Published in final edited form as:

Breast Cancer Res Treat. 2015 February ; 149(3): 743–749. doi:10.1007/s10549-014-3242-x.

The use of stereotactic radiosurgery for brain metastases from breast cancer: Who benefits most?

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Abstract

Brain metastases (BM) from primary breast cancer can arise despite use of systemic therapies that provide excellent extracranial disease control. Local modalities for treating BM include surgery, whole brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). We sought to determine the benefits of SRS for management of BM arising from different biologic breast cancer subtypes. We reviewed records of 131 patients who received SRS for breast cancer BM between 2001 and 2013. Survival was estimated by the Kaplan–Meier method. Effects of tumor biology, number and location of lesions, and number of SRS sessions on survival were evaluated by Cox proportional hazards regression. Of the 122 patients with subtypes available, 41 patients (31 %) were classified as estrogen receptor positive/HER2 negative (ER⁺HER2⁻); 30 patients (23 %), ER⁺HER2⁺; 23 patients (18 %), ER⁻HER2⁺; and 28 patients (21 %), ER⁻HER2⁻ (or triple negative breast cancer, TNBC). Median age at first SRS was 50 years. Median overall survival for ER⁺HER2⁻, ER⁺HER2⁺, ER⁻HER2⁺, and TNBC was 16, 26, 23, and 7 months, respectively ($p < 0.001$ for difference between groups). Patients with TNBC had the shortest time to retreatment with WBRT or SRS or death with hazard ratio of 3.12 ($p < 0.001$) compared to ER⁺HER2⁻. In all subtypes other than TNBC, SRS can provide meaningful control of BM even in the setting of multiple lesions and may be worth repeating for new lesions that develop metachronously. For patients with TNBC, prognosis is guarded following SRS, and there is an urgent need to develop more effective treatment strategies.

Keywords

Brain metastases; Stereotactic radiosurgery; Whole brain radiation

Introduction

Breast cancer is the second most common cause of central nervous system (CNS) metastases after lung cancer [1]. As patients with advanced breast cancer live longer due to improvements in systemic therapies, the incidence of brain metastases (BM) appears to be increasing [2]. Poor penetration of systemic therapies into the CNS can create a reservoir for tumor growth in the brain despite excellent control of extracranial disease. Local modalities for treating BM from breast cancer include surgery, whole brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). SRS is a relatively new modality of treating BM with radiation where lesions are precisely targeted with image guidance, sparing areas of unaffected brain parenchyma and thus reducing the potential for widespread and long-term neurocognitive dysfunction compared to WBRT [3]. The benefits of SRS for multiple synchronous lesions or retreatment of subsequent metachronous lesions in breast cancer are promising, but as yet unclear.

Recently, several groups have published retrospective institutional experiences using SRS for BM from breast cancer [4–6]. One group identified ER status, HER2 status, Karnofsky

Performance Score (KPS), and primary tumor control as significant factors impacting overall survival after SRS, whereas the number of brain lesions did not influence survival [4]. Another group found that age and number of lesions were significant but breast cancer subtype and KPS were not important [5]. Yet another group reported that improved survival was associated with controlled extracranial disease, HER2 status, fewer lesions, and KPS but not ER status [6].

Because of the conflicting data and several unanswered questions, we reviewed our experience using SRS as treatment for BM in breast cancer patients. Our goal was to identify which patients would benefit most from upfront therapy with SRS and which patients might furthermore benefit from salvage treatment with SRS as opposed to WBRT. We analyzed the impact of various clinical factors including breast cancer subtype, number of lesions, number of SRS sessions received, age, location of extracranial disease, and prior therapy with WBRT.

Patients and methods

Patient selection

We identified 131 consecutive women with breast cancer who received SRS for BM between March 2001 and March 2013 at the University of Washington/Harborview Medical Center. Diagnosis of BM was based on imaging findings and/or biopsy. Clinical chart records and follow-up data for these patients were reviewed, and a research medical record abstract was created for each patient. Characteristics including histology, stage at diagnosis, ER and HER2 receptor status, number of BM, location of lesions, and sites of extracranial disease were recorded in the abstract. Other treatments for BM including surgery, WBRT, and sequential treatment episodes with SRS were also captured. When available, systemic treatments with cytotoxic chemotherapy, endocrine therapy, and targeted therapy were included. Information on progression and death was obtained from medical records and Social Security Death Index. Our investigation was approved by our institution's Institutional Review Board.

