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Review Article

Tumor Bed Directed Stereotactic Radiosurgery for Surgically Resected Brain Metastases

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Abstract

While typically used for treating small intact brain metastases, an increasing body of literature examining tumor bed directed stereotactic radiosurgery (SRS) is emerging. There are now over 1,000 published cases treated with this approach, and the first prospective trial was recently published. The ideal sequencing of tumor bed SRS is unclear. Current approaches include, a neoadjuvant treatment before resection, alone as an adjuvant after resection, and following surgery combined with whole brain radiotherapy either as an adjuvant or salvage treatment. Based on available evidence, adjuvant stereotactic radiosurgery improves local control following surgery, reduces the number of patients who require whole brain radiotherapy, and is well tolerated. While results from published series vary, heterogeneity in both patient populations and methods of reporting results make comparisons difficult. Additional prospective data, including randomized trials are needed to confirm equivalent outcomes to the current standard of care. We review the current literature, identify areas of ongoing contention, and highlight ongoing studies.

Keywords: Radiosurgery; Brain metastases; Post-operative Radiosurgery

Abbreviations

SRS: Stereotactic Radiosurgery; WBRT: Whole Brain Radiation Therapy; FSRT: Fractionated Stereotactic Radiosurgery; MR: Magnetic Resonance

Introduction

An estimated 9 - 26% of cancer patients will develop a metastatic focus in the brain making it one of the most common neurologic complications of cancer [1,2]. The incidence of clinically recognized brain metastases will likely continue to increase as modern oncologic therapies improve survival and imaging continues to better detect small brain lesions. Development of brain metastases is usually a poor prognostic sign, and effective therapy is limited. Until now, whole brain radiation therapy (WBRT) has been the mainstay of treatment, but local control of individual brain metastases is suboptimal with WBRT alone [3-5]. Other treatment alternatives are quickly evolving thanks to rapid improvement in techniques, technology, and image guidance. When combined with better understanding of toxicity, these advances have shifted the paradigm to one that takes into account quality of life combined with the goal to improve oncologic outcomes.

More than half of patients present with a single metastasis [6,7]. In these cases, therapy may be localized, omitting treatment of the remaining brain. Both SRS and surgical resection are local treatments, which have been shown to improve local control, overall survival, and functional outcomes in these patients when compared to treatment of the entire brain alone [3-5]. There is now increasing evidence that in small solitary or oligometastatic disease, radiosurgery may be used as a single modality if the patient is closely monitored and higher rates of distant brain failure can be accepted [8-10]. This approach offers decreased acute toxicity and potentially improved neurocognitive function of patients [9], which is becoming increasingly important as improved systemic therapies increase life expectancy for patients with brain metastases.

Despite high rates of local control with small lesions using radiosurgery as a sole modality [10,11], there are many examples where surgery is advantageous. It can provide diagnostic information, faster symptomatic relief, better local control with larger lesions, or emergency decompression. The rate of local failure following surgical resection alone is 46-59%, leading to the routine use of WBRT following surgical resection of one to three brain metastases [10,12]. There is interest in combining the reduced side effect profile of SRS alone with the increased local control of radiotherapy in patients who have undergone a resection for metastatic disease to the brain [13-16].

Treatment of the surgical resection cavity with SRS is a relatively new treatment approach. Although limited prospective data does now exist, and Phase III trials are currently enrolling, no randomized data have been published. The majority of reported data are from single institutions and retrospective in nature [14,17-38]. Multiple ways of incorporating SRS are under investigation including: post surgical tumor bed therapy, post surgical boost to WBRT, neoadjuvant to brain metastasis that will undergo a planned resection, and as a salvage for patients who have recurred after previous resection and WBRT.

We present a comprehensive review of the currently published data on SRS directed at a surgical resection cavity.

