Clinical outcomes in patients with brain metastases from breast cancer treated with single-session radiosurgery or whole brain radiotherapy

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OBJECTIVE Gamma Knife radiosurgery (GKRS) is used to treat brain metastases from breast cancer (BMB) as the sole treatment or in conjunction with tumor resection and/or whole brain radiotherapy (WBRT). This study evaluates outcomes in BMB based on treatment techniques and tumor biological features.

METHODS The authors reviewed all patients treated with BMB between 2004 and 2014. Patients were identified from a prospectively collected radiosurgery database and institutional tumor registry; 214 patients were identified. Data were collected from aforementioned sources and supplemented with chart review where needed. Independent radiological review was performed for all available brain imaging in those treated with GKRS. Survival analyses are reported using Kaplan-Meier estimates.

RESULTS During the 10-year study period, 214 patients with BMB were treated; 23% underwent GKRS alone, 46% underwent a combination of GKRS and WBRT, and 31% underwent WBRT alone. Median survival after diagnosis of BMB in those treated with GKRS alone was 21 months, and in those who received WBRT alone it was 3 months. In those treated with GKRS plus WBRT, no significant difference in median survival was observed between those receiving WBRT upfront or in a salvage setting following GKRS (19 months vs 14 months, $p = 0.63$). The median survival of patients with total metastatic tumor volume of $\leq 7 \text{ cm}^3$ versus $> 7 \text{ cm}^3$ was 20 months vs 7 months ($p < 0.001$). Human epidermal growth factor receptor-2 (Her-2) positively impacted survival after diagnosis of BMB (19 months vs 12 months, $p = 0.03$). Estrogen receptor status did not influence survival after diagnosis of BMB. No difference was observed in survival after diagnosis of BMB based on receptor status in those who received WBRT alone.

CONCLUSIONS In this single-institution series of BMB, the addition of WBRT to GKRS did not significantly influence survival, nor did the number of lesions treated with GKRS. Survival after the diagnosis of BMB was most strongly affected by Her-2 positivity and total metastatic tumor volume.

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KEY WORDS brain metastases; breast cancer; Gamma Knife; oncology; stereotactic radiosurgery; tumor registry; whole brain radiotherapy

BRAIN metastasis may occur in up to 30% of breast cancer cases.²² Commonly used treatment options in this scenario include conventionally fractionated whole brain radiotherapy (WBRT), single- or multisession stereotactic radiosurgery (SRS, including Gamma Knife radiosurgery [GKRS]), tumor resection, or some combination of the above. The proper approach to breast cancer patients with brain metastases remains incompletely defined.

With improvements in the management of both primary and metastatic disease over recent years, in particular with the use of targeted agents, developing evidence-based strategies that focus on preservation of quality of life and neurocognition is becoming more important.

There has been a shift toward delaying WBRT in the treatment of single and multiple brain metastases in recent years due to the recognized impact of WBRT on neuro-

ABBREVIATIONS BMB = brain metastases from breast cancer; ER = estrogen receptor; GKRS = Gamma Knife radiosurgery; GPA = graded prognostic assessment; Her-2 = human epidermal growth factor receptor-2; LMC = leptomeningeal carcinomatosis; SRS = stereotactic radiosurgery; WBRT = whole brain radiotherapy.

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cognition.⁶ Attempts are also being made to modify the technique of WBRT so that, when used, it minimizes the adverse effects on normal brain.⁹ The literature continues to support this approach, but generally consists of patient series addressing metastatic disease from multiple primary malignancies. In this single-institution series, we report clinical outcomes in patients with brain metastases from breast cancer (BMB), treated with GKRS and/or WBRT.

The current series spans a 10-year period of evolving philosophy with regards to the management of BMB at our institution. The use of WBRT alone in the earlier part of the series was reflective of the lack of a cohesive strategy of management and evaluation of brain metastasis. After instituting a centralized review of all patients with brain metastasis, including initial consultation and subsequent follow-up of all patients with BMB on the neurooncology service, we were able to identify appropriate management strategies for individual patients. Careful documentation of outcomes and testing of existing stratification tools in the literature is critical in establishing guidelines for the management of these patients.

