Radiosurgery to the Surgical Cavity as Adjuvant Therapy for Resected Brain Metastasis

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BACKGROUND: The standard treatment of resected brain metastasis is whole-brain radiotherapy (WBRT). To avoid the potential toxicity of WBRT and to improve local control, we have used radiosurgery alone to the surgical cavity.

OBJECTIVE: To demonstrate the rates of local control, new intracranial metastasis, and overall survival using this treatment scheme without WBRT.

METHODS: Eighty-five consecutive patients with brain metastasis were treated with surgical resection of at least 1 lesion followed by radiosurgery alone to the surgical cavity and any unresected lesions from August 2000 to March 2011. Sixty-eight percent had gross total resections. After surgery, radiosurgery was delivered to the surgical cavity with a 2- to 3-mm margin. The median marginal radiosurgery dose was 16 Gy, and median target volume was 13.96 cm^3. Follow-up imaging and clinical examination were obtained every 2 to 3 months.

RESULTS: Median follow-up time was 11.2 months. Overall local control was 81.2%. The 6-month, 1-year, and 2-year rates of local control were 88.7%, 81.4%, and 75.7%, respectively. Forty-seven patients (55%) developed new intracranial metastases at a median time of 5.6 months. For the entire population, the rate of new metastases was 32.1%, 58.1%, and 62.9% at 6 months, 1 year, and 2 years, respectively. Median overall survival time was 12.1 months. From initial treatment until death or last follow-up, only 30 patients (35%) received WBRT as salvage treatment.

CONCLUSION: Radiosurgery to the surgical cavity without WBRT achieved excellent local control of resected brain metastasis. Close imaging follow-up allows early intervention for any new metastasis.

KEY WORDS: Brain metastasis, Radiosurgery, Surgery, Surgical cavity

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According to the 2008 American Cancer Society Registry, about 1.4 million people are diagnosed with cancer each year, and up to 40% of these patients may develop brain metastasis during their lifetime.[1] Improvements in the management of metastatic and recurrent cancers have resulted in an increasing number of patients who develop brain metastases and improved survival for patients with brain metastases. A proportion of patients will survive > 1 or 2 years after treatments for brain metastasis.[2-4] For patients with good prognostic features and a survival potential of > 1 year, aggressive therapy may help prevent neurological decline and preserve quality of life, but the decision on treatment modality must be weighed against the potential for long-term toxicity. Surgical resection followed by whole-brain radiation therapy (WBRT) has been used as the main treatment option for limited intracranial metastasis, particularly for single lesions, and can provide excellent tumor control. This is supported by randomized trials and by the recommendations of several treatment guideline committees.[5-8] Omitting WBRT after surgical resection results in local recurrence at the site of surgical cavity in 33% to 59% of patients and a higher incident of neurological death.[5,9,10] Although WBRT after surgery is an effective treatment for reducing intracranial disease progression, WBRT has been associated with neurocognitive decline and

ABBREVIATIONS: GTR, gross total resection; **SRS,** stereotactic radiosurgery; **WBRT,** whole-brain radiation therapy

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memory dysfunction.[11-14] Most recently, a single-institution phase III study using stereotactic radiosurgery (SRS) for brain metastases with or without WBRT showed a significant decline in neurocognitive function 4 months after treatment as measured by the Hopkins Verbal Learning Test in patients who received upfront WBRT in addition to SRS.[11]

Recent large randomized trials also showed that with close surveillance and proper patient selection, SRS can be used to manage brain metastasis without WBRT and without a detriment in overall survival.[9,15] In an effort to maximize local tumor control and to avoid the potential long-term effects of WBRT, postoperative SRS to the surgical bed without WBRT has emerged as a treatment option. Several retrospective series using this technique have been reported, but further evidence is clearly needed to characterize the outcomes and to more fully validate surgery followed by radiosurgery as a treatment option.[6,8,16] The goals of this study were to demonstrate the local control, time to develop new intracranial metastasis elsewhere in the brain, and overall survival for patients treated with surgery followed by radiosurgery without initial WBRT and to identify factors associated with each clinical outcome.