Pathology

Tumors were classified as ER⁺ by standard immunohistochemistry in accordance with CAP/ASCO guidelines. ER was interpreted using a modified H-score system (Allred) based on the proportion of cells staining and intensity of staining: >1 % of cells with weak staining intensity (Allred score 3 of 8) were the clinically validated threshold for a positive result [7]. Progesterone receptor (PR) status was not captured. HER2 status of primary tumors was determined using either IHC method and/or gene amplification method using fluorescent in situ hybridization (FISH) technique. Tumors were classified as HER2 positive (HER2⁺) if the protein was overexpressed by IHC (score ≥ 3) or amplified by FISH (HER2/CEP17 ratio ≥ 2).

Radiation Therapy: All patients were treated with the Leksell Gamma Knife using standard techniques with head frame immobilization. Treatments were planned from a T1 MRI obtained the same day using 1.4-mm axial slices following gadolinium contrast

administration. The lesions were targeted with a peripheral dose of 14–24 Gy in a single session to the 40–60 % isodose surface. In general, dosing was based on results from Radiation Therapy Oncology Group 90-05 dose escalation trial [8].

Patients were given steroids prior to treatment dependent on their clinical status. In general, there was an attempt to minimize the use of steroids. However, each patient was given a single dose of 10-mg intravenous or oral dexamethasone on the day of treatment prior to undergoing the radiosurgery session. After treatment, steroids were used only in patients who had clinical symptoms of cerebral edema. Patients were followed by serial brain MRI imaging, 1 month after treatment and then every 2–4 months thereafter. Surveillance imaging and clinical context were used to determine if salvage therapy was required.

Statistical methods

Overall survival was estimated using the Kaplan–Meier method. The association between mortality and the covariate of interest was assessed using hazard ratios estimated by Cox proportional hazard models ($p < 0.05$ was considered statistically significant). An interaction test was performed to assess if covariates representing multiple groups had varying hazard ratios relative to mortality. If the interaction term was deemed statistically significant, separate Cox proportional hazard models were constructed for each group of that covariate.

Results

A total of 131 patients with breast cancer who received SRS for BM had their charts reviewed. 99 patients were deceased at the time of this analysis and 32 patients were alive at the time of last follow-up. The median follow-up from time of first SRS for survivors was 24 months. Median age at time of first SRS was 50 years. Forty-one patients (31 %) were ER⁺HER2⁻, 30 patients (23 %) were ER⁺HER2⁺, 23 patients (18 %) were ER⁻HER2⁺, and 28 patients (21 %) had triple negative breast cancer (TNBC). Patients characteristics are summarized in Table 1. Seventy-nine patients (60 %) received their first session of SRS as their initial therapy of BM, 43 patients (33 %) received first SRS as salvage treatment after upfront WBRT, 4 patients (3 %) received SRS as a planned boost after WBRT, and 5 patients (4 %) received SRS as planned boost after surgery. Eleven patients received WBRT as salvage therapy after initial treatment with SRS alone and 2 patients received WBRT as salvage after upfront therapy with surgery followed by SRS boost. Neither prior WBRT ($HR = 1.18$, $p = 0.4$) nor age ($HR = 1.00$, $p = 0.5$) had a significant impact on overall survival. The only extracranial site with a significant association for mortality was the liver ($HR = 1.52$, $p = 0.039$). Fourteen patients (11 %) presented with metastatic disease only in the brain.

Survival by breast cancer subtype

In our cohort of patients, the median time from SRS to death was 15.7 months. Survival rates by subtype are shown in Fig. 1. Among patients with HER2⁺ disease, there was no significant difference in survival between patients with ER⁺ and ER⁻ disease ($p = 0.72$). Patients with TNBC had significantly lower median overall survival at 7 months, which was less than half of the median survival of any other group.

Survival by number of lesions

The median number of lesions treated with first session of SRS was 3 (range 1–22). Univariate analysis of the association of the number of lesions and overall survival was performed using the Cox proportional hazards model. Each additional lesion was associated with an increased hazard rate of 6.7 % ($p = 0.0016$). For prediction of survival, there was a significant interaction between number of lesions and subtype of breast cancer ($p = 0.0242$). Therefore, we investigated the influence of number of lesions on survival in each of the four subtypes separately (Table 2). For all subtypes other than ER⁺HER2⁺, increasing number of lesions was associated with increased risk of death. A likelihood ratio test was performed to examine whether number of lesions added significant information to the Cox regression model of survival versus breast cancer subtype. Number of lesions did indeed add predictive power ($p < 0.0001$). Likewise, the addition of breast cancer subtype to the Cox regression model of survival versus number of lesions also added predictive power ($p < 0.0001$).