Radiosurgery to a Resection Cavity with whole Brain Tadiation Therapy

WBRT can be combined with a stereotactic boost following surgical resection. This treatment strategy benefits from WBRT's

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ability to prevent some new metastases including symptomatic recurrences as well decrease the need for future therapy [5]. The addition of WBRT to postoperative SRS does raise concerns about potential neurotoxicity from treatment of the whole brain, especially in patients with a solitary resected brain metastasis who may have long survival following therapy. Still, the combination of SRS and WBRT as an adjuvant to surgical resection allows for a very high effect dose to the resection bed and removes the risk of a marginal miss.

Roberge et al. examined this treatment strategy in 27 patients and later 44 patients with high performance statuses and good Reccursive Partitioning Analysis (RPA) classifications [15,16,38]. Most patients received 30 Gy in ten fractions with an accompanying 10 Gy boost using SRS. After 11.3 months of follow up 12-month actuarial local control was 90% with a crude rate of new brain metastases of 13%. Treatment was well tolerated with two patients experiencing clinical signs of radiation treatment effect.

Luther et al. [31] examined 120 patients with a completely resected brain metastasis treated at the University of Pittsburgh between 2002 and 2012. Thirty-nine percent of patients received WBRT either immediately before or after radiosurgery as an adjuvant to surgery. There was no statistically significant difference in local control of patients who received WBRT compared to those who did not, likely because of the small number of patients for comparison and selection bias for patients who received WBRT.

Radiosurgery following surgical resection may also be reserved as a salvage treatment after failure of WBRT. Series by Wang et al. and Mathieu et al. both contain high numbers of patients who have received WBRT and then progressed [19,32]. It is unclear in these series if the index lesion was a previously treated lesion, which was refractory to WBRT, or a new lesion occurring after WBRT. Authors from Wake Forest University published the results of 79 patients treated with resection and SRS following previous WBRT failure from 2000 to 2005 [39]. Patients received a median dose of 18 Gy delivered using Gamma Knife SRS. Median survival was a surprising 17 months and crude local recurrence was only 5.1%. Rates of radionecrosis were low with only 3.8% requiring surgical intervention.

Radiosurgery to a Resection Cavity without whole Brain Radiation Therapy

The most reported approach to incorporating tumor bed directed SRS is as a sole adjuvant to surgical resection (Table 1) [14,17-19,21-37,40]. By delaying WBRT, some patients may be spared the procedure altogether with similar local control to WBRT. Despite the theoretical benefits of this approach, it is difficult to draw conclusions from the available retrospective evidence due to the variable inclusions criteria and methods of reporting outcomes. Several prospective trials investigating this approach are maturing and the first has been published.

Brennan et al. recently reported the results of a Phase II trial conducted at Memorial Sloan-Kettering Cancer Center examining the role of SRS to the postoperative cavity for resected brain metastases [40]. Forty-nine patients were enrolled from 2004 to 2009. Patients were RPA class I (24%) or II (76%) and had one to two intraparenchymal brain metastases. The postoperative tumor bed was treated with 2 mm of margin. With median follow-up of 12 months, actuarial local failure and regional failure rates at 12 months were 22% and 42%, respectively. Interestingly, ten patients never received SRS because of early intracranial progression. There was a median 31 days elapsed between surgical resection and SRS, which may have contributed to the large number of failures before SRS. Tumors larger than 3 cm with superficial dura or pial involvement had the highest risk of local failure with a local control rate of less than 50%. The rate of pathologically confirmed radionecrosis was high, at 17.5%. The authors were unable to identify significant clinical or dosimetric factors that contributed to this rate of radionecrosis.

Target volume

Large lesions are more difficult to treat with radiosurgery. It was noticed by Shaw et al. that these lesions had a lower dose threshold for development of radionecrosis [41]. Even when the index lesion has been removed, several studies have reported lower rates of control based on the preoperative tumor size or large postoperative cavity [24,27,28,40].

In a series of 47 patients, Hartford et al. demonstrated that size over 3 cm had a shorter time to recurrence and WBRT [24]. Jensen et al. showed that tumors over 3 cm had increased local failure (HR 13.6, $p < 0.01$) [28]. Luther et al. found that increasing target size correlated with a higher chance of local failure, likely as a surrogate marker for tumor size [31]. In the only prospective study published to this date, Brennan et al. found increased local failure with tumors over 3 cm (HR 4.3, $p = 0.01$).