MATERIALS AND METHODS

Patient Selection

After obtaining approval from our institutional review board, we identified a total of 85 consecutive patients treated at our institution from August 2000 to March 2011 with surgical resection followed by SRS to the surgical cavity. Among the 85 patients, 53 patients presented with single metastasis, 20 patients with 2 lesions, 5 patients with 3 lesions, and 7 patients with 4 or 5 lesions. All patients underwent surgical resection for one of the lesions. When 2 or more lesions were identified, at least 1 lesion was resected. Treatment decisions regarding surgery were based on the size, neurological symptoms, mass effect, or the need for tissue diagnosis. Radiosurgery was performed to the surgical cavity and to the lesions that were not surgically removed. WBRT was not used as adjuvant therapy for any resected lesions. After the treatment, the patients were followed up with clinical examinations and radiographic imaging studies every 2 to 3 months, along with the prospective scheme of brain tumor board, which made treatment decisions by consensus agreement. In the follow-up period, if new brain metastases were discovered, local therapy with surgery or SRS was again used when feasible. For multiple recurrences or when $>$ 3 new lesions developed, WBRT was used as a salvage treatment. To demonstrate the effectiveness of surgery followed by radiosurgery to the surgical cavity, we retrospectively reviewed patient records, imaging studies, and radiosurgery parameters. The end points of the study were local tumor control, time to develop new metastasis elsewhere in the brain, and overall survival.

Radiosurgery Treatment

All patients had preoperative and postoperative magnetic resonance imaging (MRI) scans. Early postoperative MRI scans and surgeon judgment based on operative, follow-up, and tumor board notes were used to determine the extent of resection. After surgery, patients received SRS to the tumor bed and any residual contrast-enhancing lesion at a median of 18 days after surgery to allow recovery and healing. Ninety-five percent of the patients received radiosurgery $<$ 2 months after surgery. Treatment of 2 patients was delayed $>$ 3 months because of medical problems and patient inclination, but they were eventually treated as initially intended. All patients were treated with a Novalis linear accelerator–based radiosurgery system (BrainLab, Berlin, Germany, and Varian, Palo Alto, California) with immobilization using a frameless stereotactic thermoplastic mask (BrainLab AG). After mask fixation, all patients underwent computed tomography (CT) simulation with intravenous contrast. Postoperative MRI scans with T1 postgadolinium were fused to the simulation CT and used to help delineate the postoperative tumor bed and any residual tumor. The gross tumor volume was defined as any residual contrast-enhancing lesion in the surgical cavity. Clinical tumor volume was defined as the surgical cavity based on postoperative MRI and treatment planning CT. A 2- to 3-mm margin was added to the clinical tumor volume to define a planning target volume to account for any uncertainty with resection-cavity delineation, patient movement, and any setup error. The median marginal radiosurgical dose was 16 Gy (range, 12-18 Gy) prescribed to the 90% isodose line, which usually encompassed the entire planning target volume. Any postoperative residual gross tumor volumes were treated with doses of 18 to 20 Gy. Dose selection was determined by target volume, previous radiation, presence of residual tumor, brain location, and nearby critical structures. For patient positioning and setup, the Novalis ExacTrac image guidance system (Varian) with infrared and stereoscopic guidance was used. Before radiosurgery, final position verification films were obtained from stereoscopic radiographs or cone-beam CT according to our institutional quality-assurance protocol.

Statistical Analysis

The Kaplan-Meier method was used to estimate the median survival and 6-month, 1-year, and 2-year survival rates for local control, new intracranial metastasis, and overall survival with the date of craniotomy used as the start time for analysis. The log-rank test was used to determine the significant predictors of each clinical outcome.

Univariate and multivariate analyses were performed by using Cox proportional hazards models to determine the significant predictors for each clinical outcome. With the use of a conservative cutoff of $P < .20$, predictors in the univariate analysis were then placed in a multiple Cox proportional hazards models for each outcome. The full models were noted, and then a backward elimination method was used to restrict the model to the most predictive characteristics. Effects were removed until all predictors in the model were $P < .10$. Adjusted hazard ratios and 95% confidence intervals for the adjusted hazard ratios were reported. Tests were significant at $P < .05$.

Local failure was defined as nodular enhancement in the surgical bed at any time after treatment. Duration of local control was calculated from the date of surgery to the time of recurrence. New metastasis elsewhere in the brain was defined as new contrast-enhancing lesions at any brain site other than the resection cavity. Patients were censored at the time of death or last clinical/imaging follow-up. For statistical analysis, both SAS 9.2 and SPSS 19 were used.

