[Frontiers in Bioscience, Scholar, 8, 203-214, January 1, 2016]

Recent advances in radiosurgical management of brain metastases

Hannah-Marie Devoid[1], Emory R. McTyre[1], Brandi R. Page[1], Linda Metheny-Barlow[1], Jimmy Ruiz[2], Michael D. Chan[1]

[1]Department of Radiation Oncology, Wake Forest School of Medicine, Winston-Salem, NC 27157, [2]Department of Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27157

TABLE OF CONTENTS

1. ABSTRACT

Stereotactic radiosurgery (SRS) has become a widely available treatment option for patients with brain metastases. Recent clinical trials suggest that SRS can be used without upfront whole brain radiotherapy (WBRT), resulting in several clinical dilemmas in the current daily practice of SRS. The proper patient selection for SRS or WBRT continues to evolve. Statistical models to predict when new brain metastases will occur as well as who will experience neurologic death have been developed. The optimization of imaging continues for both detection of brain metastases and response assessment. Larger brain metastases continue to pose a challenge to practitioners to find options to optimize the therapeutic ratio. The current review addresses the current state of the scientific literature for these clinical dilemmas.

2. INTRODUCTION

The past decade has seen significant improvements in the diagnosis and treatment of brain metastases. The use of stereotactic radiosurgery (SRS) has expanded exponentially over this time period. The recent expansion in the use of SRS is likely due to a combination of multiple factors including prospective trials showing improved quality of life endpoints compared to whole brain radiation therapy (WBRT) without worsening of survival, as well as improved access to patients with the advent of linear accelerator radiosurgical approaches. As there are now as many as 170,000 patients with brain metastases diagnosed in the United States each year (1), the evolution in management is quite important as patients are living longer than ever before, and because there are significant quality of life and economic implications to proper management.

SRS exploits recent technological advances to deliver high doses of radiation to small targets with little to no treatment volume margin expansion required. Biologically, the use of high doses per fraction likely increases the number of biologic targets within the metastases—including both neoplastic cells and supporting tissue,including endothelial cells (2). SRS also represents a more expensive treatment modality than the more traditional WBRT (3), so proper patient selection has become a critical issue. This review intends to cover some of the recent advances in radiosurgical patient selection and treatment planning, as well adjunct and salvage therapies. Successful performance of SRS in the modern era requires multidisciplinary collaboration between radiation oncologists, neurosurgeons, radiologists and medical oncologists.

3. RECENT PROSPECTIVE TRIALS

There have been three published randomized trials that have shown no survival benefit or decrement from using upfront SRS alone for patients with oligometastatic brain metastases and withholding WBRT for salvage. All three trials randomized patients with 1-3 brain metastases to either WBRT with SRS boost vs. SRS alone. In the first trial by Aoyama *et al*, patients randomized to the SRS alone arm had a lower local

Table 1. Prospective trials for treatment of brain metastases with stereotactic radiosurgery

Trial	Treatment	Local control (1 year)	Distant brain failure (1 year)	Overall survival (1 year)
RTOG 95-08 (23)	WBRT[1]	71%	33%	23%
	SRS[2]+WBRT	82%	27%	29%
EORTC 22952 (6)	SRS	70%	44%	47%
	SRS+WBRT	87%	28%	46%
MDACC (5)	SRS	67%	55%	60%
	SRS+WBRT	100%	27%	21%
JROSG 99-1 (4)	SRS	76%	63%	28%
	SRS+WBRT	90%	42%	39%
JLGK0901 (7)	SRS	87%	58%	50%
Alliance N0574 (64)	SRS+WBRT	N/A[3]	N/A	34%
	SRS	N/A	N/A	43%
Alliance N107C	SRS+WBRT	N/A	N/A	N/A
	SRS	N/A	N/A	N/A

Abbreviations: [1]Whole brain radiation therapy, [2]Stereotactic radiosurgery, [3]Not available

control and higher distant brain failure and neurologic death rate (4). In the second trial conducted at MD Anderson, patients randomized to the WBRT arm had a significantly higher rate of cognitive decline (5). In the third trial conducted by the EORTC, patients randomized to the WBRT arm experienced a subacute worsening in performance status and chronic worsening of health-related quality of life (6). Taken together, the results of these trials demonstrate that while salvage therapy is more likely to be necessary with SRS alone, withholding WBRT improves long-term cognition and short-term performance status.

A recent single arm prospective phase II trial from Japan has reported outcomes of radiosurgery for up to 10 brain metastases (7). In this study, patients with up to 10 brain metastases were treated with SRS. When stratified by number of metastases, patients with 5 to 10 brain metastases did not have any worse survival than those with 2 to 4 metastases. A summary of modern prospective trials assessing outcomes of patients with brain metastases treated with SRS is found in Table 1.

4. THE INCREASING USE OF RADIOSURGERY

The use of SRS for brain metastases has increased significantly over the past two decades. A recent SEER analysis revealed that the use of radiosurgery for patients with newly diagnosed brain metastases rose from 3% to 12.5.% between 2000 and 2005 (8). The rate of increase in use of radiosurgery has continued to grow since then with estimates that use will ultimately reach as many as 50% of patients with brain metastases.

Improvements in technology have been among the driving forces behind the increased use of SRS for brain metastases. Linear accelerators that can deliver SRS have become ubiquitous in community radiation oncology practices. Furthermore, the emergence of newer linear accelerator approaches have improved the efficiency of treatment of patients with multiple brain metastases as long treatment times had been one of the major limitations of treating patients with multiple metastases (9).

Several advantages have emerged for SRS while avoiding or delaying WBRT as long as possible. As mentioned above, SRS produces fewer declines in cognitive function than WBRT. This improvement is increasingly noticeable over time as cognitive function continues to decline over time after WBRT without plateau (10). Furthermore, once cognitive decline occurs, the treatment options are quite limited (11). In the more acute setting, the withholding of upfront WBRT leads to the convenience of shorter treatment times, while the improvement in performance status can improve the ability to deliver systemic therapies. In a recent recommendation statement of the American Society for Radiation Oncology (ASTRO), an expert panel suggested to not routinely add adjuvant WBRT in patients with limited brain metastases managed by SRS (12).

