, Vardy J, Nowak AK, Mandel C, Forder PM, et al. Whole brain radiotherapy after local treatment of brain metastases in melanoma patients--a randomised phase III trial. BMC Cancer. 2011;11:142.

23. Fogarty G, Dolven-Jacobsen K, Morton R, Hruby G, Nowak AK, Vardy J, et al. Phase 3 international trial of adjuvant whole brain radiotherapy (WBRT) or observation (Obs) following local treatment of 1-3 melanoma brain metastases (MBMs). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2019;37:9500.

24. Gabani P, Fischer-Valuck BW, Johanns TM, Hernandez-Aya LF, Keller JW, Rich KM, et al. Stereotactic radiosurgery and immunotherapy in melanoma brain metastases: Patterns of care and treatment outcomes. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2018;128(2):266-73.

25. Diao K, Bian SX, Routman DM, Yu C, Ye JC, Wagle NA, et al. Stereotactic radiosurgery and ipilimumab for patients with melanoma brain metastases: clinical outcomes and toxicity. J Neurooncol. 2018;139(2):421-9.

26. Lu VM, Goyal A, Rovin RA, Lee A, McDonald KL. Concurrent versus non-concurrent immune checkpoint inhibition with stereotactic radiosurgery for metastatic brain disease: a systematic review and meta-analysis. J Neurooncol. 2019;141(1):1-12.

27. Verduin M, Zindler JD, Martinussen HM, Jansen RL, Croes S, Hendriks LE, et al. Use of Systemic Therapy Concurrent With Cranial Radiotherapy for Cerebral Metastases of Solid Tumors. The oncologist. 2017;22(2):222-35.
28. Routman DM, Yan E, Vora S, Peterson J, Mahajan A, Chaichana KL, et al. Preoperative Stereotactic Radiosurgery for Brain Metastases. Front Neurol. 2018;9:959.
29. Patel KR, Burri SH, Asher AL, Crocker IR, Fraser RW, Zhang C, et al. Comparing Preoperative With Postoperative Stereotactic Radiosurgery for Resectable Brain Metastases: A Multi-institutional Analysis. Neurosurgery. 2016;79(2):279-85.
30. Siva S, Louie AV, Warner A, Muacevic A, Gandhidasan S, Ponsky L, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). Cancer. 2018;124(5):934-42.

Table – 1 | Summary of studies, patient and tumour characteristics

Study, year	Institution	Study type	Study period	Number of patients	Median age (range)	Sex	ECOG status	Primary tumour site, n (%)	Extra-cranial disease	Number of brain lesion/ patient, n (%)	Brain lesion size
Roos, 2006	Royal Adelaide Hospital, SA	Single institution retrospective	1993-2004	22	64 (36-83)	M: 12 (55%) F: 10 (45%)	n/a	Lung =12 (55%) Melanoma =3 (14%) Others =7 (32%)	n/a	1: 21 (95%) 2: 1 (5%)	Median: 19mm Range: 3-34mm
Roos, 2011	Royal Adelaide Hospital, SA	Prospective RCT	2003-2009	11*	63 (44-84)	M: 7 (64%) F: 4 (36%)	KPS 90-100: 4 (36%) KPS 70-80: 5 (45%) KPS 50-60: 2 (18%)	Lung = 5 (45%) Colorectal = 2 (18%) Others = 4 (36%)	n/a	1: 10 (100%)	Median: 17mm Range: 7-36mm
Sia, 2015	Alfred Health, VIC	Single institution retrospective	2005-2011	162	60.1 (23.8-87.1)	M: 78 (48%) F: 84 (52%)	0: 55 (34%) 1: 62 (38%) 2: 40 (25%) 3: 3 (2%) 4: 2 (1%)	Lung = 43 (27%) Melanoma = 40 (25%) Breast = 35 (22%) Renal = 23 (14%) Others = 21 (13%)	No: 36 (22%) Yes: 126 (78%)	1: 63 (39%) 2: 54 (33%) 3: 26 (16%) 4: 9 (6%) 5: 3 (2%) >5: 7 (4%)	Range: 32 - 45.7mm <20mm: 253 (80%) 20-30mm: 56 (18%) >30m: 9 (3%)
Croker, 2016	Princess Alexandra Hospital, QLD	Single institution retrospective	2012-2014	61	63 (24-87)	M: 37 (61%) F: 24 (39%)	n/a	Melanoma = 29 (48%) Lung = 20 (16%) Breast = 4 (7%) Renal = 4 (7%) Colorectal = 4 (3%) Others = 10 (15%)	No: 20 (33%) Yes: 41 (67%)	1: 49 (80%) 2-3: 10 (16%) >3: 2 (4%)	Mean: 24mm Range: 6-70mm <20mm: 28 (46%) 21-30mm: 14 (23%) 31-40mm: 13 (21%) >40mm: 6 (10%)
Choong, 2017	Melanoma Institute Australia, NSW	Single institution retrospective	2010-2015	108	64.3 (17.3-87.3)	M: 75 (69%) F: 33 (31%)	0-1: 82 (76%) 2-3: 26 (24%)	Melanoma 108 (100%) -BRAF mutant: 51 (47%) -BRAF wild-type:	No: 18 (17%) Yes: 90 (83%)	1: 50 (46%) 2-3: 33 (31%) 4-10: 21 (19%) >10: 4 (4%)	Median: 2.2cm^3 Range: 0.04-53.5cm^3 <1cm^3: 35 (32%)