RESULTS

Patient Characteristics

Table 1 details patient, tumor, and treatment characteristics. Median age at the time of brain metastasis was 58 years, and the median time from cancer diagnosis to brain metastasis was 15.5 months. Lung cancer accounted for the majority of cases (59%), and most patients (62%) had a single brain metastasis at the time of treatment. The median Karnofsky performance score

TABLE 1. Patient Characteristics[a]

Patient Characteristics	
Sex, %	
Female	52
Male	48
Age, median (range), y	58 (38-83)
Karnofsky Performance Status, median (range)	80 (60-100)
Primary site, n (%)	
Lung	50 (59)
Breast	9 (11)
Melanoma/renal	11 (13)
Gynecologic	5 (6)
Colon	4 (4)
Other	6 (7)
Extracranial metastasis, n (%)	48 (56)
Primary site controlled, n (%)	50 (59)
Median time from initial cancer diagnosis to brain metastasis (range), mo	15.5 (0-140)
CNS, median (range), n (%)	1 (1-5)
1	53 (62)
2-3	25 (29)
≥ 4	7 (8)
Brain site, n (%)	
Cerebellum	28 (33)
Frontal	22 (26)
Parietal	17 (20)
Occipital	10 (12)
Temporal	7 (8)
Surgery, n (%)	
GTR	58 (68)
STR	27 (32)
Target volume, median (range), cm^3	13.96 (1.35-59.1)
Radiosurgery dose (range), Gy	16 (12-20)
Time from surgery to radiosurgery (range), d	18 (6-232)
RPA class, median (range), n (%)	2 (1-3)
1	14 (16)
2	61 (72)
3	10 (12)
GPA score, median (range), n (%)	2.5 (0.5-4)
0.5-1	11 (13)
1.5-2.5	55 (65)
3	10 (12)
3.5-4	9 (10)

[a]CNS, central nervous system; GPA, Graded Prognostic Assessment Score; GTR, gross total resection; RPA, recursive partitioning analysis; STR, subtotal resection.

was 80 (range, 60-100). Most patients (68%) had a gross total resection (GTR). For radiosurgery, the median target volume was 13.95 cm^3, and the median marginal radiosurgery dose was 16 Gy. Although no patients received adjuvant WBRT after resection, 4 patients (5%) received whole-brain irradiation at a median of 9 months before surgery. The median follow-up was 11.2 months (range, 1-93 months).

Local Tumor Control

Overall local control rate was 81.2%. In total, 16 local failures were observed in the 85 patients. Only 8 patients (9%) experienced isolated local failure as their first intracranial recurrence. The 6-month, 1-year, and 2-year rates of local control were 88.7%, 81.4%, and 75.7%, respectively (Figure 1A). Local failure rate was 17.2% (10 of 58 patients) after GTR and 22.2% (6 of/27) after subtotal resection. This difference was not statistically significant (P = .605). However, the duration of local tumor control was significantly shorter with subtotal resection compared with GTR (median, 3.0 vs 8.3 months; P = .029). Other factors for local tumor control were target volume ≥ 15 cm^3 (74% vs 33.9%; P = .002) and marginal radiosurgery dose of < 16 Gy.

New Intracranial Metastasis Elsewhere in the Brain

Forty-seven patients (55%) developed new intracranial metastases after initial treatment with surgery and SRS. For this group, the median time to develop new metastases was 5.6 months. For the entire population, the rates of developing new metastases at 6 months, 1 year, and 2 years were 32.1%, 58.1%, and 62.9%, respectively (Figure 1B). Seven patients developed leptomeningeal metastasis at a median of 8.4 months (range, 2-59.9 months) after surgery. Univariate and multivariate analyses showed that the active systemic disease was associated with increased risk of developing new metastasis on the adjusted Cox regression model. Patients with active systemic disease were 2.4 times more likely to develop new intracranial disease after initial treatment than those without active systemic disease (Table 2).

Salvage Treatment

Salvage treatment was decided on the basis of the number of lesions, neurological status, and performance status. Surgery, radiosurgery, and WBRT were all used as salvage treatments, depending on the nature and location of the recurrence or new lesion. Eighty-nine percent of patients with local or distant intracranial recurrences received salvage treatment. Figure 2 represents a summary of the various treatments used for both local recurrence at the surgical cavity and for new distant recurrences that developed after initial treatment for the remaining duration of each patient's lifetime after treatment. A total of 47 patients had new metastasis elsewhere in the brain, and 16 patients had local tumor progression. Of these, 7 patients had simultaneous local and distant progression. Of the 16 local failures, 14 received salvage surgery (n = 6), repeat radiosurgery (n = 4), or whole-brain irradiation (n = 4). For the 47 patients who developed new distant metastasis, both SRS alone and WBRT were used almost equally, with each being used in about one-third of patients. Overall, WBRT was used as a salvage treatment in only 30 patients (35%). Thirty-one patients (36.5%) did not experience local or distant recurrence and received no additional cranial treatments after their initial surgery and SRS.