5. IMPROVING THE DETECTION OF OCCULT BRAIN METASTASES

When patients with brain metastasis are treated with SRS, there is incentive to detect occult metastases at the time of SRS so as to avoid early development of

distant brain failure after SRS. Several strategies have been assessed to improve detection for the stereotactic treatment planning MRI. For conventional MRI, thin slice images (2 mm or less) with no gap have become common amongst major radiosurgery centers (13). Optimizing contrast has included using increased contrast dose, and improved contrast agents. Use of double dose contrast with thin slice MRI has been found to improve treatment volume delineation (14), and number of occult metastases detected (15). However, given concerns for risks of high dose contrast administration-e.g. progressive system sclerosis--and the increase in the numbers of false positives (16), there has been greater enthusiasm for using high relaxivity agents. Anzalone *et al* performed a comparative study of 27 patients each receiving standard dosing of both gadobutrol (high relaxivity) and gadopentetate dimeglumine (lower relaxivity), finding that the high relaxivity agent demonstrated greater conspicuity of lesions and increased detection rate (17).

Higher magnet strength has also demonstrated an improved detection of occult metastasis. Saconn *et al* demonstrated that the use of 3T MRI increased the likelihood of detecting occult metastases in a series of 138 patients (18). Twenty-two percent of patients in this series were found to have increase in number of detected metastases as compared to the 1.5. T MRI done in the community.

One question that has arisen given the significant efforts to optimize detection of occult brain metastases for radiosurgery is whether better detection of metastases leads to improvements in pertinent clinical outcomes. Loganathan *et al* reported a series of 200 patients who were treated with SRS using either 3 T or 1.5. T MRI for treatment planning (19). This series did not detect a difference in distant brain failure, use of salvage WBRT, or overall survival between these two cohorts.

6. IMPROVING THE THERAPEUTIC RATIO FOR LARGER METASTASES

Larger metastases not amenable to surgical resection because of tumor location or the patient's ability and desire to withstand surgery present a more difficult challenge for practitioners. This is because as tumor volume increases, the dose that can safely be delivered to a tumor decreases. The RTOG 90-05 study described complications of SRS as a function of prescription dose and tumor volume (20). According to the RTOG 90-05 guidelines, tumors with 4 to 14 cc volumes fall into the dose range of 18 Gy to 15 Gy delivered to the tumor margin. Historic data suggest that local control at 1 year for patients receiving between 18 Gy and 15 Gy to the tumor margin is 60% (21). Furthermore, patients with larger metastases have been found to have a higher rate of dying from brain metastases (22).

Several options have been developed for the treatment of larger brain metastases. Many of these options combine the use of multiple modalities in order to improve upon the therapeutic ratio. Options for treating larger metastases include the use of the combination of surgery with radiotherapy, WBRT with a radiosurgical boost, two session SRS, hypofractionated stereotactic radiotherapy (SRT), and the use of concurrent systemic chemotherapy.

The RTOG 95-08 was a randomized study comparing WBRT alone to WBRT with SRS boost (23). While SRS did not improve outcomes in population as a whole, there were certain subgroups that benefited including patients with a solitary brain metastasis, Recursive Partitioning Analysis class I patients, and those who were younger than 50 years old. The nature of the subgroups with improved outcomes suggest that patients who benefit from a radiosurgical boost are the ones with a prolonged survival who will live long enough to experience a local failure after WBRT. The results of this trial have often since been extrapolated to include patients with larger brain metastases as these patients will also commonly live long enough to experience local failure, but more often because the burden of local disease leads to increased risk of early local failure.

There is currently significant interest in resection followed by SRS to the resection cavity. The Alliance for Clinical Trials in Oncology is currently conducting a phase III randomized trial (N107C) assessing the efficacy of cavity-directed radiosurgery after resection of a brain metastasis. While the primary endpoint is cognitive performance, the trial will also assess for local control and survival. Resection cavities as large as 5 cm are allowed onto this trial, and since cavities often collapse and are generally smaller than the original metastasis, surgery followed by SRS represents an excellent alternative to SRS alone for larger brain metastases. Local control with cavity-directed radiosurgery is approximately 80% at 1 year (24).

Both hypofractionated radiotherapy (25, 26) and staged two-session radiosurgery (27, 28) have been used in cases of unresectable larger brain metastases. These approaches attempt to exploit an advantage in the therapeutic ratio by fractionating radiotherapy in order to decrease the likelihood of radiation necrosis. The advantage of two-session radiosurgery is its ability to deliver the second stage of the treatment approximately one month after the first stage, when tumor regression has already started. Figure illustrates an example of two-session radiosurgery for a larger metastasis.

Recent evidence suggests that use of concurrent systemic therapy at the time of SRS can improve local control rates after SRS. This is a somewhat controversial