Methods

All patients with brain metastases and a primary diagnosis of breast cancer were identified between January 2004 and January 2014. Data were gathered from a prospectively collected radiosurgery database and an institutional tumor registry and were supplemented with retrospective chart review where necessary. All information was stored in an institutional review board–approved database. Information pertaining to biological receptor status was coded from primary tumor pathology, unless additional specimens were available subsequently (i.e., biopsy of metastasis or intracranial tumor resection).

In the majority of patients whose data were collected from the radiosurgery database, independent radiological review was performed to assess local response, distant control, and presence (or absence) of treatment-induced edema. Survival statistics were performed using Kaplan-Meier analysis within SPSS (version 22.0, IBM Corp.).

The Gamma Knife (Elekta Instruments) was used in 148 patients for 673 lesions during 1 or multiple sessions. Twenty-two percent of patients underwent GKRS for a single metastasis, and 52% underwent GKRS for < 4 lesions. Seventeen percent of patients underwent a second GKRS treatment, and 10% underwent more than 2 treatments. The mean number of lesions cumulatively treated per patient was 4.55 (range 1–32 lesions). Prescription doses ranged from 8 Gy to 25 Gy at the margin. Prescription isodose lines varied from 30% to 95%, with lower isodoses used for larger tumors. The median prescription isodose was 55%. From 1 to 11 isocenters were used in planning with a median of 2.4 isocenters.

Fifty-nine patients were treated with WBRT without GKRS. Eight patients underwent tumor resection and received WBRT in the adjuvant setting. Nineteen patients had a diagnosis of leptomeningeal carcinomatosis (LMC), necessitating WBRT as opposed to focal treatment. One patient received repeat WBRT due to intracranial progression. The median age at cancer diagnosis in this cohort

was 52 years old, and the median age at the time of WBRT was 59 years old. The most common dosing schedule was 30 Gy in 10 fractions. All treatments were performed with thermoplastic mask immobilization. Treatment was delivered using a Varian linear accelerator with opposed oblique fields and custom multileaf collimation with 6 MeV photon beams.

All patients with hormone receptor positivity were treated with hormonal therapy until deemed refractory. Patients positive for human epidermal growth factor receptor-2 (Her-2) received targeted agent therapy that predated the interventions for BMB.

Follow-up was performed with clinical examination and MRI of the brain at 60- to 90-day intervals. Follow-up MRI examinations were imported into Leksell Gamma Plan (Elekta Instruments) to provide the ability to coregister images for evaluation of outcome and to identify new lesions with accuracy.

Results

Following query of the databases, 214 patients treated for BMB were identified between January 2004 and January 2014 at our institution. GKRS was performed alone in 23%, after WBRT in 32%, and upfront with WBRT salvage in 16% of patients. WBRT alone was performed in 29% of patients. The average Karnofsky Performance Scale score of those receiving GKRS at some point in treatment was 80–90; for those receiving WBRT alone, it was 60–70. Forty-one patients (19%) underwent tumor resection as a component of their management. Median survival after diagnosis of brain metastases for patients treated with GKRS alone, GKRS plus WBRT, and WBRT alone was 21 months, 18 months, and 3 months, respectively (Fig. 1). Actuarial survivals for the 3 cohorts are reported in Table 1.

Results of Patients Treated With GKRS

Of the 503 lesions with systematic follow-up imaging, a crude control rate of 87% was observed. Radiation-induced edema was noted in 7%. Retreatment (GKRS) was required in 5% of lesions. Radiation necrosis was observed in 2 patients, for 1 lesion each.

The median survival for the entire GKRS cohort following diagnosis of BMB was 18 months (95% CI 14.6–21.3 months). The median survival from initial cancer diagnosis was 71 months. Median survival in the GKRS-alone subset was 21 months. The addition of WBRT either upfront or in the salvage setting did not significantly improve survival after BMB (19 vs 14 months, $p = 0.63$).