Compounding the issue of increased local failure in large lesions, treatment tends to be more toxic for these patients. Many institutions have sought to reduce this by use of hypo fractionation [14,17,18,21-24,34,37].

Smaller targets will presumably allow the use of a higher dose without increased risk of radionecrosis causing some to increase time time from resection to SRS. Reported times from surgery to SRS span from one day to a month or more [14,17,19,21-30,32-37,40]. It is not entirely clear how the postoperative cavity changes following surgical resection, and this has been the subject of a publication by at least two institutions [42,43]. Jarvis et al. examined MR imaging of 41 patients before surgery, within 24 hours after surgery, and at time of radiosurgery planning [43]. They demonstrated that while tumor bed volumes change, most do not collapse, and approximately one-third increase in size. Atalar et al. [42] examined 63 patients' imaging and found that most post-resection tumor beds were smaller than the preoperative tumor and larger tumors had greater decrease in size. Since the greatest changes occur immediately after surgery (on day one to three) they concluded it was better to proceed with radiosurgery within one to two weeks.

Margin

The desire to add margin comes from two basic principles. First, it can be difficult to correctly delineate the tumor bed. Marginal misses may occur. Second, although brain metastases are usually well encapsulated, there is some concern for tumor spread to the surround parnnchyma [44]. It is unlikely that local failures in postoperative brain metastases are an issue of only insufficient dose. Rogers et al. reported experience with the GliaSite system in the resected brain metastases population [45]. Despite doses of above 300 Gy at the balloon surface,

Table 1: Postoperative Tumor Bed Radiosurgery Series.

Author	Year	Patients (n)	Technology	Previous WBRT (%)	GTR (%)	Median Marginal Dose (Gy)	Crude LC (%)	Crude New BM (%)	Crude No WBRT (%)
Iwai	2008	21	Gamma Knife	0	100	17	76	48	90
Do	2008	30	Linear Acc.	0	NR	NR	87	63	53
Soltys/	2008	72	CyberKnife	0	85	18.6	86	49	81
Choi	2012	112	CyberKnife	NR	90	NR	89	59	72
Mathieu	2008	40	Gamma Knife	25	80	16	73	54	84
Quigley/	2008	52	Linear Acc.	0	92	15	92	44	70
Karlovits	2009								
Jagannathan	2009	47	Gamma Knife	6	100	19	94	NR	72
Limbrick	2009	15	Gamma Knife	NR	80	NR	73	60	60
Hwang	2010	25	Gamma Knife	NR	95	NR	100	33	NR
Kelley	2010	17	Linear Acc.	6	94	18	89	35	59
Wang	2011	37	CyberKnife	49	NR	24 (3 FX)	NR	20	NR
Jensen	2011	106	Gamma Knife	NR	96	17	89	54	63
Prabhu	2012	62	Linear Acc.	0	81	18	83	NR	NR
Ogiwara	2012	56	Gamma Knife	0	NR	17.1	91	38	86
Steinmann	2012	33	Linear Acc.	NR	75	NR	72	NR	61
Luther	2013	120	Gamma Knife	23	100	16	86	40	NR
Minniti	2013	101	Linear Acc.	NR	100	27 (3 FX)	92	53	76
Hartford	2013	47	Linear Acc.	0	76	10	84	63	55
Brennan*	2014	49	Linear Acc.	0	92	18	70	47	NR

*Prospective, Phase II

NR: Not Reported, FX: fractions, BM: Brain Metastases, WBRT: whole brain radiation therapy

local recurrence was still above 15%. Soltys et al. demonstrated that a less conformal plan increased local control in their series of 76 patients treated with postoperative CyberKnife radiosurgery. This led to the adoption of a 2 mm margin at this institution on all postoperative cavities as a surrogate for a less conformal plan. Choi et al. [22] subsequently published the Stanford experience with the addition of a 2 mm margin, and demonstrated increased local control (3% vs 16%, p = 0.04) and similar toxicity (3% vs 8%, p = 0.27). Several reported series use a margin to construct a target volume [17-19,21-24,27,34,37,40], and others do not [14,25,26,28-30,32,33,35]. Increasing the difficulty of drawing conclusions for the data, some authors include a margin only in select cases, usually with larger tumors that are felt to be at a higher risk of recurrence.