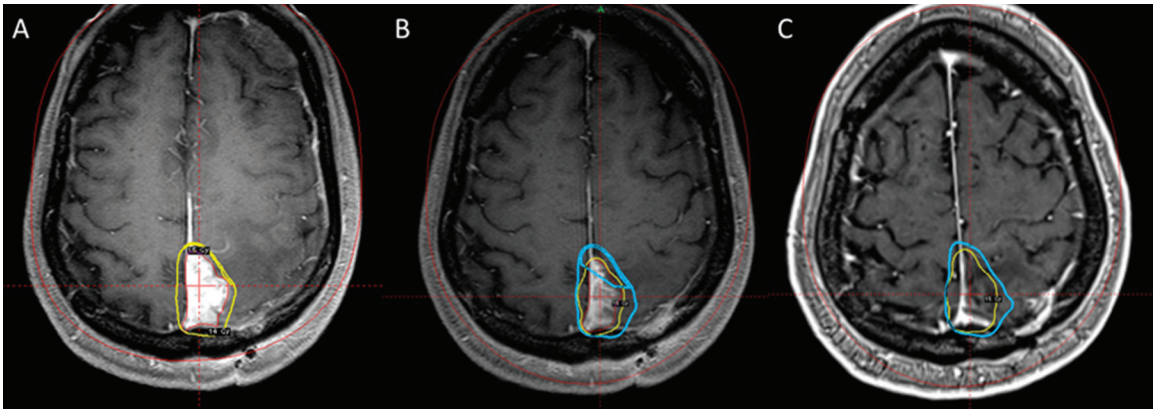

Figure 1. A) T1 Axial MRI on day of first stage radiosurgery showing a parasagittal metastasis. 15 Gy was prescribed to the 50% isodose line (yellow line). B) T1 Axial MRI on day of second stage radiosurgery showing tumor regression. Blue line represents prior treatment prescription. A second dose of 15 Gy was prescribed to the 50% isodose line, this time to a smaller volume. C) T1 Axial MRI at 6 month follow-up showing near complete regression of the original tumor. First stage (blue) and second stage (yellow) prescription isodose lines are super-imposed.

hypothesis as the traditional dogma had been that most systemic agents do not cross the blood brain barrier in a high enough concentration to significantly impact the natural history of the brain metastases. However, recent data for brain metastases from both renal cell carcinoma (29) and small cell lung cancer (30) suggest that using targeted agents (with renal cell carcinoma) or cytotoxic chemotherapy (with small cell cancer) within 30 days of SRS significantly improves the local control rate of SRS. Studies are currently underway to validate these findings in other histologies (31).

7. PREDICTION OF THE NEED FOR WHOLE BRAIN RADIOTHERAPY

The decision to use WBRT in the upfront setting for the management of brain metastases has become more controversial since recent prospective trials showed no worsening of survival with the use of SRS alone for fewer than 4 brain metastases, as well as the feasibility of treating as many as 10 brain metastases with SRS (7). Unfortunately, guidelines have been proposed that would deny patients with more than 3 brain metasatses SRS (32). There are several factors that may affect the decision for upfront WBRT: 1) risk of rapid development of new brain metastases (distant brain failure), 2) risk of inability to control local disease, 3) development of leptomeningeal dissemination, 4) life expectancy.

Several attempts have been made to predict life expectancy in patients with brain metastases. Gaspar *et al* performed a recursive partitioning analysis of patients from three consecutive RTOG trials conducted in the 1980's and found age, performance status and control of extracranial disease as the dominant factors affecting life expectancy in patients with brain metastases (33). More recently, an analysis of a large multi-institutional database has created a Graded Prognostic Assessment of patients with brain metastases and found that primary tumor type is a significant factor predicting outcome of patients (34).

The factors that appear to predict distant brain failure after primary SRS include a greater number of metastases and melanoma histology (35-37). A multi-institutional effort has created a nomogram for the prediction of distant brain failure after primary SRS without WBRT (38). While the absolute number of brain metastases was an important factor in predicting distant brain failure after SRS, histology also played a large role. This effect echoes other series within the literature demonstrating that both histology and molecular subtype have significant effects on distant brain failure rates (39, 40). Other factors that have been found to have a higher rate of requiring early WBRT include larger brain metastases, larger burden of intracranial metastases, and progressive systemic disease (35).

8. IDENTIFICATION OF POPULATIONS THAT WILL EXPERIENCE NEUROLOGIC DEATH

The ability to control intracranial disease contributes to the incidence of neurologic death, while non-neurologic death is typically determined by progression of extracranial disease or from toxicity associated with chemotherapy. Although the poor prognosis in brain metastasis patients is often instinctively attributed to neurologic causes, in the modern era, these patients are actually at equal or greater risk of death from non-neurologic causes, with overall rates of neurologic death from brain metastases reported at approximately 20% in a recent randomized study (4). This shift in clinical outcomes has significant implications on the management of patients with brain metastasis, and in the future will likely inform decisions on the intensification and de-intensification of therapies for intracranial and

extracranial disease depending upon each patient's relative risk of experiencing these competing events.

Recent studies have shown that patients with brain metastases who are symptomatic at presentation are at an increased risk of neurologic death as compared to asymptomatic patients (3). For those treated upfront with SRS, there is no definitive evidence that the addition of WBRT decreases rates of neurologic death. One trial concluded that the incidence of neurologic death was lower for patients receiving both SRS and WBRT (41), while another showed no difference (4).

To date, several factors have been shown to contribute to either neurologic or non-neurologic death. The presence of large and increasing numbers of brain metastases are associated with an increased incidence of neurologic death, while progressive systemic disease and lung primary tumors favor non-neurologic death (22). Presence of brainstem metastases has also been implicated in neurologic deaths (22, 42). Predictive models are currently being developed to estimate the risk of experiencing either of these competing events (43).

9. DISTINGUISHING RADIATION NECROSIS FROM TUMOR PROGRESSION

Radiation necrosis (RN) after SRS is one of the most significant late toxicities following SRS. It can mimic tumor progression on imaging and is reported to occur in 7-10% of SRS cases (44). Risk factors for developing RN include large size of brain metastasis, higher doses of radiosurgery, use of chemotherapy, and re-treatment with radiosurgery, with shorter intervals between treatment being an additional risk factor (20, 45). The timing of RN has been noted to occur slightly later than tumor progression in the majority of patients. In one study, tumor progression started between 3-7 months whereas in the same series, RN was noted starting between 7.6. months to 3 years (46).

Standard MRI based imaging modalities have been found to be insufficient to distinguish RN from tumor progression. A region of RN often appears similarly as a contrast-enhancing lesion with surrounding edema. Newer methods have been attempted to increase the sensitivity and specificity of conventional MRI, including calculation of the lesion quotient (LQ). The LQ ratio is a number obtained by taking the maximal nodular cross sectional area on T2 weighted imaging and comparing it to the same area of enhancement found on the T1-post contrast MRI. Additionally, the T1/T2 mismatch technique is sometimes utilized. This technique accounts for the volume of enhancement on T1- weighted MRI that does not correspond to T2 weighted images. Together these methods have been reported with a sensitivity of 80-83.3.%, but a more recent study suggested utilizing these calculation methods have extreme variability to sensitivity as low as 8% for detecting radiation necrosis (44). This suggests the need for more sophisticated imaging modalities than conventional MRI.

