

A Paradigm Shift in the Radiation Treatment of Brain Metastases

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ABSTRACT

Treatment for patients with brain metastases has been evolving towards increased use of stereotactic radiosurgical techniques. This paradigm shift is based on technological developments and increased understanding about the potential negative consequences of whole brain radiation therapy. In this editorial review, we discuss the background of these changes. We also outline the pros and cons of four major developments in the treatment of brain metastases: (1) stereotactic radiosurgery in lieu of whole brain radiation therapy; (2) fractionated radiosurgery; (3) radiosurgery to the post-operative tumor bed; and (4) radiosurgery to numerous brain metastases.

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Key words: Stereotactic radiosurgery; Brain metastases; Fractionation; Whole brain radiation therapy; Post-operative

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INTRODUCTION

Neuro-oncology is in the midst of a paradigm shift in the management of radiation therapy for patients with brain metastasis. Whole brain radiation therapy (WBRT) is now being deferred in favor of radiosurgical techniques. Since the seminal work by Patchell *et al*^[1], the standard of care for patients with single brain metastasis has been WBRT following surgical resection of the single brain metastasis^[2,3] or stereotactic radiosurgery (SRS) followed by WBRT^[4]. Two major factors are responsible for the recent change in treatment patterns for patients with brain metastases. The first is data indicating that WBRT can be associated with negative side effects in many patients. The second is the adoption of alternative approaches, in lieu of WBRT, based on technological developments, which include fractionated SRS; tumor bed radiosurgery; and radiosurgery for numerous metastases. In this paper, we discuss the reasons for this paradigm shift, the technological developments permitting the shift, and the current applications of SRS.

WHOLE BRAIN RADIATION THERAPY CONCERNS

WBRT consists of providing patients small doses (1.5-2Gy) of external beam radiation to the brain in 10 to 30 sessions. The principles behind this form of therapy are commonly described as the 4Rs—repair, reoxygenation, redistribution, and repopulation^[5]. Repair indicates that small doses of radiation limit DNA damage and allow the normal cells to repair while reoxygenation suggests that the small doses allow for increased circulation and limit the hypoxic cells in the tumor bed, which are radioresistant. Redistribution refers to the fact that multiple sessions allow cells to redistribute through the cell cycle and decrease the chance of the cells being in the radioresistant S-phase^[6,7]. Finally, the concept of repopulation signifies that irradiated cells repopulate quickly so treatment will not be excessively delayed. Several studies have shown that WBRT alone increases median survival in patients with cerebral metastases

by 3-6 months, a therapeutic effect unmatched by any other adjunctive modality. Furthermore, when combined with a surgical extirpation of a solitary cerebral metastasis, survival is significantly increased. Proponents of WBRT argue that this modality confers increased survival to patients because radiation of the whole brain allows treatment of micrometastases that are not visible on imaging, thus preventing progression into larger lesions which compromises patients' survival^[8,9].

However, as systemic treatments improved and patients survived for longer periods of time after diagnosis, a number of practitioners became concerned about the potential detrimental effects of WBRT. Studies indicate that WBRT contributes to intellectual impairment due to its deleterious effects on the neurogenesis of the developing brain^[10,11]. These same mechanisms are also considered to underlie the cognitive decline in adults treated with WBRT by causing inflammatory changes resulting in injury to the neural stem cells in the hippocampus. These specific cells produce dentate neurons that contribute to new memory function by continually dividing and forming new neurons throughout an adult's life^[12-16]. As a result of the damage to these cells by WBRT, patients may be unable to develop neurons that are essential in high level cognitive function. Another detrimental side effect of WBRT may be cerebral occlusive disease^[17]. Also, brain atrophy can be seen as early as 6 to 12 months after WBRT^[18]. In addition, WBRT has been associated with complications such as decline in verbal and non-verbal memory, executive function, sustained attention, and information processing speed. Gait abnormalities may also occur^[18,19]. These effects are more evident in patients given higher doses of treatment, undergo longer treatment, or have longer survival^[6].

