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# Stereotactic radiosurgery with concurrent HER2-directed therapy is associated with improved objective response for breast cancer brain metastasis

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**Abstract**

**Background.** Patients with breast cancer positive for human epidermal growth factor receptor 2 (HER2) remain at high risk of intracranial relapse following treatment and experience increased rates of intracranial failure after stereotactic radiosurgery (SRS). We hypothesized that the addition of concurrent lapatinib to SRS would improve intracranial complete response rates.

**Methods.** Patients with newly diagnosed *HER2*-amplified breast cancer brain metastases from 2005–2014 who underwent SRS were included and divided into 2 cohorts based on timing of treatment with lapatinib. Outcome variables included the proportion of patients who achieved an intracranial complete response or progressive disease according to the RECIST 1.1 criteria, as well as individual lesion response rates, distant intracranial failure, and radiation necrosis.

**Results.** Eighty-four patients with 487 brain metastases met inclusion criteria during the study period. Over 138 treatment sessions, 132 lesions (27%) were treated with SRS and concurrent lapatinib, while 355 (73%) were treated with SRS without lapatinib. Compared with patients treated with SRS alone, patients treated with concurrent lapatinib had higher rates of complete response (35% vs 11%, $P = 0.008$). On a per-lesion basis, best objective response was superior in the concurrent lapatinib group (median 100% vs 70% reduction, $P < 0.001$). Concurrent lapatinib was not associated with an increased risk of grade 2+ radiation necrosis (1.0% with concurrent lapatinib vs 3.5% without, $P = 0.27$). Lapatinib had no protective effect on distant intracranial failure rates (48% vs 49%, $P = 0.91$).

**Conclusion.** The addition of concurrent lapatinib to SRS was associated with improved complete response rates among patients with HER2-positive brain metastases.

## Key Points

1. Complete response rates were higher with concurrent SRS and lapatinib compared with SRS alone.

2. Best objective response and complete response increased as lapatinib was administered closer to SRS.
3. There was no difference in the rate of radiation necrosis between the 2 cohorts.

## Importance of the Study

Breast cancer amplified by HER2 represents an aggressive subtype of breast cancer with a high rate of brain metastasis. Lapatinib, a dual *HER2*/epidermal growth factor receptor small molecule tyrosine kinase inhibitor has shown promise for use in the metastatic breast cancer setting, particularly in the context of brain metastasis due to its ability to cross the blood–brain barrier. In our study, the concurrent administration of lapatinib with SRS demonstrated superior complete response and best objective response to treatment of brain metastases without an increase in radiation necrosis. This result supports the safety and efficacy of the administration of concurrent lapatinib and SRS for the treatment of *HER2*-amplified breast cancer brain metastases.

Breast cancer is the second leading cause of brain metastasis and cancer-specific mortality among women in the United States.[1] Breast cancer amplified by human epidermal growth factor receptor 2 (HER2) represents an aggressive subtype that accounts for 25–30% of invasive breast cancer, and is associated with a greater rate of brain metastasis relative to other molecular subtypes.[2] Although the use of HER2-directed antibodies has significantly improved patient outcomes, translational studies have demonstrated that trastuzumab has poor penetration of the blood–brain barrier, leaving the brain vulnerable to metastatic relapse.[3] In fact, approximately one-third of patients with *HER2*-positive metastatic disease will develop CNS metastases despite trastuzumab therapy.[4] This increased rate of CNS failure adds to morbidity and mortality in this population, with high rates of salvage radiotherapy and surgery for intracranial failure.[2] With trastuzumab alone, high rates of death from CNS progression have been reported despite stable extracranial disease.[5] In contrast to trastuzumab, lapatinib is a dual *HER2*/epidermal growth factor receptor small molecule tyrosine kinase inhibitor with greater penetration of the blood–brain barrier in preclinical studies.[6,7] Recently, this agent nearly doubled progression-free survival and objective response when delivered with trastuzumab in the metastatic setting.[8] However, the indications for lapatinib are currently limited, and its role in the treatment of brain metastases remains unclear.

With the development of small molecule targeted therapies such as lapatinib, intracranial control may be improved beyond that currently offered by local therapies, including whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgical resection. In particular, the addition of concurrent targeted therapies to SRS is desirable, as recently published data have suggested that most classes of targeted therapies are safe to deliver with SRS without increased rates of radiation necrosis.[9] This strategy is particularly desirable in this population, as patients with *HER2*-amplified brain metastases have high rates of local failure and radiation necrosis (RN), limiting the opportunity to dose-escalate in this population with relatively long median survival.[10–12] We hypothesized that the addition of concurrent lapatinib to SRS alone would increase the rate of complete response (CR) in measurable brain metastases, decrease the rate of progressive disease, and increase the magnitude of best objective response in individual lesions without increased rates of RN.