Historically, MR spectroscopy has been used to distinguish tumor progression from RN. This modality utilizes amino acid consumption by neoplastic cells to differentiate necrosis from neoplastic tissue. By characterizing the chemical composition of tissues, the N-acetyl Aspartate (NAA) and choline ratio can be obtained which can suggest RN versus tumor progression. One disadvantage to this modality is the inability to distinguish between pure RN and mixed partial tumor recurrence. Furthermore, MR spectroscopy is highly operator-dependent, and may have lower rates of accuracy at institutions that have less expertise in this modality. Delayed contrast extravasation MRI (DCE-MRI) assesses the relative cerebral blood volume to the area of interest. Due to the expected increase in relative cerebral blood volume in regions of recurrence, a decrease in cerebral blood volume suggests necrosis. DCE-MRI is a modality being studied in several clinical trials for both primary and metastatic brain tumors with some encouraging results. Perfusion-weighted MRI has been utilized to differentiate between RN and tumor progression by studying relative cerebral blood volume and other hemodynamic variables to characterize the area of interest. Sensitivity for this modality is estimated to be between 56-100% (45). Flurodeoxyglucose positron emission tomography (FDG-PET) as well as more novel amino acid tracers such as *L*-methyl-^{11}C-Methionine (11C-Met), O-2-F-fluoroethyl-*L*-tyrosine (^{18}F-FET), 3,4-hydroxy-6-^{18}F-Fluro-*L*-phenylalanine (^{18}F-FDOPA have been used in primary brain tumors and are currently being studied in brain metastases (47-49). Table 2 summarizes some of the prior studies for the use of advanced imaging studies for the diagnosis of radiation necrosis.

Once diagnosis of RN has been established, treatment for symptomatic control is considered. High dose corticosteroids provide first line therapy, but due to adverse side effects from prolonged use, other modalities are also used. These include anticoagulation, antiplatelet therapy, and antiangiogenic pharmacologic agents such as bevacizumab (50). Hyperbaric oxygen has been described in case reports as well as prophylactically with mixed results (51, 52). Oral Vitamin E administration with pentoxyphylline has been studied in a pilot study for patients with radiation necrosis, with mixed results owing to difficulty with adverse side effects of the medication, including persistent nausea and gastrointestinal discomfort (53). Surgical resection and laser interstitial thermal therapy (LITT) have been described for medically refractory cases (54). One advantage to surgical resection or LITT therapy is the ability to biopsy and remove or ablate the region in the same procedure. Standard monitoring after SRS has included serial MRI

Table 2. Imaging modalities used to distinguish radiation necrosis from tumor progression after radiosurgery for brain metastases

Institution	Imaging modality	Sensitivity for radiation necrosis (%)	Specificity for radiation necrosis (%)
Cleveland clinic (44)	Standard MRI[1] (lesion quotient)	8	91
Gainesville (65)	Standard MRI (lesion quotient)	80	96
Pittsburgh (66)	Standard MRI (T1/T2 mismatch)	83	91
Cleveland clinic (67)	FDG PET[2]	86	80
Asahikawa, Japan (68)	MRS	82	33
Yokohama, Japan (69)	Thalium SPECT	83	84
Shizoaka, Japan (70)	Perfusion MRI	100	96
Abbreviations: [1]Magnetic resonance imaging, [2]Fluorodeoxyglucose positron emission tomography			

imaging. There is a great need for the development of imaging techniques that more reliably distinguish RN from tumor progression.

10. ADVANCEMENTS IN SALVAGE THERAPY

Several advances have been made over the past decade with regards to salvage therapy after local failure of SRS. The classic salvage options for SRS failure include surgical resection and WBRT. The advantage of surgical resection is that it distinguishes tumor progression from radiation necrosis. The disadvantage, however, is that surgical resection as a single modality treatment yields a high local failure rate (55). The use of WBRT can be used in the setting of unresectable disease, though in patients with a longer life expectancy, WBRT can lead to late toxicity as discussed above. Placement of BCNU wafers at time of surgery has been reported as an effective adjuvant therapy to surgery after failure of SRS (56). Laser interstitial thermal therapy (LITT) has also been described as a successful salvage therapy after local recurrence (57, 58).

Performing repeat SRS on a lesion that has already failed SRS is a somewhat controversial practice since there is little data on the safety of this practice. A single series from Stanford has been reported showing acceptable rates of local control, but with radiation necrosis rates higher than what would be seen in a single treatment (59). Further studies will be necessary to determine the dose volume tolerances for repeat SRS on metastases experiencing local failures.

Leptomeningeal failure occurs in up to 10% of patients receiving SRS as upfront therapy for brain metastases (60). WBRT has commonly been used in the past for patients with leptomeningeal failure. While WBRT may palliate symptoms such as cranial nerve palsy, it is unclear whether it affects overall survival (61). A subset of patients with metastatic breast cancer with active disease confined to leptomeningeal spread may benefit from craniospinal irradiation (62). Systemic therapy has been reported to lead to prolonged regression of leptomeningeal disease, particularly in cases of patients with breast cancer (63).

11. CONCLUSIONS AND FUTURE DIRECTIONS

The role of SRS in the management of brain metastases continues to evolve. In the near future, the role of SRS will be defined by increasing accessibility and thus, increasing use. In the intermediate term, the results of current prospective clinical trials such as the Alliance N107C study will be critical in defining the role of SRS in the adjuvant setting after resection of metastases, and as a means of preserving cognition and quality of life. In the future, the integration of advanced imaging will serve as an important adjunct to radiosurgical management, while further prospective studies will be necessary to justify the role of SRS in more non-traditional populations, such as those with a greater number of metastases. Furthermore, future studies will need to better define which patients are most likely to truly benefit from SRS so as to properly allocate resources for a limited and costly modality. Academicians and private practitioners alike will need to justify the increased cost of SRS, whether it be on an individual basis or amongst populations.