In contrast to WBRT, SRS uses a single, large, very precise highly cytotoxic dose of radiation to a discrete volume, resulting in minimal damage to the surrounding brain tissue^[6]. SRS has been shown by several studies to have the same survival benefits as WBRT, but self-reported cognition and verbal learning have been shown to be superior in patients treated with only SRS compared to WBRT^[20-25]. Quality of life is also better in those treated with SRS while deferring WBRT^[26]. Due to the observation of decreased adverse side effects associated with SRS, a shift away from WBRT towards SRS has gained momentum.

STEREOTACTIC RADIOSURGERY TECHNOLOGICAL ADVANCES

Based on the work of Horsley, Clark, and Spiegel^[27-31], Leksell developed an arc-based frame which, when secured to the patient's head, allowed precise determination of targets in the brain using x-ray localization. By combining gamma rays with his system, Leksell installed his Gamma Unit at Sophiahemmet Hospital in Stockholm, Sweden in 1968^[32] and treated 762 patients with radiosurgery over 14 years^[33]. As neuroimaging techniques improved, especially computed tomography (CT) scanning, localization and lesion placement became highly accurate and specific. The first Gamma Knife Unit in the United States was installed at the University of Pittsburgh in 1985; subsequently, widespread adoption of this treatment modality has occurred throughout the world^[34]. Device development and adaptation have led to the four types of devices most often used to deliver radiation for radiosurgery: Gamma Knife; linear accelerator (LINAC) based systems; Hi-Art Tomotherapy; and Cyberknife^[35]. Proton beam radiosurgery is also an option in a few centers^[36].

Further improvements in neuroimaging techniques such as Magnetic Resonance Imaging (MRI), CT, and angiography, as well as development of computer software programs, have led to improved planning algorithms that increase accuracy, precision, and safety of the treatment. The planning algorithms allow for fusion of the different imaging modalities and use of the fused images to accurately delineate the lesion, and define the target volume, including soft tissues and bone. The planning algorithms improve safety and precision by defining isodose distribution, dose volume histogram, conformity index, as well as the feasibility of utilizing the radiosurgery device to perform the treatment plan^[37]. This combination of images increases the ability to localize metastatic lesions with a precision of 0.3 mm^[35,38-42]. Additional accuracy and precision of treatment can be obtained to within 0.1 mm by obtaining localizing imaging on the day of treatment^[37,43].

Cone-beam CT is another means utilized to improve the accuracy of localization by imaging the lesion during treatment. In cone-beam CT, images from multiple angles in a conical fashion are obtained to construct digital 3D images^[44]. Under this localization concept, the radiosurgery device obtains CT imaging of the lesion during treatment and links the image to the stereotactic space. The device can then adjust the application of radiation to these areas. This technique effectively increases the accuracy and precision of the applied radiation dose and ensures the tumor is properly treated^[42,45,46].

New immobilization techniques have also helped increase the accuracy and precision of the radiosurgery devices while simultaneously facilitating a more comfortable and easier treatment for patients. Two devices most often used are the Gill-Thomas-Cosman (GTC) frame and the thermoplastic head mask. The GTC device is a halo that is attached to the patient via custom dental molding device which fits into the maxillary dentition and conforms to the patient's head at the occipital region. The daily accuracy of this device can be checked via the depth conformational helmet, which allows for measurement of the frame at various positions on the head. The thermoplastic head mask, in contrast, is a custom-fitted face mask that is shaped to fit the patient's face and head. These masks have adjustment spacers to improve the fit to the patient's head. Accuracy of the GTC frame with the custom molding device is 2.2 mm \pm 1.1 mm while accuracy of the thermoplastic helmet is 3.0 mm \pm 1.5 mm. The GTC frame without the custom molding has accuracy of 3.7 mm \pm 2.8 mm^[47]. Frame-based immobilization, such as the Radionics (Burlington, Massachusetts) BRW Halo head ring, have a superior accuracy of 0.3 mm. Patient motion during treatment contributes to some of the inaccuracy. Comparison of intra-treatment motion of the frame base treatment modalities and frameless systems showed motion of 0.7 mm to 1mm for frameless system with a bite block and 0.4 mm for frame based systems^[48]. For frameless immobilization, accuracy is slightly better with dental fixation, though this improvement is not statistically significant. Although these frameless devices may be slightly less accurate than the frame-based systems, they do increase patient comfort during treatment^[49]. Some patients describe the frame as intolerable and unpleasant and it increases their dislike for radiosurgery treatments^[49]. For example, patients queried about their experience with frame based SRS described the procedure "as very traumatic (with a sensation of) severe sun burn on my scalp. I didn't realized the (procedure) would hurt that much"^[50].