Survival by location of lesions: Univariate analysis of the association of the location of lesions and overall survival was performed using the Cox proportional hazards model. The strongest associations for mortality were seen for lesions in the cerebellum ($n = 66$, $HR = 1.46$, $p = 0.059$) and brain stem ($n = 12$, $HR = 2.66$, $p = 0.002$). Significant associations were not detected between the locations of the lesions and breast cancer subtypes. However, a separate analysis performed on patients with cerebellar lesions alone identified a difference between risks of mortality by subtype (Table 3). Patients with TNBC had a significant increased hazard of death with cerebellar lesions whereas the other groups did not.

Survival by repeat sessions of SRS

Forty-seven patients (36 %) received two or more sessions of SRS and the mean time between first and second SRS sessions for these patients was 13 months. Median time from first to second session of SRS differed by breast cancer subtype. Median time to second SRS for ER⁺HER2⁻ patients was 17 months ($n = 10$); ER⁺HER2⁺ patients, 12 months ($n = 17$); ER⁻HER2⁺ patients, 10 months ($n = 13$); and TNBC patients, 6 months ($n = 6$). The association between subtype and time to second SRS, WBRT, or death was assessed as a surrogate for failure of disease control in the brain. On Cox regression, TNBC patients had a significantly shorter time to the surrogate endpoint than non-TNBC patients (Table 4). Fifteen patients received three sessions of SRS, 5 patients received four sessions, and 1 patient received five sessions. Mean time from second to third, third to fourth, and fourth to fifth sessions was 9, 15, and 7 months, respectively. Each additional session of SRS was associated with a decreased hazard ratio for death at 0.5384 ($p < 0.0001$).

Effect of targeted therapies for HER2⁺ patients: For the 53 patients with HER2⁺ disease, receipt of systemic HER2-targeted therapies was tracked. All 53 patients received trastuzumab, 31 patients (58.5 %) received lapatinib, and 3 patients (5.7 %) received ado-trastuzumab emtansine (no patients received pertuzumab). In a univariate analysis of HER2-targeted therapies in HER2^{POS} patients, having received lapatinib was associated with a decreased hazard ratio for death at 0.4233 ($p = 0.0143$).

Discussion

For patients with BM from primary breast cancer, local therapies include surgery, WBRT, and SRS. While algorithms in systemic therapies have evolved to reflect the differences in biology and natural history of different breast cancer subtypes, the same is not true in the treatment of BM. At present, there are no guidelines incorporating differences in outcomes for BM arising from different subtypes of breast cancer. There is also no consensus on how SRS should be utilized in the setting of multiple synchronous lesions or subsequent new metachronous lesions.

Historically, the first strategies for SRS in patients with BM from all cancers involved SRS with WBRT. A prospective randomized trial from the Radiation Therapy Oncology Group (RTOG) showed a significant improvement at 6 months in KPS and less steroid use in patients who had a boost treatment of SRS with WBRT compared with those who did not [9]. Japanese investigators conducted a prospective randomized trial evaluating survival and neurocognitive changes for patients with 1–4 BM from any cancer treated with SRS alone versus SRS with WBRT [10, 11]. There was no survival difference between the two groups although patients who received SRS alone had a higher rate of intracranial relapse. A phase III trial through the European Organization for Research and Treatment of Cancer (EORTC) randomizing patients to adjuvant WBRT or observation after SRS or surgery showed no improvement in duration of functional independence or overall survival with WBRT despite reduction of intracranial relapses [12].

In our present series, we show that there are significant differences in overall survival between patients based on their breast cancer subtype. TNBC patients had a median overall survival of only 7 months from time of SRS, whereas the other groups all had survival greater than 1 year. TNBC patients had a significantly increased hazard of next event as defined by second SRS, WBRT, or death. For the 6 patients with TNBC who had a second session of SRS, median time from first SRS to second was only 6.5 months. One other group has previously reported a grim prognosis in patients with BM from TNBC. In their report, patients treated with upfront WBRT, the median overall survival after diagnosis of BM was only 3.7 months [13]. Patients with TNBC appear to have poor overall survival and truncated period of CNS control regardless of upfront SRS or WBRT. With a median overall survival of only 7 months in our study, TNBC patients would be the least likely to suffer the long-term neurocognitive effects of WBRT; however, the short term side effects and increased duration of therapy compared to SRS remain potential concerns. From our dataset, we are not able to distinguish if the deaths in patients in TNBC are due to CNS relapse or to poor systemic control, but given the short time to CNS retreatment in our TNBC patients, we speculate that it is likely a combination of both factors.