Overall Survival

Overall median survival was 12.1 months. Overall survival at 6 and 12 months was 84.4% and 51.5%, respectively (Figure 1C). Long-term survival was also seen, with 25% living > 2 years and 7% living > 5 years. Patients with graded prognostic assessment

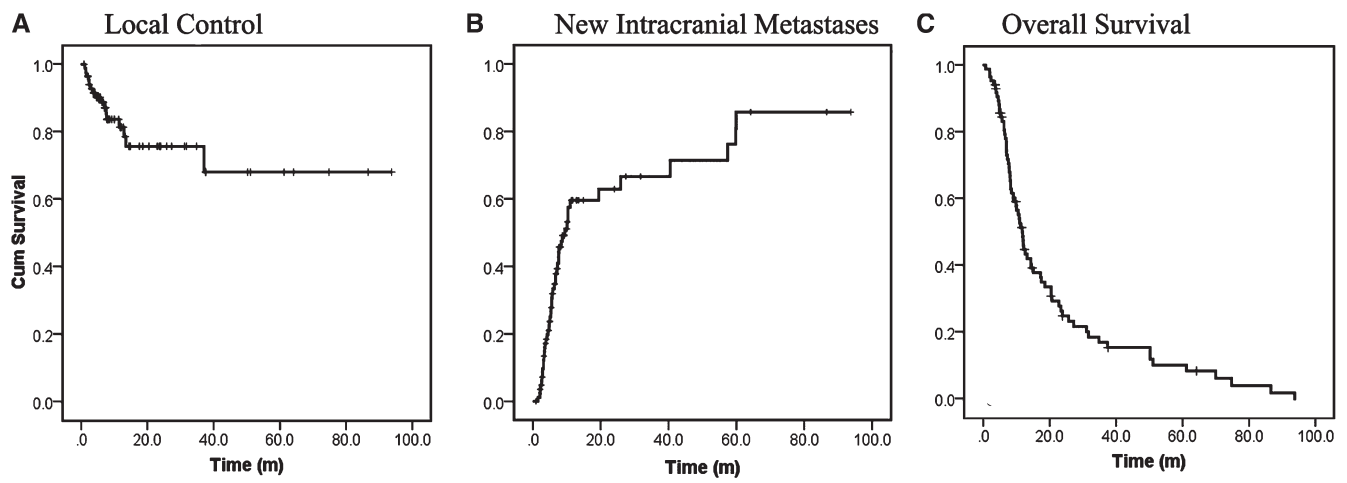

FIGURE 1. *Kaplan-Meier plots showing local control (A), new intracranial metastases (B), and overall survival (C) calculated from the time of craniotomy.*

score ≥ 3.5 or Radiation Therapy Oncology Group recursive partitioning analysis class 1 had excellent survival outcomes, with an estimated 2-year overall survival of 50.0% and 53.8%, respectively. In fact, 37.5% of patients with graded prognostic assessment score ≥ 3.5 and 28.6% of patients with recursive partitioning analysis class I survived ≥ 5 years. Based on the full proportional hazard model for overall survival, 2 variables were associated with increased longevity: longer time from initial cancer diagnosis to brain metastasis and solitary brain metastasis. Local and distant failure did not negatively affect overall survival.

TABLE 2. Univariate and Multivariate Analyses: Individual Predictors of Local Failure, Developing New Metastasis, and Overall Survival[a]