The development of BrainLab's ExacTrac system (Brainlab, Munich, Germany) has helped to improve the accuracy and precision

of the frameless system in radiosurgery. ExacTrac works by using high resolution X-rays to pinpoint the metastatic lesion seconds before treatment, thereby allowing the system to correct for patient set-up errors and patient movement during treatment^[51]. When combined with ExacTrac, the Cone-beam CT patient positioning imaging can be derived and fused with the pre-treatment CT. This fusion allows for detection of patient motion during treatment and directs automatic correction for these movements, further increasing the accuracy and precision of the frameless system^[51].

The availability and combination of these technological developments has led to the paradigm shift in radiosurgery and radiation therapy for brain metastases. These frameless systems with improved localization precision permits the ability to treat the same target volume on multiple occasions, thereby being able to fractionate the radiosurgery dose. The resulting treatment options will be discussed below.

CHANGES IN THE PARADIGM

Five primary parameters of treatment efficacy should be considered when examining the treatment options being offered to patients. The first, local control, is the measure of the response of the brain lesion(s) being treated with the radiosurgery. High efficacy is the second parameter and is defined by high percentages of local control. The third, distant recurrence, describes the development of new lesions within the brain. Since radiosurgery techniques do not treat micrometastases throughout the brain (in contrast to WBRT), the possibility of distant metastases occurring determines if these radiosurgery techniques should even be considered without WBRT. Low levels of distant recurrence are obviously desired; high levels suggest that WBRT should be included in any treatment option, despite concerns of side effects. Overall survival is the fourth parameter and provides an understanding of the patients' cancer burden in the context of treatments provided. The percentage of patients succumbing to neurological death helps us to understand how successfully the brain disease was controlled. Lastly, to decrease negative side effects, the reduction of radiation toxicity, particularly tissue-confirmed radiation necrosis, should be considered as one goal for changing treatment paradigms.

As one considers the changes in treatment that are occurring, one should keep in mind that the published data, with few exceptions, is derived from retrospective case series. Three prospective trials are currently in progress: N107C, which randomizes resected metastatic brain tumor patients to SRS or WBRT; a study at MD Anderson Cancer Center comparing post-operative SRS to no additional treatment; and a study at McGill University comparing post-operative SRS to post-operative SRS plus WBRT^[52]. The results of these yet-unpublished studies may add significant support for adopting the changes.

SRS in lieu of WBRT

Due to concerns regarding consequences of WBRT and studies which do not show a survival advantage when WBRT is included, treatment plans utilizing SRS without WBRT are becoming more widespread. While Level 2 evidence, well-summarized by Linskey, *et al*^[4] supports this option, the authors caution about the risk of delayed loss of local control and distance recurrence in the group utilizing SRS alone. On the other hand, a key driver of SRS alone for treatment of brain metastases is a study by Chang *et al*^[22], which compared neuro-cognition in patients treated with SRS versus those treated with SRS plus WBRT. In this small, prospective, randomized study, (which was not included by Linskey *et al*^[4] in their analysis), neuro-cognition was significantly impaired in the SRS plus WBRT

group relative to the SRS alone group, while CNS progression was more common in the SRS alone group. The cognitive deficits persisted beyond six months. Based on these results, the authors suggest an initial treatment plan of SRS alone, with close clinical monitoring. WBRT can be delivered in a delayed fashion for patients who have a recurrence that is distant to the site of origin in the brain. The general impression is that the cognitive risks justify avoiding WBRT for as long as possible. Table 1 lists a number of studies describing results of SRS in lieu of WBRT. The results for local control are comparable to historical results for WBRT; SRS distant brain recurrence is not as good for WBRT^[1]. However, WBRT still remains an option for these distant recurrences.