## Materials and Methods

### Patient Selection and Data Collection

We conducted an institutional review board (IRB)–approved retrospective cohort study including all patients with newly diagnosed *HER2*-amplified breast cancer brain metastasis between 2005 and 2014 who underwent SRS with or without WBRT or resection at a single tertiary-care institution. Patients treated with surgery and/or WBRT alone were excluded, as were patients without radiographic follow-up. Cohorts were defined according to the timing of lapatinib with respect to SRS. Breast molecular subtype was based upon immunohistochemistry (IHC) surrogates, such that only patients with a diagnosis of HER2-positive disease by IHC were included. Patients with hormone receptor–positive disease were considered luminal B, while the remainder had HER2-type disease.

The following data were collected in an IRB-approved registry: age, estrogen receptor status, Karnofsky performance status (KPS), number of brain metastases, presence of extracranial metastases, disease-specific graded prognostic assessment (GPA), overall survival, lesion location, maximum diameter, prescription dose, conformality and heterogeneity indexes, and timing of systemic therapies, SRS, WBRT, and surgical resection.

The size of each lesion was recorded by measuring the maximum diameter on axial slices of all T1 post-contrast MRIs, starting from the time of diagnosis through treatment and each follow-up MRI. Response assessment was censored after salvage local or systemic therapy for progressive disease. Target lesions were up to 2 of the largest measurable (≥1.0 cm) lesions at baseline for each treatment session. For each pre- and post-SRS MRI, the sum of the diameters of all target lesions was calculated. Then, for each treatment session and individual lesion, changes in follow-up diameter were calculated by comparing each follow-up diameter with the smallest diameter (or sum of

diameters) to date. Treatment responses for each measurable treatment session and lesion were then categorized as CR (disappearance of all lesions), partial response (PR, at least 30% reduction), stable disease (SD, 29% diameter reduction to 19% diameter increase), or progressive disease (PD, ≥20% diameter increase compared with the smallest lesion diameter to date [nadir], with a minimum 5 mm increase over the nadir) according to the updated Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria.[13]

### Systemic Therapies

All cytotoxic, hormone, and targeted systemic therapies were recorded for each patient. Cytotoxic agents were divided into the following classes: nucleoside analogs, taxanes, alkylating agents, intercalating agents, and vinca alkaloids. Targeted therapies included HER2 antibodies (trastuzumab, pertuzumab, and T-DM1) and lapatinib. Concurrent therapy with lapatinib was defined as the agent administered on the same day as SRS, or within 5 biological half-lives of the date of SRS (~5 days, corresponding to ~97% metabolism or elimination).[9,14] Lapatinib that was stopped more than 5 biological half-lives before SRS, or initiated more than 5 biological half-lives after SRS, was not considered to be concurrent with SRS.

### Stereotactic Radiosurgery Delivery and Clinical Follow-Up

SRS was delivered with a 201- or 192-source Gamma Knife system (models 4C and Perfexion, Elekta Instruments). For planning, the dose prescribed to the peripheral margin was typically chosen based on lesion size according to Radiation Therapy Oncology Group (RTOG) trial 90-05.[15] Patients were seen in clinic with repeat MRI 4–6 weeks after SRS, and were subsequently followed every 2–3 months.

### Outcome Measures

Outcome variables included the CR rate, best objective response rate, and PD rate for measurable disease throughout radiographic follow-up for each treatment session. Additional outcomes included the best objective response and overall response among individual lesions. To study change in lesion size over time between cohorts, median objective response rates were reported at 1, 3, 6, and 12 months after SRS (grouped within ±0.5 mo). Finally, the cumulative incidences of radiographic RN and distant intracranial failure were reported as previously defined.[11,12] Briefly, ring-enhancing lesions demonstrating enlargement with surrounding edema were suspicious for RN. Short-interval follow-up imaging was performed to distinguish PD from RN. For equivocal cases, a multidisciplinary brain tumor board met to achieve a clinical consensus. If a consensus was not reached, patients typically underwent positron emission tomography (PET), MRI with cerebral blood volume, short interval imaging follow-up, or biopsy/resection to establish a diagnosis of tumor recurrence or RN.