Patients were grouped as having 1 or multiple lesions, and by < 4 or ≥ 4 lesions. The median survival after diagnosis of BMB was 19 months and 18 months for < 4 and ≥ 4 lesions, respectively ($p = 0.39$). For single and multiple lesions, median survival after BMB diagnosis was 23 months versus 18 months, respectively ($p = 0.17$). The median survival of patients with total metastatic tumor volume of $\leq 7 \text{ cm}^3$ versus $> 7 \text{ cm}^3$ was 20 versus 7 months, respectively ($p < 0.001$; Fig. 2).

After the initial diagnosis of breast cancer, estrogen receptor (ER) positivity conferred a survival advantage over those who were ER-negative (96 vs 50 months, $p < 0.01$).

FIG. 1. Kaplan-Meier survival curves after diagnosis of brain metastases according to treatment modality. Cum = cumulative; GK = Gamma Knife.

This advantage did not persist after diagnosis of BMB (19 vs 14 months in ER-positive vs ER-negative, respectively; $p = 0.18$). Her-2-positivity did confer a survival advantage following a diagnosis of BMB (19 vs 12 months, $p = 0.03$; Fig. 3). The median survival following a diagnosis of BMB by receptor profile was as follows: ER-positive/Her-2-positive 29 months; ER-positive/Her-2-negative 13 months; ER-negative/Her-2-positive 19 months; ER-negative/Her-2-negative 12 months ($p = 0.03$).

Results of Patients Treated With WBRT Alone

The median survival in this group following a diagnosis of BMB (or LMC) was 3 months (95% CI 1.4–4.6 months). The median survival from initial cancer diagnosis was 45 months (95% CI 37.2–52.8 months). No significant difference was observed pertaining to ER or Her-2 receptor status (49 vs 32 months for ER-positive and -negative, respectively, $p = 0.08$, and 49 vs 32 months for Her-2-positive and -negative, respectively, $p = 0.71$). No difference was observed with ER or Her-2 receptor status.

Graded Prognostic Assessment of Entire Cohort

Subbiah et al. published a validated, graded prognostic assessment (GPA) scoring guide for BMB.²⁰ Kaplan-Meier survival curves are shown in Fig. 4.

Discussion

In this retrospective, single-institution series, we observed no improvement in survival with the use of WBRT plus GKRS versus GKRS alone in patients with BMB. In addition, no significant difference was noted in patients with 1 versus multiple lesions, or < 4 versus ≥ 4 lesions. There is, however, a greater dependence of patient outcomes based on the total lesion volume (a disease burden surrogate). This difference demonstrated a 7-cm³ volume threshold in our data and mirrors the findings of Bhat-

TABLE 1. Actuarial survival by treatment modality

Time After Onset of CNS Disease (mos)	GKRS (%)	GKRS+WBRT (%)	WBRT (%)
6	76	91	35
12	60	67	11
18	58	52	6
24	46	35	4
30	40	24	0
36	36	19	0

nagar et al., who published results from a series of 205 patients, 23% of whom were breast cancer patients.^{4,5} Various GPA scores have been published with breast-specific scores available from publications by Sperduto et al.¹⁹ and Subbiah et al.²⁰ Based on the available data, we found the latter to be most applicable to our data set. Our results are consistent with those reported by Subbiah et al.

Our results suggest that GKRS may be an appropriate modality without the addition of WBRT in the patient population, while sparing the excess toxicity associated with WBRT.^{6,18} There is evidence (albeit limited by the retrospective nature of this study) that criteria for making treatment decisions based on number of lesions may be less relevant, and perhaps more exact indicators such as the total lesion volume may be more appropriate. The present findings are consistent with a similar series from Jaboin et al., who also saw no significant improvement in survival after diagnosis of BMB when using WBRT.¹² Survival may, in fact, be adversely affected by WBRT according to Halasz et al.¹⁰ Others, however, have reported data that trends in favor of the addition of WBRT to SRS for BMB.¹⁵

Our results confirm the findings of the randomized trial published by Aoyama et al., which revealed that survival is not improved with the addition of WBRT to GKRS. Intracranial relapse was more common, however, necessitating

FIG. 2. Kaplan-Meier survival curves after diagnosis of brain metastases based on total metastatic tumor volume ≤ 7 cm³ (cc) versus > 7 cm³ (cc).