Table 1 SRS in lieu of WBRT.

Author, year	Patients ¹	Overall Survival ¹	Local Control ²	Distant Control ²	Radiation Necrosis ³
Quigley <i>et al</i> 2008 ^[53]	32	16.4	12:93.75	12:88.5	
Chang <i>et al</i> 2009 ^[22]	58	9.2			17
Ogura <i>et al</i> 2012 ^[54]	39		6:92.1 12:86.7	6:54.6 12:41	2.6
Luther <i>et al</i> 2013 ^[55]	120		12:85.8	12: 60	
Hartford <i>et al</i> 2013 ^[56]	47	9.3	12:85.5 24:66.9	12:44 24: 68.3	
Gans <i>et al</i> 2013 ^[57]	106	14	12:80	12:51	10
Connolly <i>et al</i> 2013 ^[58]	33	16	12:90.3 24:85.8		0
Broemme <i>et al</i> 2013 ^[59]	42	15.9	6:91 12:77		2.4
Ammirati <i>et al</i> 2014 ^[60]	40	16			7.7
Brennan <i>et al</i> 2014 ^[61]	50	14.7	12:78	12:56	17.5

¹ median, in months; ² A:B months: percent of total patients; ³ percent.

Fractionated radiosurgery

The utilization of relocatable immobilization devices yields a potential application of radiosurgery which provides the backdrop for one paradigm change. Specifically, with untethering radiosurgery treatment from a head-fixated stereotactic frame, the opportunity for multiple treatments to the same target becomes much easier. The ability to deliver fractionated stereotactic radiosurgery (FSRS), also known as hypofractionated radiation therapy (HFRT), allows the potential to treat larger lesions or lesions closer to eloquent structures while reducing potential toxicity^[48,54,59-68]. Because relocatable immobilization precision is admittedly less than frame-based localization, most fractionated protocols utilize a 1 mm to 3 mm expansion of the gross tumor volume to create the prescribed tumor volume (PTV).

This ability to fractionate can mitigate some of the negative features of SRS. For instance, SRS has been demonstrated to have poor responses for brain metastases greater than 3 cm in diameter. SRS is relatively contraindicated for patients with metastases causing greater than 1 cm of midline shift because of increased risk of local worsening cerebral edema after treatment. Finally, SRS has been shown to have increased toxicity profile (relative to WBRT) when used to treat lesions of any size that are in close proximity to critical brain structures or into tumor bed that has already been irradiated^[60,69-71]. With fSRS or HFRT, 2 to 5 fractions on multiple days can be delivered. This modality has been shown to have good local control of metastases greater than 2 cm with low toxicity profile^[54].

Debate regarding the need for fractionation is ongoing. Opponents of fractionation suggest that inaccuracy in localization from non-

frame based immobilization is the only rationale for fractionation^[72]. Since local failure after SRS tends to occur with lower doses, and dose is limited by tumor size, one reason for fractionation is to permit larger doses to the tumor margin in anticipation of better local control without increasing toxicity. This decision is somewhat compromised because the formulations for dose calculations relative to multiple fractions based on single-fraction SRS is somewhat uncertain^[5,73]. Furthermore, the potential toxicity to surrounding structures may possibly be reduced by fractionation^[74]. This rationale is supported by a number of studies comparing SRS and fSRS or HFRT which demonstrated comparable efficacy without increasing toxicity^[54,74]. Table 2 summarizes many of the studies focused on fSRS or HFRT. Local control remains comparable to WBRT; distant control again is not as good as with WBRT.

Table 2 Fractionated Radiosurgery.