12. REFERENCES

1. Ellis TL, Neal MT, Chan MD: The role of surgery, radiosurgery and whole brain radiation therapy in the management of patients with metastatic brain tumors. *Int J Surg Oncol* 2012, 952345 (2011) DOI: 10.1155/2012/952345
2. Truman JP, Garcia-Barros M, Kaag M, Hambardzumyan D, Stancevic B, Chan M, Fuks Z, Kolesnick R, Haimovitz-Friedman

A: Endothelial membrane remodeling is obligate for anti-angiogenic radiosensitization during tumor radiosurgery. *PLoS One* 5, e12310 (2010)
DOI: 10.1371/annotation/6e222ad5-b175-4a00-9d04-4d120568a897

3. Lester SC, Taksler GB, Kuremsky JG, Lucas JT, Jr., Ayala-Peacock DN, Randolph DM, 2nd, Bourland JD, Laxton AW, Tatter SB, Chan MD: Clinical and economic outcomes of patients with brain metastases based on symptoms: an argument for routine brain screening of those treated with upfront radiosurgery. *Cancer* 120, 433-41 (2014)
DOI: 10.1002/cncr.28422

4. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Hayakawa K, Katoh N, Kobashi G: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 295, 2483-91 (2006)
DOI: 10.1001/jama.295.21.2483

5. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shui AS, Maor MH, Meyers CA: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 10, 1037-44 (2009)
DOI: 10.1016/S1470-2045(09)70263-3

6. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Mueller RP, Tridello G, Collette L, Bottomley A: 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. *J Clin Oncol* 31, 65-72 (2013)
DOI: 10.1200/JCO.2011.41.0639

7. Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, Yamanaka K, Sato Y, Jokura H, Yomo S, Nagano O, Kenal H, Moriki A, Suzuki S, Kida Y, Iwai Y, Hayashi M, Onishi H, Gondo M, Sato M, Akimitsu T, Kubo K, Kikuchi Y, Shibasaki T, Goto T, Takanashi M, Mori Y, Takakura K, Saeki N, Kunieda E, Aoyama H, Momoshima S, Tsuchiya K: Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* 15, 387-95 (2014)
DOI: 10.1016/S1470-2045(14)70061-0

8. Halasz LM, Weeks JC, Neville BA, Taback N, Punglia RS: Use of stereotactic radiosurgery for brain metastases from non-small cell lung cancer in the United States. *Int J Radiat Oncol Biol Phys* 85, e109-16 (2013)
DOI: 10.1016/j.ijrobp.2012.08.007

9. Thomas EM, Popple RA, Wu X, Clark GM, Markert JM, Guthrie BL, Yuan Y, Dobelbower MC, Spencer SA, Fiveash JB: Comparison of plan quality and delivery time between volumetric arc therapy (RapidArc) and Gamma Knife radiosurgery for multiple cranial metastases. *Neurosurgery* 75, 409-17 (2014)
DOI: 10.1227/NEU.0000000000000448

10. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD: Radiation-induced brain injury: A review. *Front Oncol* 2, 73 (2012)
DOI: 10.3389/fonc.2012.00073

11. Attia A, Page BR, Lesser GJ, Chan M: Treatment of radiation-induced cognitive decline. *Curr Treat Options Oncol* 15, 539-50 (2014)
DOI: 10.1007/s11864-014-0307-3

12. Sahgal A, Larson D, Knisely J: Stereotactic radiosurgery alone for brain metastases. *Lancet Oncol* 16, 249-50 (2015)
DOI: 10.1016/S1470-2045(14)71106-4

13. Engh JA, Flickinger JC, Niranjan A, Amin DV, Kondziolka DS, Lunsford LD: Optimizing intracranial metastasis detection for stereotactic radiosurgery. *Stereotact Funct Neurosurg* 85, 162-8 (2007)
DOI: 10.1159/000099075

14. Subedi KS, Takahashi T, Yamano T, Saitoh J, Nishimura K, Suzuki Y, Ohno T, Nakano T: Usefulness of double dose contrast-enhanced magnetic resonance imaging for clear delineation of gross tumor volume in stereotactic radiotherapy treatment planning of metastatic brain tumors: a dose comparison study: *J Radiat Res* 54, 135-9 (2013)
DOI: 10.1093/jrr/rrs053

15. Yuh WT, Tali ET, Nguyen HD, Simonson TM, Mayr NA, Fisher DJ: The effect of contrast dose, imaging time, and lesion size in the MR detection of intracerebral metastasis. *AJNR Am J Neuroradiol* 16, 373-80 (1995)
No DOI found

16. Sze G, Johnson C, Kawamura Y, Goldberg SN, Lange R, Friedland RJ, Wolf RJ: Comparison of single- and triple-dose contrast material in the MR screening of brain metastases. *AJNR Am J Neuroradiol* 19, 821-8 (1998)
No DOI found

17. Anzalone N, Gerevini S, Scotti R, Vezzulli P, Picozzi P: Detection of cerebral metastases on magnetic resonance imaging: intraindividual comparison of gadobutrol with gadopentetate dimeglumine. *Acta Radiol* 50, 933-40 (2009)
DOI: 10.1080/02841850903095385

18. Saconn PA, Shaw EG, Chan MD, Squire SE, Johnson AJ, McMullen KP, Tatter SB, Ellis TL, Lovato J, Bourland JD, Ekstrand KE, DeGuzman AF, Munley MT: Use of 3.0.-T MRI for stereotactic radiosurgery planning for treatment of brain metastases: a single-institution retrospective review. *Int J Radiat Oncol Biol Phys* 78, 1142-6 (2009)
DOI: 10.1016/j.ijropb.2010.05.049