Dose and fractionation

The optimal dose and fractionation are unknown for postoperative SRS. Many institutions select single fraction dose based on published results from the RTOG 90-05 dose escalation trial [41]. Some institutions have selected a lower dose, as low as 10 Gy with good local control in the absence of worrisome radiographic factors, although authors indicate they are now using higher doses [24].

The majority of data available use single fraction regimens, likely because of the difficulty in giving multiple fractions when frameless systems were unavailable. The popularity of SRS using frameless linear accelerator or robotic-based systems is rising, and investigators are increasingly exploring fractionated stereotactic radiosurgery (FSRT) [17-19]. These studies use different multi fraction regimens for control of large lesions over 3 cm with the addition of a 2-4 mm margin on the postoperative cavity.

Steinmann et al. examined FSRT in 33 patients with a single resected brain metastasis [18]. Doses were selected, taking into account how large lesions were. After 10.7 months of follow-up, actuarial 1-year local control was 71%. Wang et al. published results of 37 patients treated with Cyber Knife radiosurgery for resected tumors greater than 3 cm [19]. A 2-3 mm margin was added on to the resection cavity and treatment was delivered in three 8Gy fractions with local control of 80%. In another study, Minniti and colleagues reported a large series of 101 patients with single resected brain metastases treated with FSRT [17]. All resection cavities were greater than 3 cm and a 2 mm margin was included for target delineation. Patients received three 9 Gy fractions. The median follow-up was 16 months, and the authors reported a local control at one year of 93% and two years of 84%. Other authors have reported series with a mix of FSRT and SRS but it is difficult to draw conclusions because numbers are small and patients with larger tumors, or when there was more concern of recurrence were treated with FSRT in a non-randomized fashion [14,21-23,34,37].

This approach offers the potential advantage of delivering hypofractionated treatment when radiosurgery could not previously be given because of adjacent critical structures such as the brainstem or optic apparatus. Furthermore, there is potential for additional toxicity when delivering single fraction radiosurgery to large targets. Large lesions or the addition of margin, exponentially increase the amount of normal brain at risk for radiation necrosis [46]. Investigators hope that by fractionation, the risk to normal brain is

minimized. The radiobiological benefit of fractionation in resected brain metastases remains unknown.

Complications

Treatment seems to be well tolerated for most patients. Many studies report transient neurologic symptoms that can be treated adequately with steroids and anticonvulsants. The reported rate of clinical toxicity of any type is 0 – 26.6% [14,17,19,21-23,26,27,32,34-37]. Rates of reported surgical radionecrosis are around 3% in retrospective studies [17,19,21,22,28,32,34,37]. It is difficult to draw any conclusions from this heterogeneous reporting aside from the general tolerability of postoperative radiosurgery and as with all retrospective series, toxicity is likely underreported because of potential bias in both data collection and publication.

Radiosurgery Before Planned Surgical Resection

There is increasing interest in neoadjuvant radiosurgery despite very limited clinical data. Delivering the radiotherapy before resection allows for a clearer delineation of the target and at least a theoretically reduced risk of intraoperative tumor spread. Some proponents of this approach believe that neoadjuvant delivery allows for a vascular mediated effect, which may improve outcomes. This approach, however, is not without potential problems. First, without histologic examination of surgical specimen patients who have either primary brain neoplasms or non-malignant pathology may be needless irradiated. The rate of these findings at time of surgery is widely debated, but Patchell et al. reported a rate of 11% non-metastatic histology [12]. Second, radiosurgery may cause a transient increase in size, and possible additional mass effect complicating the surgical resection. Finally, it would be difficult to deliver additional radiotherapy following resection if there was a sub-total resection or other negative prognostic factor.