### Statistical Analysis

For baseline characteristics, continuous data were compared across cohorts with Student's *t*-tests or Wilcoxon rank-sum tests, while categorical data were compared with Fisher's exact or chi-squared tests. Best objective response was compared across cohorts using Wilcoxon rank-sum tests. No pre-specified power calculation was performed. Cumulative incidences were used to estimate the time-dependent risk of local failure, RN, and distant failure. Non-informative censoring was performed only at loss to radiographic follow-up. Death was a second competing cause. To test for differences in cumulative incidences across cohorts, Gray's tests were utilized.[16,17]

Multivariable analyses for CR rate and best objective response were conducted on a per-patient and per-lesion basis using multivariable logistic and linear regression. Models were adjusted for the following covariates: use of concurrent lapatinib, age, presence of extracranial metastases, number of brain metastases, KPS, estrogen receptor positivity, prior or concurrent WBRT, prior surgery, lesion location, use of concurrent trastuzumab, treatment era, and baseline maximum diameter. Covariates were chosen based upon previously described risk factors for local failure, variables prognostic for survival, and the use of concurrent lapatinib to test the research hypothesis. Covariates demonstrating association ($P \leq 0.20$) with objective response or overall survival on univariate analysis were evaluated in a multivariable model including all 2-way interactions. Multivariable model quality was evaluated using the Akaike information criterion. Analyses were conducted using the R statistical software package including the cmprsk package.[18,19] Two-sided tests with $P < 0.05$ were considered statistically significant.

## Results

### Patient and Treatment Characteristics

Within the study period, 84 patients presented with 487 *HER2*-amplified brain metastases and met inclusion criteria (Table 1). For this study, a total of 1004 MRIs were reviewed and a total of 3435 measurements were made (average of 7 measurements per lesion, R: 2–31 measurements). There were 138 total treatment sessions among the 84 patients. After development of brain metastasis, 18 patients (21%) were treated at least once with SRS and concurrent lapatinib, while the remainder (66 patients, 79%) underwent SRS alone. Fifty-one patients (61%) had luminal B disease, whereas 33 (39%) had *HER2*-amplified disease. The median time from developing metastatic disease to first brain metastasis was 13.8 months (R: 0–154 mo). At presentation with brain metastasis (first treatment session), the 2 cohorts were similar with respect to age, presence of extracranial metastasis, KPS, number of brain metastasis, and diagnosis-specific GPA. Upfront intracranial therapy (WBRT, SRS, and surgery) was similar between cohorts. Patients who received lapatinib developed first brain metastasis slightly later in the study period (39% vs 29% in 2010–2014 vs 2005–2009, $P = 0.419$). Most patients received HER2 antibodies (76%) or

**Table 1** Patient characteristics at presentation with brain metastasis

| Characteristic | All Patients | SRS + Concurrent Lapatinib | SRS Alone | *P*-value |
|---|---|---|---|---|
| No. patients | 84 | 18 (21) | 66 (79) | |
| *ER*+ | 51 (61) | 9 (50) | 42 (64) | 0.415 |
| Age | 52 [31–84] | 50 [31–71] | 52 [34–84] | 0.459 |
| <50 | 34 (40) | 9 (50) | 25 (38) | |
| 50–59 | 29 (35) | 5 (28) | 24 (36) | |
| ≥60 | 21 (25) | 4 (22) | 17 (26) | |
| Extracranial metastasis | 74 (88) | 16 (89) | 58 (88) | 1.000 |
| Karnofsky performance status | 90 [60–100] | 90 [60–100] | 90 [60–100] | 0.757 |
| <70 | 4 (5) | 1 (6) | 3 (5) | |
| 70–80 | 33 (39) | 7 (39) | 26 (39) | |
| 90–100 | 47 (56) | 10 (55) | 37 (56) | |
| Number of brain metastases | 2 [1–25] | 2 [1–13] | 2 [1–25] | 0.736 |
| 1 | 31 (37) | 7 (39) | 24 (37) | |
| 2–3 | 26 (31) | 4 (22) | 22 (33) | |
| >3 | 27 (32) | 7 (39) | 20 (30) | |
| DS-GPA | 3.5 [2.5–4.0] | 3.5 [3.0–4.0] | 3.5 [2.5–4.0] | 0.502 |
| 0.0–1.0 | 0 (0) | 0 (0) | 0 (0) | |
| 1.5–2.0 | 0 (0) | 0 (0) | 0 (0) | |
| 2.5–3.0 | 28 (33) | 6 (33) | 22 (33) | |
| 3.5–4.0 | 56 (67) | 12 (67) | 44 (67) | |
| Upfront Intracranial Therapy | | | | |
| WBRT | 61 (73) | 14 (78) | 47 (71) | 0.767 |
| SRS | 51 (61) | 8 (44) | 43 (65) | 0.172 |
| Surgery | 17 (20) | 4 (22) | 13 (20) | 0.753 |
| Systemic Therapy* | | | | |
| Hormone therapy | 39 (46) | 7 (39) | 32 (48) | 0.596 |
| HER2 antibody | 64 (76) | 16 (89) | 48 (73) | 0.217 |
| Trastuzumab | 64 (76) | 16 (89) | 48 (73) | 0.217 |
| Pertuzumab | 0 (0) | 0 (0) | 0 (0) | — |
| T-DM1 | 2 (2) | 2 (11) | 0 (0) | 0.044 |
| Lapatinib | 43 (51) | 18 (100) | 25 (38) | <0.001 |
| Cytotoxic chemotherapy | 63 (75) | 16 (89) | 47 (71) | 0.218 |
| Nucleoside analog | 43 (51) | 15 (83) | 28 (42) | 0.003 |
| Taxane | 26 (31) | 8 (44) | 18 (27) | 0.249 |
| Alkylating agent | 22 (26) | 7 (39) | 15 (23) | 0.226 |
| Intercalating agent | 16 (19) | 7 (39) | 9 (14) | 0.036 |
| Vinca alkaloid | 13 (15) | 1 (6) | 12 (18) | 0.281 |
| Other** | 18 (21) | 8 (44) | 10 (15) | 0.019 |