								57 (53%)			1-3cm^3: 28 (26%) >3cm^3: 45 (42%)
Izard, 2019	Macquarie University, NSW	Single institution retrospective	2010-2017	180	60 (21-90)	M =76 (42%) F = 104 (58%)	n/a	Lung = 48 (27%) Breast = 48 (27%) Melanoma = 43 (24%) Others = 41 (22%)	No: 116 (64%) Yes: 64 (36%)	Median 5.5 (range: 1-47) 1: 29 (17%) 2-5: 61 (34%) 6-10: 43 (24%) 11-20: 30 (17%) >20: 17 (10%)	Median: 0.57cm^3 Range: <0.005-5.44 cm^3
Nicholls, 2019	Princess Alexandra Hospital, QLD	Single institution retrospective	2015-2017	146	60 (mean)	M=70 (48%) F=76 (52%)	0: 51 (35%) 1: 86 (59%) 2: 9 (6%)	Lung = 47 (32%) -EGFR/ALK mutant: 12 (26%) -EGFR/ALK wild-type: 35 (74%) Melanoma = 42 (29%) -BRAF mutant: 18 (43%) -BRAF wt: 24 (57%) Breast = 22 (15%) -Her2+ve: 9 (41%) -Her2-ve: 13 (59%) Colorectal = 11 (8%) Renal = 9 (6%)	n/a	n/a	n/a
Or, 2019+	Royal Northshore Hospital, NSW	Single institution retrospective	2010-2017	166+	65 (30-92)	n/a	0: 21 (13%) 1: 90 (54%) 2: 43 (26% 3: 12 (7%)	Lung = 63 (38%) Melanoma = 28 (17%) Breast = 25 (15%) Colorectal = 18 (11%) Renal = 16 (10%)	No: 14 (8.4%) Yes: 152 (92%)	1: 101 (61%) 2-4: 54 (33%) 5-10: 11 (7%)	n/a

*1 patient did not receive SRS as randomized

+include all patients who had limited BM in the study, of which only 129 had SRS/ stereotactic RT to intact lesions/ surgical cavity

Table – 2 | Summary of dose and technical aspects of treatment planning and delivery, and addition of surgery and/or whole brain RT (WBRT)