Author, year	Patients ¹	Overall Survival ¹	Local Control ²	Distant Control ²	Radiation Necrosis
Manning <i>et al</i> 2000 ^[75]	32	12		12:45%	6%
Aoyama <i>et al</i> 2003 ^[76]	87	8.7	12:81%		2.7%
Ernst-Stecken <i>et al</i> 2006 ^[77]	51	11	12:76%	12: 67%	
Fahrig <i>et al</i> 2007 ^[78]	150	16		12:42%	
Narayana <i>et al</i> 2007 ^[79]	20	8.5	12:70%		
Kwon <i>et al</i> 2009 ^[80]	27	10.8	12:68%		
Kim <i>et al</i> 2011 ^[81]	40	8	6:97% 12:69%	12:15%	5%
Eaton <i>et al</i> 2013 ^[62]	42	8	12: 61%	12:55%	10%
Matsuyama <i>et al</i> 2013 ^[65]	299	17.1	6:96.3% 12:94.5%		2%
Minniti <i>et al</i> 2014 ^[66]	135	12	12:88% 24: 72%	12:48% 24: 27%	7%
Feuvret <i>et al</i> 2014 ^[63]	36	16.8	12: 75%	12:67%	0%

¹ median, in months; ² A:B months: percent of total patients.

Tumor Bed Radiosurgery

Another possibility in the application of radiosurgery relative to the treatment of metastatic brain tumors is the management of the tumor bed after surgical resection. Traditionally, after resection of a solitary metastatic lesion-particularly ones that are very large--patients have been given WBRT. The rationale for this treatment regimen was that most tumors, by the time they were clinically symptomatic or radiographically evident, have already proliferated via micrometastases or local microinvasion and therefore will later recur either at a distant site or adjacent to the surgical site. WBRT, in conjunction with resection of the solitary lesion, has led to excellent local and CNS control of the metastatic lesions, but patients are more susceptible to neurotoxicity and neurocognitive decline. Therefore, the rationale for supporting the use of SRS in lieu of WBRT is that the same benefits are achieved but with a decrease rate of serious neurologic side effects. An important consideration when utilizing SRS is the difficulty in identifying the postoperative target volume, which is defined by the radiographically determined normal margins of the resected metastatic lesions and the collapsed cavity. Treatment of these collapsed cavities has been shown to lead to adverse side effects such as steroid dependence and brain necrosis, with recent studies quoting figures that range from 5 to 17%^[58,82,83]. But the issue

of microinvasion may be less important than was once thought, as pathological examination often does not show microinvasion^[84]. So, despite these technical issues and concern for late effects, SRS to the tumor bed has been shown to have local control rate of 74 to 100% at one year^[56], and SRS increases survival by 9 to 21 months, similar to WBRT^[58]. SRS has somewhat poorer CNS control compared to WBRT with a rate of new brain lesion development in these studies ranging from 28 to 63%, which is further worsened by larger tumor size (diameter >3.0 cm)^[56]. The rate of salvage therapy with delayed WBRT was 7 to 31%. These results, summarized in table 3, thus suggest the feasibility of SRS radiation to the tumor bed.

Table 3 Tumor Bed Radiosurgery.

Author, year	Patients ¹	Overall Survival ¹	Local Control ²	Distant Control ²	Radiation Necrosis
Soltys <i>et al</i> 2008 ^[85]	72	15.1	12: 86	12: 54.6	10
Mathieu <i>et al</i> 2008 ^[86]	40	13	12: 73	12:46	5.4
Do <i>et al</i> 2009 ^[87]	30	12	12: 87	12:37	
Karlovits <i>et al</i> 2009 ^[88]	52	15	12:93		
Jagannathan <i>et al</i> 2009 ^[89]	47	11	12:94		11
Jensen <i>et al</i> 2010 ^[90]	106	10.9	12:80	12:35	7
Kalani <i>et al</i> 2010 ^[91]	68	13.2	12:80	12:40	
Rwigema <i>et al</i> 2011 ^[92]	77	14.5	12: 74		
Choi <i>et al</i> 2012 ^[93]	120	17	12:89		
Wang <i>et al</i> 2012 ^[94]	37	5.5	12:80		9
Prabhu <i>et al</i> 2012 ^[95]	64	13.4	12: 83		
Kelly <i>et al</i> 2012 ^[96]	18		12:89		
Steinmann <i>et al</i> 2012 ^[97]	33	20.2	12:76%		0
Gans <i>et al</i> 2013 ^[97]	106	14	12:81%	12: 51	10
Hartford <i>et al</i> 2013 ^[56]	47		12:85.5% 24:66.9%	12:44 24:24	
Luther <i>et al</i> 2013 ^[55]	120		12:85.8%	12: 60	
Broemme <i>et al</i> 2013 ^[99]	44	15.9	6:91% 12: 77%		2.3
Brennan <i>et al</i> 2013 ^[61]	50	14.7	12:78%	12:56	7%