Values presented as number (percent) or median [range].
No., number; *ER*, estrogen receptor; DS-GPA, diagnosis-specific graded prognostic assessment; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor. *Any use following brain metastasis (subtotals may exceed 100%). **Folate analog, topoisomerase inhibitor, eribulin, platinum agents, or epothilones.

cytotoxic chemotherapy (75%) after brain metastasis, with similar rates between cohorts. Many patients (72%) also received concurrent trastuzumab within 5 half-lives of SRS. This proportion was lower in the lapatinib cohort (66% vs 75%, $P = 0.056$). Only 2 patients received trastuzumab emtansine (T-DM1), and no patient received pertuzumab. Among patients not treated with concurrent lapatinib, 23 (35%) received lapatinib at other times during their disease course.

## Lesion Characteristics

During their disease course, the 84 included patients were treated with SRS to 487 metastases (Table 2). Among these, 132 (27%) were treated with SRS and concurrent lapatinib, while 355 (73%) were treated with SRS alone. The distribution of lesion location was similar between cohorts. A greater number of lesions treated with concurrent lapatinib had been previously treated with WBRT (80% vs 53%, $P < 0.001$), whereas fewer (2% vs 10%, $P = 0.005$) received SRS as a boost with WBRT. A greater number of lesions treated with SRS alone had been previously resected (2% vs 19%, $P < 0.001$), and few lesions (6 in total) were resected and treated with SRS boost.

Median prescription dose, conformality index, and heterogeneity index were quantitatively similar. Median lesion diameter was slightly smaller (0.70 vs 0.84 cm, $P = 0.001$) in the concurrent lapatinib cohort. Median radiographic follow-up was longer among lesions treated with concurrent lapatinib (11.0 vs 6.7 mo, $P = 0.548$). The median survival after SRS with concurrent lapatinib was 27.4 months (95% CI: 15.1–48.4).

## Radiographic and Clinical Outcomes

Among the 138 individual treatment sessions, 110 (80%) had measurable disease (ie, at least one lesion ≥1.0 cm). The median sum of baseline diameters (up to 2 measurable lesions) was 2.61 cm (interquartile range 1.6–3.7 cm). The proportion of patients who achieved a CR in measurable target lesions was significantly higher among those