19. Loganathan AG, Chan MD, Alphonse N, Peiffer AM, Johnson AJ, McMullen KP, Urbanic JJ, Saconn PA, Bourland JD, Munley MT, Shaw EG, Tatter SB, Ellis TL: Clinical outcomes of brain metastases treated with Gamma Knife radiosurgery with 3.0. T versus 1.5. T MRI-based treatment planning: have we finally optimised detection of occult brain metastases? *J Med Imaging Radiat Oncol* 56, 554-60 (2012)
DOI: 10.1111/j.1754-9485.2012.02429.x

20. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, Farnan N: Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 47, 291-8 (2000)
DOI: 10.1016/S0360-3016(99)00507-6

21. Shiau CY, Sneed PK, Shu HK, Lamborn KR, McDermott MW, Chang S, Nowak P, Petti PL, Smith V, Verhey LJ, Ho M, Park E, Wara WM, Gutin PH, Larson DA: Radiosurgery for brain metastases: relationship of dose and pattern of enhancement to local control. *Int J Radiat Oncol Biol Phys* 37, 375-83 (1997)
DOI: 10.1016/S0360-3016(96)00497-X

22. Lucas J, Colmer H, White L, Fitzgerald N, Isom S, Bourland JD, Laxton AW, Tatter SB, Chan MD: Competing Risk Analysis of Neurologic vs. Non-Neurologic Death in Patients Undergoing Radiosurgical Salvage Following Whole Brain Radiotherapy Failure (WBRT): Who Actually Dies of Their Brain Metastases? *Int J Radiat Oncol Biol Phys* 92, 1008-15 (2015)
No DOI found

23. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP, Curran WJ: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 363, 1665-72 (2004)
DOI: 10.1016/S0140-6736(04)16250-8

24. Jensen CA, Chan MD, McCoy TP, Bourland JD, deGuzman AF, Ellis TL, Ekstrand KE, McMullen KP, Munley MT, Shaw EG, Urbanic JJ, Tatter SB: Cavity-directed radiosurgery as adjuvant therapy after resection of a brain metastasis. *J Neurosurg* 114, 1585-91 (2011)
DOI: 10.3171/2010.11.JNS10939

25. Eaton BR, Gebhardt B, Prabhu R, Shu HK, Curran WJ, Jr., Crocker I: Hypofractionated radiosurgery for intact or resected brain metastases: defining the optimal dose and fractionation. *Radiat Oncol* 8, 135 (2013)
DOI: 10.1186/1748-717X-8-135

26. Feuvret L, Vinchon S, Martin V, Lamproglou I, Halley A, Calugaru V, Chea M, Valery CA, Simon JM, Mazeron JJ: Stereotactic radiotherapy for large solitary brain metastases. *Cancer Radiother* 18, 97-106 (2014)
DOI: 10.1016/j.canrad.2013.12.003

27. Yomo S, Hayashi M, Nicholson C: A prospective pilot study of two-session Gamma Knife surgery for large metastatic brain tumors. *J Neurooncol* 109, 159-65 (2012)
DOI: 10.1007/s11060-012-0882-8

28. Yomo S, Hayashi M: A minimally invasive treatment option for large metastatic brain tumors: long-term results of two-session Gamma Knife stereotactic radiosurgery.

Radiat Oncol 9, 132 (2014)
DOI: 10.1186/1748-717X-9-132

29. Cochran DC, Chan MD, Aklilu M, Lovato JF, Alphonse NK, Bourland JD, Urbanic JJ, McMullen KP, Shaw EG, Tatter SB, Ellis TL: The effect of targeted agents on outcomes in patients with brain metastases from renal cell carcinoma treated with Gamma Knife surgery. *J Neurosurg* 116, 978-83 (2012)
DOI: 10.3171/2012.2.JNS111353

30. Harris S, Chan MD, Lovato JF, Ellis TL, Tatter SB, Bourland JD, Munley MT, deGuzman AF, Shaw EG, Urbanic JJ, McMullen KP: Gamma knife stereotactic radiosurgery as salvage therapy after failure of whole-brain radiotherapy in patients with small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 83, e53-9 (2012)
DOI: 10.1016/j.ijrobp.2011.11.059

31. Johnson AG, Ruiz J, Hughes R, Page BR, Isom S, Lucas JT, McTyre ER, Houseknecht KW, Ayala-Peacock DN, Bourland JD, Hinson WH, Laxton AW, Tatter SB, Debinski W, Watabe K, Chan MD: Impact of Systemic Targeted Agents on the Clinical Outcomes of Patients with Brain Metastases. *Oncotarget* (2015)
No DOI found

32. MedSolutions I: *MedSolutions Radiation Oncology Guidelines Version 3.0*. 2015 (cited 2015 May 19, 2015)
No DOI found

33. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG, Byhardt R: Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 37, 745-51 (1997)
DOI: 10.1016/S0360-3016(96)00619-0

34. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, Sneed PK, Chao ST, Weil RJ, Suh J, Bhatt A, Jensen AW, Brown PD, Shih HA, Kirkpatrick J, Gaspar LE, Fiveash JB, Chiang V, Knisely JP, Sperduto CM, Lin N, Mehta M: Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 30, 419-25 (2012)
DOI: 10.1200/JCO.2011.38.0527

35. Ayala-Peacock DN, Peiffer AM, Lucas JT, Isom S, Kuremsky JG, Urbanic JJ, Bourland JD, Laxton AW, Tatter SB, Shaw EG, Chan MD: A nomogram for predicting distant brain failure in patients treated with gamma knife stereotactic radiosurgery without whole brain radiotherapy. *Neuro Oncol* 16, 1283-8 (2014)
DOI: 10.1093/neuonc/nou018

36. Sawrie SM, Guthrie BL, Spencer SA, Nordal RA, Meredith RF, Markert JM, Cloud GA, Fiveash JB: Predictors of distant brain recurrence for patients with newly diagnosed brain metastases treated with stereotactic radiosurgery alone. *Int J Radiat Oncol Biol Phys* 70, 181-6 (2008)
DOI: 10.1016/j.ijrobp.2007.05.084