For subtypes other than TNBC, survival at 1 year was greater than 50 %. For patients with any HER2⁺ disease, survival at 2 years was approximately 50 %. These patients, if treated upfront with WBRT, would be at risk of developing long-term toxicities associated with WBRT. Patients with ER⁺HER2⁻ disease had the longest time between first and second sessions of SRS, which suggests that the indolent nature of extracranial disease in this subtype may also be true for the intracranial disease burden. The hazard ratio of next event

as defined by second SRS, WBRT, or death was not statistically different between the three non-TNBC groups.

HER2⁺ patients in our series showed the greatest benefit from SRS and were more likely to receive subsequent sessions of SRS. While pertuzumab was not clinically available during the period of our analysis, all patients received trastuzumab and other effective systemic therapies to control extracranial disease. In our analysis, there was no significant interaction between survival and the number of lesions with first SRS in patients with ER⁺ HER2⁺ disease. Location of lesions in this group was also unlikely to affect survival. For patients with ER⁺HER2⁺ disease, upfront treatment with SRS (even for multiple lesions) as well as subsequent treatment with SRS for recurrent BM should be considered because of their long overall survival and duration of benefit. These conclusions drawn from our experience are consistent with the latest guidelines from the American Society of Clinical Oncology (ASCO) for treatment of BM in HER2⁺ patients. The recommendations endorse use of SRS for initial treatment of favorable prognosis patients with up to 4 BM and also for select patients with progressive intracranial disease [14]. Recommendations from the American Society of Radiation Oncology (ASTRO) similarly support the use of SRS for single and multiple brain lesions in patients with a good prognosis. For breast cancer patients, HER2⁺ disease, good performance status, and age <70 are important factors in determining favorable prognosis [15].

Interestingly, patients who received lapatinib had a marked decrease in hazard of death on a univariate analysis. Lapatinib is a HER2-targeted agent that has some ability to penetrate the blood–brain barrier [16], and there is clinical data to suggest activity against BM [17]. Other explanations for the differences observed in our population may be that patients who received lapatinib were treated more recently in a time period with improved systemic agents and/or that these patients represent those with better tumor biology who lived long enough to receive another line of HER2-targeted therapy.

In the study by Aoyama et al., serial neurocognitive evaluations with Mini-Mental State Examination (MMSE) showed that at 3 months, more patients in the SRS plus WBRT versus SRS alone group had a preserved MMSE (76 % vs. 59 %) but at 36 months, the SRS alone group had higher rates of preserved MMSE (52 % vs 15 %) [11]. The investigators postulated that WBRT was effective at preventing the neurocognitive decline from brain tumor recurrence in the early phase but perhaps contributed to continuous deterioration of neurocognitive function in long-term survivors. A different study from MD Anderson Cancer Center comparing neurocognitive function after SRS vs SRS plus WBRT showed that the addition of WBRT resulted in significant decline in learning and memory at 4 months after treatment [3]. These data are consistent with the literature on neurocognitive effects from prophylactic cranial irradiation (PCI) used for patients with limited stage small cell lung cancer [18]. Late adverse events usually develop 6–24 months after PCI and can consist of mild symptoms such as inattention and memory loss or more severe sequelae such as dementia. While there are no prospective studies on the neurocognitive effects of WBRT on breast cancer patients, we can assume similar late toxicity risks for long-term survivors. Because patients with BM from non-TNBC breast cancer generally live longer than patients

with BM from other primary histologies [19, 20], we can expect that overall, breast cancer patients are at higher risk for late toxicities from WBRT [15].

Limitations of our study include that it is a retrospective analysis. We were not able to assess the impact of KPS on survival as performance status was difficult to capture by chart review. However, SRS in our institution was generally only offered to patients with KPS >70. Information on primary disease control was also difficult to extract as two-thirds of the patients received at least some of their systemic care outside of our medical system. We were also unable to extract tumor volume from our treatment records, which would be another interesting factor to consider in assessing the efficacy of SRS.

Future directions for further defining the best use of SRS as local therapy in BM from breast cancer could include a prospective multi-institutional registry study. Factors noted to have a significant impact on survival from retrospective experiences could be better captured in such a prospective approach. The addition of quality of life metrics in new studies would further aid clinicians and patients in making treatment decisions.