¹ median, in months; ² A:B months: percent of total patients; ³ percent.

Numerous Brain metastases

Another change in radiosurgery involves treatment of patients with numerous metastases. Historically, these patients are usually treated with WBRT because of the need for coverage of the whole brain. However, these patients have poor prognoses and practitioners often worry about exposing these patients to the adverse effects of WBRT. To that end, SRS has been tried in the treatment of these patients. Studies using SRS in the treatment of numerous metastases have shown that with up to four metastatic lesions, SRS has the same rate of local control, overall survival, and progression free survival as WBRT^[98]. But when patients have 5 or more metastatic lesions, the data is conflicting. Khalsa *et al*^[99] concluded that patients with brain metastases of 5 or greater have better outcome when treated with WBRT instead of SRS. On the other hand, Salvetti *et al*^[100]

reviewed the literature and found that the number of lesions did not predict survival and that SRS provided as good of a local control as WBRT. Other studies support radiosurgery for numerous metastases, even as many as 20 or more, because such patients usually have poor prognosis and SRS has been shown to have local control, progression free survival, and overall survival comparable to WBRT^[98,101]. Despite the conflicting data, some consensus exists since it is recommended that patients can be considered for SRS if they have good prognoses (i.e. KPS >80 or RPA 1-2) while those with poor prognoses (KPS <80 or RPA 3 or greater) should be considered for WBRT^[98,101,102]. Patient comfort for treatment of numerous lesions, as well as radiation dosimetry should be assessed. The time that the patient must remain on the radiation couch for treatment may be excessive with numerous lesions. As such, SRS for numerous metastatic lesions (Table 4) is being deemed less optimal than previously considered. Basically, WBRT is probably easier for the patient and the physician with comparable results in cases of numerous metastatic lesions.

Table 4 Radiosurgery for numerous metastases.

Author, year	Patients ¹	Number of Metastases	Overall Survival ¹	Local Control ²	Distant Control ²	Radiation Necrosis ³
Bhatnagar <i>et al</i> 2006 ^[102]	205	4-18	8	12:71		
Kim <i>et al</i> 2008 ^[98]	26	10-37	5	6:79.5		
Lee <i>et al</i> 2011 ^[103]	36	4-10	9.1			
Hunter <i>et al</i> 2012 ^[104]	64	5-10	7.5			
Grandhi <i>et al</i> 2012 ^[105]	61	13.2	4	6:90.5 12:58.3		
Salveti <i>et al</i> 2013 ^[100]	96	5-15	4.7	6:92.4 12:84.8 24:74.9	4:59	
Yamamoto <i>et al</i> 2013 ^[101]	1096	1-89	7.9	12: 58		10.6

¹ median, in months; ² A:B months: percent of total patients; ³ percent.

CONCLUSION

We are in the midst of a paradigm shift regarding radiation treatments for patients with brain metastases. Because of this shift, a number of treatment options are being utilized with the goal of ascertaining the most effective method of treatment. The documentation of these treatments-both prospective and retrospective-has been instrumental in the pursuit of this goal. Further study, as well as continued meticulous evaluation of patient outcomes, are essential as we move forward.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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