37. Neal MT, Chan MD, Lucas JT, Jr., Loganathan A, Dillingham C, Pan E, Stewart JH 2nd, Bourland JD, Shaw EG, Tatter SB, Ellis TL: Predictors of survival, neurologic death, local failure, and distant failure after gamma knife radiosurgery for melanoma brain metastases. *World Neurosurg* 82, 1250-5 (2014)
DOI: 10.1016/j.wneu.2013.02.025

38. Ayala-Peacock D, Attia A, Hepel J, Lucas J, Onyeuku N, Stavas M, Taylor RB, Chung C, Fiveash J, Chan MD: A Multi-institutional Predictive Nomogram for Distant Brain Failure in Patients Treated with Upfront Stereotactic Radiosurgery Without Whole Brain Radiation Therapy. *Int J Radiat Oncol, Biol, Phys* 90, S126 (2014)
No DOI found

39. Kuremsky JG, Urbanic JJ, Petty WJ, Lovato JF, Bourland JD, Tatter SB, Ellis TL, McMullen KP, Shaw EG, Chan MD: Tumor Histology Predicts Patterns of Failure and Survival in Patients with Brain Metastases from Lung Cancer Treated with Gamma Knife Radiosurgery. *Neurosurgery* 73, 641-7 (2013)
DOI: 10.1227/NEU.0000000000000072

40. Vern-Gross TZ, Lawrence JA, Case LD, McMullen KP, Bourland JD, Metheny-Barlow LJ, Ellis TL, Tatter SB, Urbanic JJ, Chan MD: Breast cancer subtype affects patterns of failure of brain metastases after treatment with stereotactic radiosurgery. *J Neurooncol* 110, 381-8 (2012)
DOI: 10.1007/s11060-012-0976-3

41. Kocher M, Soffietti R, Abacioglu U, Villa S,

Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Collette S, Collette L, Mueller RP: 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, 134-41 (2011)
DOI: 10.1200/JCO.2010.30.1655

42. Kilburn JM, Ellis TL, Lovato JF, Urbanic JJ, Daniel Bourland J, Munley MT, DeGuzman AF, McMullen KP, Shaw EG, Tatter SB, Chan MD: Local control and toxicity outcomes in brainstem metastases treated with single fraction radiosurgery: is there a volume threshold for toxicity? *J Neurooncol* 117, 167-74 (2014)
DOI: 10.1007/s11060-014-1373-x

43. Lucas J, Ayala-Peacock D, Piazza M, Kuremsky J, Page B, Randolph D, Fitzgerald N, Holmes JA, Soike M, Tatter SB, Chan MD: A Propensity Score Adjusted Analysis of Patients Receiving Up-Front SRS Versus WBRT: Does the Use of Upfront WBRT Really Affect Neurologic Death? *Int J Radiat Oncol, Biol, Phys* 90, S315-6 (2014)
No DOI found

44. Stockham AL, Tievsky AL, Koyfman SA, Reddy CA, Suh JH, Vogelbaum MA, Barnett GH, Chao ST: Conventional MRI does not reliably distinguish radiation necrosis from tumor recurrence after stereotactic radiosurgery. *J Neurooncol* 109, 149-58 (2012)
DOI: 10.1007/s11060-012-0881-9

45. Ruzevick J, Kleinberg L, Rigamonti D: Imaging changes following stereotactic radiosurgery for metastatic intracranial tumors: differentiating pseudoprogression from tumor progression and its effect on clinical practice. *Neurosurg Rev* 37, 193-201 (2014)
DOI: 10.1007/s10143-013-0504-8

46. Kim YZ, Kim DY, Yoo H, Yang HS, Shin SH, Hong EK, Cho KH, Lee SH: Radiation-induced necrosis deteriorating neurological symptoms and mimicking progression of brain metastasis after stereotactic-guided radiotherapy. *Cancer Res Treat* 39, 16-21 (2007)
DOI: 10.4143/crt.2007.39.1.16

47. Chung JK, Kim YK, Kim SK, Lee YJ, Paek S, Yeo JS, Jeong JM, Lee DS, Jung HW, Lee MC: Usefulness of 11C-methionine PET in the evaluation of brain lesions that are hypo- or isometabolic on 18F-FDG PET. *Eur J Nucl Med Mol Imaging* 29, 176-82 (2002)
DOI: 10.1007/s00259-001-0690-4

48. Chen W, Silverman DH, Delaloye S, Czernin J, Kamdar N, Pope W, Satyamurthy N, Schlepers C, Cloughesy T: 18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy. *J Nucl Med* 47, 904-11 (2006)
No DOI found

49. Li DL, Xu YK, Wang QS, Wu HB, Li HS: (1)(1) C-methionine and (1)(8)F-fluorodeoxyglucose positron emission tomography/CT in the evaluation of patients with suspected primary and residual/recurrent gliomas. *Chin Med J (Engl)* 125, 91-6 (2012)
No DOI found

50. Boothe D, Young R, Yamada Y, Prager A, Chan T, Beal K: Bevacizumab as a treatment for radiation necrosis of brain metastases post stereotactic radiosurgery. *Neuro Oncol* 15, 1257-63 (2013)
DOI: 10.1093/neuonc/not085

51. Kohshi K, Imada H, Nomoto S, Yamaguchi R, Abe H, Yamamoto H: Successful treatment of radiation-induced brain necrosis by hyperbaric oxygen therapy. *J Neurol Sci* 209, 115-7 (2003)
DOI: 10.1016/S0022-510X(03)00007-8

52. Parvez K, Parvez A, Zadeh G: The diagnosis and treatment of pseudoprogression, radiation necrosis and brain tumor recurrence. *Int J Mol Sci* 15, 11832-46 (2014)
DOI: 10.3390/ijms150711832

53. Williamson R, Kondziolka D, Kanaan H, Lunsford LD, Flickinger JC: Adverse radiation effects after radiosurgery may benefit from oral vitamin E and pentoxifylline therapy: a pilot study. *Stereotact Funct Neurosurg* 86, 359-66 (2008)
DOI: 10.1159/000163557