FIG. 3. Kaplan-Meier survival curves after diagnosis of brain metastases based on receptor status in the GKRS cohort. MS = median survival.

close surveillance.¹ Yamamoto et al. reported the results of a prospective clinical trial enrolling almost 1200 patients with brain metastases from various primary histologies treated with SRS alone.²³ These authors concluded that SRS without WBRT might be a feasible approach with up to 10 lesions, given noninferior survival compared with patients with 2–4 treated lesions. Survival following SRS alone was superior in the Phase 3 trial reported by Sahgal et al.¹⁷

Prognosis following diagnosis of BMB has been evaluated in other recent publications. Aversa et al. reported on 115 patients diagnosed with CNS metastases from breast cancer, and concluded that Her-2 positivity was associated with survival.² Others have similarly found a correlation between longer survival after diagnosis of BMB and Her-2 positivity.^{3,8,14} Whether this is due to improved systemic control of disease or implicit behavior of these tumors

within the CNS is unclear.¹³ At least 1 series reported an increased need for salvage therapy following SRS in Her-2–positive disease.²¹ In a retrospective series from the University of Washington, tumors with triple negative receptor profiles had the shortest time to retreatment (either WBRT or SRS), implying that all others could be managed with reasonable expectations for intracranial control following SRS alone.⁷

Further study will be warranted to ascertain whether treatment paradigms for metastatic brain disease should be tailored by cell of origin. In this paper, we present local control and retreatment rates for breast-specific histology, but comparative data for other histologies are lacking. Iyer et al. correlated type of response to SRS with survival in breast cancer, positing a potential role for prognosticating based on imaging response.¹¹ Rades et al. suggest improved control with doses of 20 Gy as opposed to lower doses in a breast cancer–specific series.¹⁶

Several important limitations of this series are worth noting. The retrospective design creates opportunity for imbalanced treatment cohorts and excludes accountability for treatment selection. Certain relevant clinical information is not available to include in the analysis (e.g., performance status, systemic disease control, and chemotherapeutic/targeted agent usage), and may weaken the strength of the conclusions.

Conclusions

In this single-institution series of BMB, the addition of WBRT to GKRS did not significantly influence survival, nor did the number of lesions treated with GKRS. Survival after diagnosis of BMB was most strongly affected by Her-2 positivity and total metastatic tumor volume.

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FIG. 4. Kaplan-Meier survival curves based on validated graded prognostic assessment. 1 = Breast-GPA 0–1; 2 = Breast-GPA 1.5–2; 3 = Breast-GPA 2.5–3; 4 = Breast-GPA 3.5–4.²⁰