Asher and colleagues recently published their institutional experience with neoadjuvant radiosurgery followed by surgical resection of brain metastases [20]. Forty-seven consecutively treated patients had one to three brain metastases and controlled systemic disease. Lesions received a median dose of 14 Gy (range 11.6 – 18 Gy) prescribed to the 80% isodose line with no margin added on the gross disease. All patients underwent GTR with the exception of one, who died within two months of local progression. No perioperative morbidity or mortality was observed and no patients were found to have other pathologies. With a median follow up of 12 months, actuarial local control was 97.8%, 85.6%, and 71.8% at six months, 12 months, and 24 months, respectively. On follow-up, any contrast enhancement in the tumor bed was considered recurrence or radionecrosis. Increasing contrast enhancement over time was considered recurrence. The authors acknowledge that this method likely overestimates tumor recurrence while underestimating radionecrosis, as post-radiation changes would likely be considered recurrent tumor. As expected, no cases of radionecrosis were reported.

This series offers an interesting new paradigm for the local treatment of disease. While the authors report encouraging outcomes with large lesions, care must be taken in the interpretation of these results. Twenty-three of 47 patients in the study were examined retrospectively. Results are promising; however, much remains unknown regarding the ideal dose, timing of resection following SRS, and additional risk of surgical complications.

Future Directions

There are several ongoing studies examining tumor bed directed SRS. A single institution, Phase III trial is currently enrolling at the M.D. Anderson Cancer Center (NCT00950001) comparing postoperative SRS with observation for patients with a resected brain metastasis. The accrual goal is 132 patients with a primary endpoint of surgical bed control. This trial should provide information regarding the actual reduction in local recurrence afforded by radiosurgery. Another single institution, Phase III trial is being run by the Maria Sklodowska-Curie Memorial Cancer Center in Poland (NCT01535209). It is comparing postoperative radiosurgery directly with WBRT for resected brain metastases and will provide a direct comparison of postoperative radiotherapy with the current standard of care at a single institution. Case Comprehensive Cancer Center is currently conducting a Phase I/II trial examining neoadjuvant radiosurgery for brain metastases before resection (NCT01891318). This trial will provide information on the ideal dose of radiosurgery for preoperative treatment.

Perhaps the most anticipated ongoing study for tumor bed directed radiosurgery is the Intergroup N107C Trial (NCT01372774). This multicenter randomized Phase III trial is directly comparing postoperative radiosurgery with postoperative WBRT for patients who have undergone resection for brain metastases. Patients with up to three brain metastases are included. Patients will be stratified and randomized after resection to receive either SRS to the surgical bed with SRS alone to additional lesions or WBRT with SRS to any additional lesions. The trial includes survival, neurocognitive function, tumor control and quality of life endpoints and total accrual is planned for 192 patients. This trial will provide the best comparison yet between the current standard of care and postoperative SRS.

Conclusion

Care for the patient with brain metastases is constantly evolving. Once considered an extremely poor prognostic factor with poor survival, patients continue to live longer and have better functional status. This places importance on quality of life outcomes when selecting a treatment strategy. While small brain metastases are often managed with radiosurgery alone, many patients will receive surgery for a variety of reasons. Radiotherapy has been an integral part of the care of these patients since Patchell et al. published randomized data showing improved local control and decreased neurologic death. Recent studies, reviewed here, challenge this current standard of care. Retrospective and Phase II data now demonstrate similar or improved local control when compared to adjuvant WBRT with an acceptable acute side effect profile. This data is encouraging, that for a well selected patient population, WBRT and its acute, and potential long term adverse effect profile may be avoided. Despite a growing body of literature, much is still unknown about radiosurgery when no true tumor is present. Dosing, fractionation, and target margins are all being extrapolated from the intact setting and may not apply. Ongoing trials such as the Intergroup N107C will provide high quality evidence to aid treatment decisions.

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