Conclusion

SRS is a noninvasive and effective treatment modality for BM from breast cancer. Patients with ER⁺HER2⁻ disease and patients with HER2⁺ disease have significantly longer overall survival following SRS compared to patients with TNBC. Patients with TNBC have a guarded prognosis and better treatments are needed. In the meantime, the driving factor for deciding which treatment to use should factor in minimizing side effects due to the relative short survival time. Patients with ER⁺HER2⁺ disease have the longest duration of overall survival following SRS, and SRS should be strongly considered even for patients who have multiple lesions and for patients in the salvage setting for recurrent brain lesions after initial therapy.

Acknowledgments

We would like to recognize the many donors to the VK Gadi Research Fund for their generous contributions, which have made this manuscript possible. Eunpi Cho is the recipient of a National Cancer Institute funded postdoctoral fellowship (T32 CA009515).

References

1. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973–2001) in the metropolitan detroit cancer surveillance system. *J Clin Oncol*. 2004; 22(14):2865–2872. doi:10.1200/JCO.2004.12.149. [PubMed: 15254054]
2. Frisk G, Svensson T, Backlund LM, Lidbrink E, Blomqvist P, Smedby KE. Incidence and time trends of brain metastases admissions among breast cancer patients in Sweden. *Br J Cancer*. 2012; 106(11):1850–1853. doi:10.1038/bjc.2012.163. [PubMed: 22531629]
3. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009; 10(11):1037–1044. doi:10.1016/S1470-2045(09)70263-3. [PubMed: 19801201]

4. Kased N, Binder DK, McDermott MW, Nakamura JL, Huang K, Berger MS, Wara WM, Sneed PK. Gamma knife radiosurgery for brain metastases from primary breast cancer. *Int J Radiat Oncol Biol Phys.* 2009; 75(4):1132–1140. doi:10.1016/j.ijrobp.2008.12.031. [PubMed: 19345514]
5. Jaboin JJ, Ferraro DJ, Dewees TA, Rich KM, Chicoine MR, Dowling JL, Mansur DB, Drzymala RE, Simpson JR, Magnuson WJ, Patel AH, Zoberi I. Survival following gamma knife radiosurgery for brain metastasis from breast cancer. *Radiat Oncol.* 2013; 8(1):131. doi: 10.1186/1748-717X-8-131. [PubMed: 23718256]
6. Kondziolka D, Kano H, Harrison GL, Yang HC, Liew DN, Niranjan A, Brufsky AM, Flickinger JC, Lunsford LD. Stereotactic radiosurgery as primary and salvage treatment for brain metastases from breast cancer. *Clinical article. J Neurosurg.* 2011; 114(3):792–800. doi:10.3171/2010.8.JNS10461. [PubMed: 20887087]
7. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol.* 1999; 17(5):1474–1481. [PubMed: 10334533]
8. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, Farnan N. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys.* 2000; 47(2):291–298. [PubMed: 10802351]
9. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP, Curran WJ Jr. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet.* 2004; 363(9422):1665–1672. doi:10.1016/S0140-6736(04)16250-8. [PubMed: 15158627]
10. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N, Kobashi G. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA.* 2006; 295(21):2483–2491. doi:10.1001/jama.295.21.2483. [PubMed: 16757720]
11. Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, Hirota S, Shioura H, Inomata T, Kunieda E, Hayakawa K, Nakagawa K, Kobashi G, Shirato H. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys.* 2007; 68(5):1388–1395. doi:10.1016/j.ijrobp.2007.03.048. [PubMed: 17674975]
12. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Collette S, Collette L, Mueller RP. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol.* 2011; 29(2):134–141. doi:10.1200/JCO.2010.30.1655. [PubMed: 21041710]
13. Niwinska A, Murawska M, Pogoda K. Breast cancer brain metastases: differences in survival depending on biological subtype, RPA RTOG prognostic class and systemic treatment after whole-brain radiotherapy (WBRT). *Ann Oncol.* 2010; 21(5):942–948. doi:10.1093/annonc/mdp407. [PubMed: 19840953]
14. Ramakrishna N, Temin S, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, Giordano SH, Gonzalez-Angulo AM, Kirshner JJ, Krop I, Levinson J, Modi S, Patt DA, Perez EA, Perlmutter J, Winer EP, Lin NU. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2014; 32(19):2100–2108. doi: 10.1200/JCO.2013.54.0955. [PubMed: 24799487]
15. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, Sperduto PW, Vogelbaum MA, Radawski JD, Wang JZ, Gillin MT, Mohideen N, Hahn CA, Chang EL. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol.* 2012; 2(3):210–225. [PubMed: 25925626]
16. Morikawa A, Peereboom DM, Thorsheim HR, Samala R, Balyan R, Murphy CG, Lockman PR, Simmons A, Weil RJ, Tabar V, Steeg PS, Smith QR, Seidman AD. Capecitabine and lapatinib