	Univariate		Multivariate (Full)		Multivariate (Adjusted)	
	HR	*P*	HR	*P*	aHR	*P*
Local failure						
Dose	1.31	.088	1.358	.11	. . .	. . .
Single metastasis (single vs ≥ 2[b])	.36	.056	.48	.163	. . .	. . .
Brain site (frontal[b] vs other sites)	6.19	.079	5.97	.091	. . .	. . .
New metastasis						
Time (diagnosis to brain metastasis)	.99	.081	.990	.109	.992	.088
Solitary metastasis (yes vs no[b])	.44	.029	.64	.213	. . .	. . .
Uncontrolled primary (yes vs no[b])	2.22	.011	.90	.82	. . .	. . .
Systemic disease (yes vs no[b]	2.44	.01	3.28	.141	2.41	.011
Overall survival						
Time (diagnosis to brain metastasis)	.985	.004	.988	.026	.985	.004
Dose	1.179	.035	1.078	.359	. . .	. . .
KPS at time of brain metastasis	.970	.008	.987	.488	. . .	. . .
GPA score	.651	.007	1.142	.617	. . .	. . .
Extent of surgery (GTR[b] vs STR)	2.16	.005	1.59	.114	. . .	. . .
Solitary metastasis (yes vs no[b])	.45	.01	.35	.041	. . .	. . .
Systemic disease (yes vs no[b])	1.70	.051	.49	.136	. . .	. . .
RPA class (1[b] vs 2-3)	2.39	.011	2.23	.084	2.41	.011

[a]aHR, adjusted hazard ratio; GPA, graded prognostic assessment; GTR, gross total resection; HR, hazard ratio; KPS, Karnofsky performance score; RPA, recursive partitioning analysis; STR, subtotal resection.
[b]Reference for HR calculations.

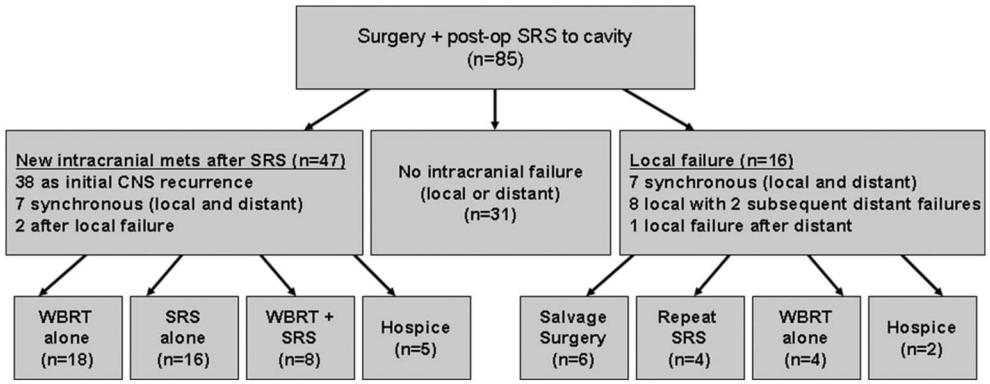

FIGURE 2. *Flowsheet illustrating treatments received for distant failures and local failures in the surgical cavity. CNS, central nervous system; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.*

Complications

Patients tolerated the combination of surgery followed by radiosurgery well in the acute setting. Radiation necrosis was seen in 7 patients (8%) at a median time of 8.4 months (range, 5.8-16.5 months). These were diagnosed by surgical excision (n = 3), CT perfusion studies (n = 2), and suggestive MRI findings and clinical symptoms, which improved with steroids and resolved on follow-up imaging (n = 2).

DISCUSSION

For select patients with brain metastasis, surgical resection and WBRT have been shown to improve local control and to reduce intracranial progression in randomized studies.[5,9,17] Randomized evidence also suggests that WBRT after local treatment of metastasis has minimal impact on patient overall survival.[5,9,15] However, omitting WBRT resulted in inferior local tumor control in 2 randomized trials. Patchell et al[5] and Kocher et al[9] reported local failure at the surgical site in 46% and 59% without WBRT compared with 10% and 27% after WBRT, respectively. In both studies, the rate of new distant intracranial failure in the observation arms (no WBRT) was 42% and 37%, lower than the rate of local failures for these patients. These data suggest that one of the primary roles of WBRT is to improve the local control at the surgical site. Therefore, we questioned whether local treatment with radiosurgery to the surgical bed could be used instead of WBRT and how and when salvage treatments would need to be delivered with this treatment paradigm. The salient features of our study are that local control was certainly achieved and that additional salvage treatments were safely performed. With this treatment scheme, WBRT was largely avoided, and only one-third of the patients ever received it. In fact, one-third of the patients with new intracranial metastasis needed only local salvage therapy. Additionally, more than one-third of the patients required no further treatments to the brain during their lifetime.