54. Rahmathulla G, Recinos PF, Valerio JE, Chao S, Barnett GH: Laser interstitial thermal therapy for focal cerebral radiation necrosis: a case report and literature review. *Stereotact Funct Neurosurg* 90, 192-200 (2012)
DOI: 10.1159/000338251

55. Patchell RA, Tibbs PA, Regine WF, Dempsey

RJ, Mohiuddin M, Kryscio RJ, Markesbery WR, Foon KA, Young B: Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 280, 1485-9 (1998)
DOI: 10.1001/jama.280.17.1485

56. Mu F, Lucas JT, Jr., Watts JM, Johnson AJ, Daniel Bourland J, Laxton AW, Chan MD, Tatter SB: Tumor resection with carmustine wafer placement as salvage therapy after local failure of radiosurgery for brain metastasis. *J Clin Neurosci* 22, 561-5 (2015)
DOI: 10.1016/j.jocn.2014.08.020

57. Rao MS, Hargreaves EL, Khan AJ, Haffty BG, Danish SF: Magnetic resonance-guided laser ablation improves local control for postradiosurgery recurrence and/or radiation necrosis. *Neurosurgery* 74, 658-67 (2014)
No DOI found

58. Torres-Reveron J, Tomasiewicz HC, Shetty A, Amankulor NM, Chiang VL: Stereotactic laser induced thermotherapy (LITT): a novel treatment for brain lesions regrowing after radiosurgery. *J Neurooncol* 113, 495-503 (2013)
DOI: 10.1227/NEU.0000000000000332

59. Jayachandran P, Shultz D, Modlin L, Von Eyben R, Gibbs IC, Chang S, Harsh G, Li G, Adler J, Hancook SL, Soltys SG: Repeat Stereotactic Radiosurgery (SRS) for Brain Metastases Locally Recurrent Following Initial SRS. *Int J Radiat Oncol, Biol, Phys* 90, S320 (2014)
No DOI found

60. Huang AJ, Huang KE, Page BR, Ayala-Peacock DN, Lucas JT, Jr., Lesser GJ, Laxton AW, Tatter SB, Chan MD: Risk factors for leptomeningeal carcinomatosis in patients with brain metastases who have previously undergone stereotactic radiosurgery. *J Neurooncol* 120, 163-9 (2014)
DOI: 10.1007/s11060-014-1539-6

61. Wasserstrom WR, Glass JP, Posner JB: Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. *Cancer* 49, 759-72 (1982)
DOI:10.1002/1097-0142(19820215)49:4%3C759::AID- CNCR2820490427%3E3.0.CO;2-7

62. Hermann B, Hultenschmidt B, Sautter-Bihl ML: Radiotherapy of the neuroaxis for palliative treatment of leptomeningeal carcinomatosis. *Strahlenther Onkol* 177, 195-9 (2001)
DOI: 10.1007/PL00002398

63. Vincent A, Lesser G, Brown D, Vern-Gross T, Metheny-Barlow L, Lawrence J, Chan MD: Prolonged regression of metastatic leptomeningeal breast cancer that has failed conventional therapy: a case report and review of the literature. *J Breast Cancer* 16, 122-6 (2013)
DOI: 10.4048/jbc.2013.16.1.122

64. Brown PD, Asher AL, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Barker FG, Deming RL, Burri S, Menard C, Chung C, Stieber VW, Pollock BE, Galanis E, Buckner JC, Jaeckle KA: NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 go 3 brain metastases. *J Clin Oncol* 33, abstr LBA4 (2015)
No DOI found

65. Dequesada IM, Quisling RG, Yachnis A, Friedman WA: Can standard magnetic resonance imaging reliably distinguish recurrent tumor from radiation necrosis after radiosurgery for brain metastases? A radiographic-pathological study. *Neurosurgery* 63, 898-903 (2008)
DOI: 10.1227/01.NEU.0000333263.31870.31

66. Kano H, Kondziolka D, Lobato-Polo J, Zorro O, Flickinger JC, Lunsford LD: T1/T2 matching to differentiate tumor growth from radiation effects after stereotactic radiosurgery. *Neurosurgery* 66, 486-91 (2010)
DOI: 10.1227/01.NEU.0000360391.35749.A5

67. Chao ST, Suh JH, Raja S, Lee SY, Barnett G: The sensitivity and specificity of FDG PET in distinguishing recurrent brain tumor from radionecrosis in patients treated with stereotactic radiosurgery. *Int J Cancer* 96, 191-7 (2001)
DOI: 10.1002/ijc.1016.abs

68. Kimura T, Sako K, Tanaka K, Gotoh T, Yoshida H, Aburano T, Tanaka T, Arai H, Nakada T: Evaluation of the response of metastatic brain tumors to stereotactic radiosurgery by proton magnetic resonance spectroscopy, 201TlCl single-photon emission computerized tomography, and gadolinium-enhanced magnetic resonance imaging. *J Neurosurg* 100, 835-41. (2004)
DOI: 10.3171/jns.2004.100.5.0835

69. Matsunaga S, Shuto T, Takase H, Ohtake M, Tomura N, Tanaka T, Sonoda M: Semiquantitative analysis using thallium-201 SPECT for differential diagnosis between tumor recurrence and radiation necrosis after gamma knife surgery for malignant brain tumors. *Int J Radiat Oncol Biol Phys* 85, 47-52. (2013) DOI: 10.1016/j.ijrobp.2012.03.008

70. Mitsuya K, Nakasu Y, Horiguchi S, Harada H, Nishimura T, Bando E, Okawa H, Furukawa Y, Hiral T, Endo M: Perfusion weighted magnetic resonance imaging to distinguish the recurrence of metastatic brain tumors from radiation necrosis after stereotactic radiosurgery. *J Neurooncol* 99, 81-8 (2010) DOI: 10.1007/s11060-009-0106-z

Key Words: Brain Metastasis, Stereotactic Radiosurgery, Review

Send correspondence to: Michael Chan, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, Tel: 336-713-3600, Fax: 336-713-6515, E-mail: mchan@wakehealth.edu