- uptake in surgically resected brain metastases from metastatic breast cancer patients: a prospective study. *Neuro Oncol.* 2014 doi:10.1093/neuonc/nou141.
17. Bachelot T, Romieu G, Campone M, Dieras V, Cropet C, Dalenc F, Jimenez M, Le Rhun E, Pierga JY, Goncalves A, Leheurteur M, Domont J, Gutierrez M, Cure H, Ferrero JM, Labbe-Devilliers C. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol.* 2013; 14(1):64–71. doi:10.1016/S1470-2045(12)70432-1. [PubMed: 23122784]
 18. Wolfson AH, Bae K, Komaki R, Meyers C, Movsas B, Le Pechoux C, Werner-Wasik M, Videtic GM, Garces YI, Choy H. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2011; 81(1):77–84. doi:10.1016/j.ijrobp.2010.05.013. [PubMed: 20800380]
 19. Kocher M, Muller RP, Staar S, Degroot D. Long-term survival after brain metastases in breast cancer. *Strahlenther Onkol.* 1995; 171(5):290–295. [PubMed: 7770785]
 20. Akyurek S, Chang EL, Mahajan A, Hassenbusch SJ, Allen PK, Mathews LA, Shiu AS, Maor MH, Woo SY. Stereotactic radiosurgical treatment of cerebral metastases arising from breast cancer. *Am J Clin Oncol.* 2007; 30(3):310–314. doi:10.1097/01.coc.0000258365.50975.f6. [PubMed: 17551311]

Fig. 1.
Overall survival and 2-year survival rates by breast cancer subtypes

Table 1

Patient characteristics

Median age	50 (41-57, interquartile range)
Lesions treated (median)	3 (1-5 interquartile range)
Tumor biology	Number of patients
ER ⁺ HER2 ⁻	41 (31%)
ER ⁺ HER2 ⁺	30 (23%)
ER ⁻ HER2 ⁺	23 (18%)
TNBC	28 (21%)
ER ⁺ HER2 ^{unknown}	7 (5%)
ER ^{unknown} HER2 ^{unknown}	2 (2%)
SRS sessions	
1	131
2	47
3	15
4	5
5	1
WBRT prior to SRS	43
Intracranial sites	
Cerebellum	66
Brain stem	12
Lobar	101
Ventricle	8
Basal ganglia	10
Other	11
Extracranial sites	
Lung	56
Chest	22
Liver	54
Bone	74
Lymph node	41
Other	21
None (Brain only)	14

Table 2

Hazard ratio of death for each additional brain lesion at time of first SRS by breast cancer subtype

Subtype	Hazard ratio (95 % CI)	<i>p</i> value
ER ⁺ HER2 ⁻	1.17 (1.07–1.28)	0.0005
ER ⁺ HER2 ⁺	1.03 (0.96–1.12)	0.4
ER ⁻ HER2 ⁺	1.19 (1.10–1.40)	0.04
TNBC	1.15 (1.04–1.27)	0.0044

Table 3

Hazard ratio of death for patients with cerebellar lesions by breast cancer subtype

Subtype	Hazard Ratio (95 % CI)	<i>p</i> value
ER ⁺ HER2 ⁻	1.76 (0.86–3.60)	0.12
ER ⁺ HER2 ⁺	0.74 (0.30–1.87)	0.53
ER ⁻ HER2 ⁺	1.37 (0.50–3.70)	0.53
TNBC	2.89 (1.22–6.83)	0.016

Table 4

Hazard ratio of time from first SRS to second SRS, WBRT, or death by breast cancer subtype

Subtype	Hazard ratio (CI)	<i>p</i> value
ER ⁺ HER2 ⁻	1	Reference
ER ⁺ HER2 ⁺	0.98 (0.55–1.74)	0.93
ER ⁻ HER2 ⁺	0.96 (0.52–1.75)	0.89
TNBC	0.33 (1.88–5.67)	0.00003