In the present study, local failures occurred in 18% of patients after SRS to the surgical cavity, and only 8 patients (9%) experienced isolated local failure as their first intracranial recurrence. Other smaller similar experiences of radiosurgery to the surgical cavity have reported 1-year local control rates ranging from 74% to 100%.[18-23] After gross total excision and WBRT to 50.4 Gy, Patchell et al[5] reported a 10% local failure rate with local failure being defined as reappearance of metastasis in exactly the same site in the brain as the first site of metastasis. DeAngelis et al[10] reported a 1-year rate of

TABLE 3. Summary of Contemporary Series of Patients With Brain Metastasis Treated With Surgical Resection Followed by Radiosurgery[a]

Author	n	Technique	GTR, %	Single Metastasis, %	1-y LC	mOS, mo
Soltys et al[20] (2008)	72	Cyberknife	85	65	79	15
Mathieu et al[21] (2008)	40	GKS	80	68	74	13
Do et al[19] (2009)	30	LINAC	NR	43	82	12
Karlovits et al[27] (2009)	52	LINAC	92	65	Crude, 93	15
Jagannathan et al[24] (2009)	47	GKS	100	28	Crude, 94	10
Jensen et al[26] (2011)	106	GKS	96	58	80	11
Present study	85	LINAC	68	62	81	12

[a]GKS, Gamma Knife radiosurgery; GTR, gross total resection; LC, local control; LINAC, linear accelerator; mOS, median overall survival.

local failure of about 17% after complete resection but with a slightly lower dose of WBRT (20-40 Gy). It is difficult to equate this to the local control rate in our study because not all of our patients had complete resection and we defined local failure as recurrence in the surgical bed at any time.

The impact of the extent of surgery for brain metastasis is not well characterized in the medical literature, particularly in patients who received SRS alone to the surgical cavity. Because most previous reports of surgery followed by SRS to the surgical cavity had rates of complete excision ranging from 80% to 100%, limited analysis of the impact of the extent of surgical resection has been made.[18-23] In our cohort, GTR was achieved in 68% of patients. There was a tendency toward a slightly higher local failure rate after incomplete resection, but the difference was not statistically significant. We think that comparable local control can be achieved by the higher dose of radiosurgery to the residual contrast-enhancing tumor.

One of the benefits of whole-brain radiation is the improved control of new intracranial metastases.[5,9,10,15] Reported rates of distant intracranial metastasis range from 24% to 87% without WBRT.[9,15,19,21,22,24-26] Table 3 highlights several of the contemporary series of surgery followed by radiosurgery to the resection cavity. Our series omitting WBRT resulted in 55% of patients developing new distant brain metastases. For those who developed new metastasis elsewhere in the brain, the median time was 5.6 months, whereas the overall median time to develop new metastasis was 10.1 months. In some select patient groups from our cohort (those with controlled primary disease, time from cancer diagnosis to brain metastasis of $>$ 12 months, or no systemic disease), the median freedom from new metastasis time was almost double ($>$ 19 months for each group). This reflects the importance of proper patient selection.

When WBRT is omitted, close clinical and imaging follow-up is required so that new metastases can be treated as effectively as possible.[9,11,15,28] Ultimately in our study, WBRT was used in only 35% of patients. Complete local and distant intracranial control was seen in 36.5%, and these patients did not require any additional therapy to the brain. We believe this justifies the local therapy for select patients with brain metastasis. Considerations for the potential complication of neurocognitive decline after WBRT must be weighed against the risk of developing additional intracranial metastasis.[4,11-14] The treatment of brain metastasis should be individualized with the oncological and neurological status of each patient to improve the general therapeutic outcome. Careful patient selection is necessary because not all patients with brain metastasis are candidates for surgical resection.