Study, year	Dose/ fractionations	Prescription point	GTV-PTV expansion	Technique	Pre-SRS surgical debulking	Previous history of intracranial RT	Adjuvant WBRT with SRS
Roos, 2006	Median 19Gy/1# Range: 15-23Gy/1#	60-90% isodose line	n/a	LINAC-based	No=20 (91%) Yes=2 (9%) (denominator: number of patients)	No=2 (9%) Yes=	No=14/22 (64%) Yes=8/22 (36%)
Roos, 2011	20Gy/1# (<20mm) 18Gy/1# (21-30mm) 15Gy/1#(31-40mm)	70-90% isodose	n/a	LINAC-based	No=10 (100%) Yes=0 (0%) (denominator: number of patients)	No=0 (0%) Yes=10 (100%)	No=0/10 (0%) Yes=10/10 (100%)
Sia, 2015	Range: 10-25Gy/1# <18Gy: 57 (18%) 18-20Gy: 240 (75%) >20Gy: 21 (7%)	80% isodose line (range; 80-100%)	No GTV-PTV expansion 166 (52%) 1mm GTV-PTV: 96 (30%) 2mm GTV-PTV: 56 (18%) (denominator: lesions)	LINAC-based	No=291 (92%) Yes=27 (8%) (denominator: number of lesions)	n/a	No=273/318 (86%) Yes=45/318 (14%) (denominator: lesions)
Croker, 2016	Median: 24Gy/ 3# Range: 22-40Gy/2-10# 24Gy/3#: 44 (72%) 25Gy/5#: 3 (5%) 30Gy/5#: 4 (7%) 30Gy/6#: 4 (7%) Other: 6 (10%)	n/a	GTV-CTV: 2-3mm CTV-PTV: 2-3mm	LINAC-based	No=29 (48%) Yes=32 (52%) (denominator: number of patients)	No= Yes (WBRT)=10 (%) Yes (SRS)=1 (%)	No=61/61 (100%) Yes= 0/61 (0%)
Choong, 2017	n/a	n/a	n/a	LINAC-based Gamma-knife	n/a	n/a	No=66/108 (61%) Yes=42/108 (39%)
Izard, 2019	20Gy/1# (<1.5cm lesion) 16-18Gy/1# (≥1.5cm lesion)	50% isodose line (60-90% isodose line for lesions ≤3mm)	No GTV-PTV expansion	Gamma-knife	No=119 (66%) Yes=61 (34%) (denominator: number of patients)	No=122 (68%) Yes(WBRT)=58 (32%)	No=180 (100%) Yes=0 (0%)
Nicholls, 2019	15-24Gy/1#	n/a	No GTV-PTV expansion	Gamma knife	No=149/156 (96%) Yes=7/156 (4%)	No=105/156 (67%)* Yes=51/156 (33%)*	No=146 (100%) Yes=0 (0%)

					(denominator: number of SRS session)		
Or, 2019	18-20Gy/1# (intact lesion) 25-30Gy/5# (surgical cavity/ intact lesion)	80% isodose line	Single fraction SRS: 1mm GTV-PTV Multi-fraction RT: 3mm GTV-PTV	LINAC-based	No=73/147 (50%) Yes=74/147 (50%) (denominator: number of lesions treated with RT)	n/a	No=129 (100%) Yes=0 (0%)

*by number of SRS sessions (instead of number of patients)