References

- Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. **JAMA** **295**:2483–2491, 2006
- Aversa C, Rossi V, Geuna E, Martinello R, Milani A, Redana S, et al: Metastatic breast cancer subtypes and central nervous system metastases. **Breast** **23**:623–628, 2014
- Bachmann C, Schmidt S, Staebler A, Schittenhelm J, Wallwiener D, Grischke EM: Risk factors and survival outcome in cerebral metastatic breast cancer. **Med Oncol** **31**:862, 2014
- Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD: Stereotactic radiosurgery for four or more intracranial metastases. **Int J Radiat Oncol Biol Phys** **64**:898–903, 2006
- Bhatnagar AK, Kondziolka D, Lunsford LD, Flickinger JC: Recursive partitioning analysis of prognostic factors for patients with four or more intracranial metastases treated with radiosurgery. **Technol Cancer Res Treat** **6**:153–160, 2007
- Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. **Lancet Oncol** **10**:1037–1044, 2009
- Cho E, Rubinstein L, Stevenson P, Gooley T, Philips M, Halasz LM, et al: The use of stereotactic radiosurgery for brain metastases from breast cancer: who benefits most? **Breast Cancer Res Treat** **149**:743–749, 2015
- Fokas E, Henzel M, Hamm K, Grund S, Engenhart-Cabillie R: Brain metastases in breast cancer: analysis of the role of HER2 status and treatment in the outcome of 94 patients. **Tumori** **98**:768–774, 2012
- Gondi V, Tolakanahalli R, Mehta MP, Tewatia D, Rowley H, Kuo JS, et al: Hippocampal-sparing whole-brain radiotherapy: a “how-to” technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. **Int J Radiat Oncol Biol Phys** **78**:1244–1252, 2010
- Halasz LM, Uno H, Hughes M, D’Amico T, Dexter EU, Edge SB, et al: Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. **Cancer** **122**:2091–2100, 2016
- Iyer A, Harrison G, Kano H, Weiner GM, Luther N, Niranjan A, et al: Volumetric response to radiosurgery for brain metastasis varies by cell of origin. **J Neurosurg** **121**:564–569, 2014
- Jaboin JJ, Ferraro DJ, DeWees TA, Rich KM, Chicoine MR, Dowling JL, et al: Survival following gamma knife radiosurgery for brain metastasis from breast cancer. **Radiat Oncol** **8**:131, 2013
- Kaplan MA, Isikdogan A, Koca D, Kucukoner M, Gumusay O, Yildiz R, et al: Biological subtypes and survival outcomes in breast cancer patients with brain metastases (study of the Anatolian Society of Medical Oncology). **Oncology** **83**:141–150, 2012
- Minisini AM, Moroso S, Gerratana L, Giangreco M, Iacono D, Poletto E, et al: Risk factors and survival outcomes in patients with brain metastases from breast cancer. **Clin Exp Metastasis** **30**:951–956, 2013
- Rades D, Huttenlocher S, Hornung D, Blanck O, Schild SE, Fischer D: Do patients with very few brain metastases from breast cancer benefit from whole-brain radiotherapy in addition to radiosurgery? **Radiat Oncol** **9**:267, 2014
- Rades D, Huttenlocher S, Rudat V, Hornung D, Blanck O, Phuong PC, et al: Radiosurgery with 20 Gy provides better local control of 1–3 brain metastases from breast cancer than with lower doses. **Anticancer Res** **35**:333–336, 2015
- Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al: Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. **Int J Radiat Oncol Biol Phys** **91**:710–717, 2015
- Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al: A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. **J Clin Oncol** **31**:65–72, 2013
- Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al: Effect of tumor subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases. **Int J Radiat Oncol Biol Phys** **82**:2111–2117, 2012
- Subbiah IM, Lei X, Weinberg JS, Sulman EP, Chavez-MacGregor M, Tripathy D, et al: Validation and development of a modified breast graded prognostic assessment as a tool for survival in patients with breast cancer and brain metastases. **J Clin Oncol** **33**:2239–2245, 2015
- Tam M, Narayana A, Raza S, Kunnakkat S, Golfinos JG, Parker EC, et al: Role of HER2 status in the treatment for brain metastases arising from breast cancer with stereotactic radiosurgery. **Med Oncol** **31**:832, 2014
- Tsukada Y, Fouad A, Pickren JW, Lane WW: Central nervous system metastasis from breast carcinoma. Autopsy study. **Cancer** **52**:2349–2354, 1983
- Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, et al: Stereotactic radiosurgery for patients with multiple brain metastases (JLKG0901): a multi-institutional prospective observational study. **Lancet Oncol** **15**:387–395, 2014

Disclosures

Dr. Dheerendra Prasad is a consultant to Elekta AB on matters unrelated to the current work.

Author Contributions

Conception and design: Prasad, Mix, O’Connor. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Prasad, Mix, O’Connor, Plunkett. Critically revising the article: Prasad, Mix, O’Connor, Plunkett. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Prasad. Statistical analysis: Prasad, Mix.

Supplemental Information

Previous Presentations

Portions of this work were presented in abstract form at the 57th annual meeting of ASTRO (American Society of Radiation Oncology) in San Antonio, Texas, October 18–21, 2015. Portions of this work were also presented at the 18th Annual Leksell Gamma Knife Society Meeting, Amsterdam, The Netherlands, May 15–19, 2016.

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