This study is one of the largest reports of patients who underwent surgical excision followed by SRS to the surgical cavity. The length of the follow-up helps support the outcomes and aids in the understanding of the risk of local and distant brain progression without whole-brain radiation treatments. For select patients with a good chance of longer survival, limited brain disease, and a lower risk of developing new metastasis, the aggressive local therapy approach of surgical excision plus radiosurgery is a good treatment option.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Kalkanis SN, Linskey ME. Evidence-based clinical practice parameter guidelines for the treatment of patients with metastatic brain tumors: introduction. *J Neurooncol*. 2010;96(1):7-10.
2. Pollock BE, Brown PD, Foote RL, Stafford SL, Schomberg PJ. Properly selected patients with multiple brain metastases may benefit from aggressive treatment of their intracranial disease. *J Neurooncol*. 2003;61(1):73-80.
3. Chao ST, Barnett GH, Liu SW, et al. Five-year survivors of brain metastases: a single-institution report of 32 patients. *Int J Radiat Oncol Biol Phys*. 2006;66(3): 801-809.
4. Varlotto JM, Flickinger JC, Niranjan A, Bhatnagar AK, Kondziolka D, Lunsford LD. Analysis of tumor control and toxicity in patients who have survived at least one year after radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys*. 2003;57(2):452-464.
5. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA*. 1998;280 (17):1485-1489.
6. Kalkanis SN, Kondziolka D, Gaspar LE, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2010;96(1):33-43.
7. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Central Nervous System Cancers. Version 2.2011*. Fort Washington, PA: NCCN; 2011.
8. Suh JH, Videtic GM, Aref AM, et al. ACR appropriateness criteria: single brain metastasis. *Curr Probl Cancer*. 2010;34(3):162-174.
9. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol*. 2011;29(2): 134-141.
10. DeAngelis LM, Mandell LR, Thaler HT, et al. The role of postoperative radiotherapy after resection of single brain metastases. *Neurosurgery*. 1989;24(6): 798-805.
11. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10(11):1037-1044.
12. Roman DD, Sperduto PW. Neuropsychological effects of cranial radiation: current knowledge and future directions. *Int J Radiat Oncol Biol Phys*. 1995;31(4):983-998.
13. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology*. 1989;39(6):789-796.
14. Welzel G, Fleckenstein K, Schaefer J, et al. Memory function before and after whole brain radiotherapy in patients with and without brain metastases. *Int J Radiat Oncol Biol Phys*. 2008;72(5):1311-1318.
15. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295(21):2483-2491.
16. Linskey ME, Andrews DW, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2010;96(1):45-68.
17. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*. 1990;322(8):494-500.
18. Iwai Y, Yamanaka K, Yasui T. Boost radiosurgery for treatment of brain metastases after surgical resections. *Surg Neurol*. 2008;69(2):181-186; discussion 186.
19. Do L, Pezner R, Radany E, Liu A, Staud C, Badie B. Resection followed by stereotactic radiosurgery to resection cavity for intracranial metastases. *Int J Radiat Oncol Biol Phys*. 2009;73(2):486-491.
20. Soltys SG, Adler JR, Lipani JD, et al. Stereotactic radiosurgery of the post-operative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys*. 2008; 70(1):187-193.

21. Mathieu D, Kondziolka D, Flickinger JC, et al. Tumor bed radiosurgery after resection of cerebral metastases. *Neurosurgery*. 2008;62(4):817-823; discussion 823-824.
22. Limbrick DD Jr, Lusis EA, Chicoine MR, et al. Combined surgical resection and stereotactic radiosurgery for treatment of cerebral metastases. *Surg Neurol*. 2009;71 (3):280-288; discussion 288-289.
23. Kelly PJ, Lin YB, Yu AY, et al. Stereotactic irradiation of the postoperative resection cavity for brain metastasis: a frameless linear accelerator-based case series and review of the technique. *Int J Radiat Oncol Biol Phys*. 2012;82(1):95-101.
24. Jagannathan J, Yen CP, Ray DK, et al. Gamma Knife radiosurgery to the surgical cavity following resection of brain metastases. *J Neurosurg*. 2009;111(3):431-438.
25. Hwang SW, Abozed MM, Hale A, et al. Adjuvant Gamma Knife radiosurgery following surgical resection of brain metastases: a 9-year retrospective cohort study. *J Neurooncol*. 2010;98(1):77-82.
26. Jensen CA, Chan MD, McCoy TP, et al. Cavity-directed radiosurgery as adjuvant therapy after resection of a brain metastasis. *J Neurosurg*. 2011;114:1585-1591.
27. Karlovits BJ, Quigley MR, Karlovits SM, et al. Stereotactic radiosurgery boost to the resection bed for oligometastatic brain disease: challenging the tradition of adjuvant whole-brain radiotherapy. *Neurosurg Focus*. 2009;27(6):E7.
28. Sheehan JP, Yen CP, Nguyen J, Rainey JA, Dassoulas K, Schlesinger DJ. Timing and risk factors for new brain metastasis formation in patients initially treated only with Gamma Knife surgery: clinical article. *J Neurosurg*. 2011;114(3):763-768.