Table – 3 | Summary of oncological and toxicities outcomes

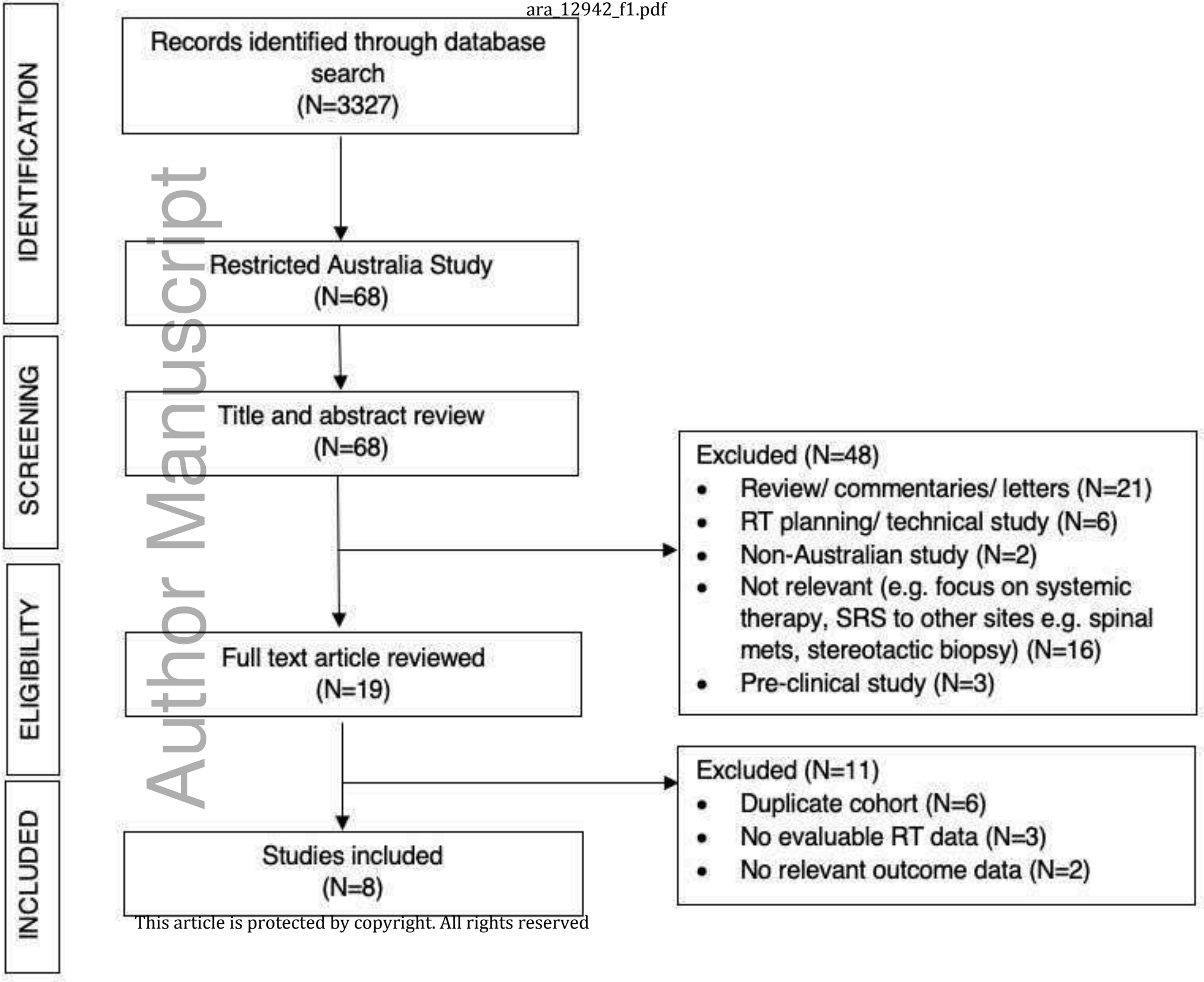
Study, year	Follow-up protocol	Follow-up duration, median (range)	Overall survival (OS)				Intracranial control (ICC)					Toxicities
			Median OS (month)	1yr OS	2yr OS	Prognostic factors for OS	ICC at last follow-up	6mth ICC	1yr ICC	2yr ICC	Prognostic factors for ICC	
Roos, 2006	1st month, then 3 monthly (imaging modalities not specified)		10.1 month	n/a	35%	n/a	n/a	n/a			n/a	n/a
Roos, 2011	MRI at 3, and 6 month	6.2 month (2.1-36.7 month)	6.2 month	46%	36%	n/a	73%	n/a	n/a	n/a	n/a	G3+=3 (30%) (severe fatigue)
Sia, 2015	MRI 3 monthly	7.7 month (0.4-75.3 month)	8.4 month (all) 5.1 month (melanoma) 12.2 month (lung) 14.7 month (breast)	43%	20%	ECOG status Uncontrolled systemic disease Histology (melanoma)	n/a	87%	82%	56%	GTV volume Melanoma histology	n/a
Croker, 2016	MRI 4-6 week post SRS; then 2-3 monthly	21 month (0.5-26 month)	21 month	60%	n/a	n/a	74%	n/a	n/a	n/a	n/a	G1= 234 (39%) G2= 8 (13%) G3+= 4 (7%)
Choong, 2017	3-monthly MRI Brain 3-monthly CT +/- PET	8.6 month (0.4-39.6 month)	14.2 month	56%	34%	ECOG status GPA Use of BRAF inhibitor	32%	67%	48%	n/a	Age ECOG status GPA Symptomatic BM	Radionecrosis=3 (3%), pathologically confirmed
Izard, 2019	3-monthly MRI	11 month (mean)	9.2 month	37%	20%	Age	n/a	n/a	n/a	n/a	n/a	Radionecrosis=22

						Sex Tumour volume						/180 (12%) (21 radiological diagnosis, 1 pathologically confirmed)
Nicholls, 2019	3-monthly MRI	[$]6.6 month (IQR:4.8-10.5)	[$]Not reached	[$]59.3%	n/a	n/a	*Not reached	n/a	*57.2%-86.2%	n/a	n/a	n/a
Or, 2019	n/a	[+]13 month	[+]15 months	n/a	n/a	Symptomatic extracranial disease Early intracranial relapse (within 6 months)	[+]50%	n/a	n/a	n/a	n/a	G3+= 0 (0%) Radionecrosis=2/129 (1.5%) radiological diagnosis

[$]include 95 patients of the cohort;

*include 93 patients; 57.2% in patients who had significant change in diagnostic and treatment MRI volume, and 86.2% in patients who did not have significant change in diagnostic and treatment MRI volume

[+]include 166 in the entire cohort, of which only 129 had SRS



Author/s:
Ong, WL; Wada, M; Ruben, J; Foroudi, F; Millar, J

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