**Table 2** Lesion characteristics at stereotactic radiosurgery

| Characteristic | All Lesions | SRS + Concurrent Lapatinib | SRS Alone | *P*-Value |
|---|---|---|---|---|
| No. lesions | 487 | 132 (27) | 355 (73) | |
| Supratentorial | 320 (66) | 86 (65) | 234 (66) | 0.915 |
| Location | | | | 0.609 |
| Frontal | 119 (24) | 39 (30) | 80 (23) | |
| Parietal | 66 (14) | 20 (15) | 46 (13) | |
| Temporal | 46 (9) | 10 (8) | 36 (10) | |
| Occipital | 41 (8) | 8 (6) | 33 (9) | |
| Cerebellar | 158 (32) | 43 (33) | 114 (32) | |
| Basal ganglia | 25 (5) | 5 (4) | 20 (6) | |
| Brainstem | 10 (2) | 3 (2) | 7 (2) | |
| Other | 22 (6) | 4 (2) | 19 (5) | |
| WBRT with SRS boost | 39 (8) | 3 (2) | 36 (10) | 0.005 |
| WBRT prior to SRS | 292 (60) | 105 (80) | 187 (53) | <0.001 |
| Surgery with SRS boost | 6 (1) | 0 (0) | 6 (2) | 0.133 |
| Surgery prior to SRS | 71 (15) | 3 (2) | 68 (19) | <0.001 |
| Maximum diameter (cm) | 0.80 [0.50–1.40] | 0.70 [0.47–1.03] | 0.84 [0.60–1.60] | 0.001 |
| Prescription dose (Gy) | 24 [18–24] | 22 [18–24] | 24 [18–24] | 0.164 |
| Conformality index | 1.91 [1.66–2.25] | 1.97 [1.74–3.18] | 1.88 [1.61–2.21] | 0.020 |
| Heterogeneity index | 1.75 [1.64–1.89] | 1.70 [1.54–1.82] | 1.76 [1.66–1.90] | 0.001 |
| Radiographic follow-up | 8.2 [3.3–17.5] | 11.0 [3.7–17.5] | 6.7 [3.0–20.5] | 0.548 |
| Lapatinib exposure | | | | <0.001 |
| Never | 111 (23) | 0 (0) | 111 (31) | |
| Prior (>3 mo) | 94 (19) | 0 (0) | 94 (27) | |
| Concurrent (±5 days) | 132 (27) | 132 (100) | 0 (0) | |
| Adjuvant (>5 days) | 150 (31) | 0 (0) | 150 (42) | |
| 0–3 mo | 29 (6) | 0 (0) | 29 (8) | |
| 3–6 mo | 46 (10) | 0 (0) | 46 (13) | |
| >6 mo | 75 (15) | 0 (0) | 75 (21) | |
| Concurrent HER2 antibody | 352 (72) | 87 (66) | 265 (75) | 0.056 |
| Trastuzumab | 352 (72) | 87 (66) | 265 (75) | |
| Pertuzumab | 0 (0) | 0 (0) | 0 (0) | |
| T-DM1 | 0 (0) | 0 (0) | 0 (0) | |

Values presented as number (percent) or median [interquartile range]. No., number; WBRT, whole-brain radiation therapy; mo., months.

receiving concurrent lapatinib (35% vs 11%, $P$ = 0.008), without a significant increase in objective response rate (CR + PR, 75% vs 57%, $P$ = 0.121). The proportion of patients who developed PD in measurable target lesions was not significantly lower among those receiving concurrent lapatinib (25% vs 43%, $P$ = 0.121). The median best objective response throughout clinical follow-up among patients treated with or without concurrent lapatinib was 69% vs 54% ($P$ = 0.037). Among patients who were treated with ($n$ = 18) or without ($n$ = 66) SRS + concurrent lapatinib, median survival was 40.4 vs 25.1 months ($P$ = 0.155). Fewer patients treated with concurrent lapatinib required salvage WBRT (6% vs 20%) and surgery (0% vs 20%). Among patients who ever ($n$ = 43) or never ($n$ = 41) received lapatinib following brain metastasis, median survival was 33.3 vs 23.6 months ($P$ = 0.009). Among the 43 patients who were ever treated with lapatinib, median survival was not significantly different among patients treated concurrently versus adjuvantly (40.4 vs 33.3 mo, $P$ = 0.775).

Lesion-specific best objective response, a secondary outcome, was superior in the concurrent lapatinib group (median 100% vs 70% reduction, $P$ < 0.001; Table 3, Fig. 1A–D). The median objective responses at 1, 3, 6, and 12 months after SRS with or without concurrent lapatinib were: 50% vs 47% ($P$ = 0.506), 56% vs 60% ($P$ = 0.504), 100% vs 60% ($P$ < 0.001), and 100% vs 71% ($P$ < 0.001). Among all lesions treated concurrently with lapatinib, there were a greater number of complete responses (57% vs 38%, $P$ < 0.001) and lower rates of progressive disease (11% vs 19%, $P$ < 0.001).

The timing of lapatinib administration on objective response rate was also investigated. Among the 132 lesions treated concurrently (±5 half-lives), lapatinib was delivered on the day of SRS for 114 (86%) lesions, and 1–5 days before or after SRS for 12 (9%) and 6 (5%) lesions, respectively. Among the 355 lesions treated with SRS alone, 111 (31%) were never exposed to lapatinib, 94 (27%) developed in patients previously treated with lapatinib (>3 mo), and 150 (42%) were exposed to lapatinib adjuvantly (29 [8%] within 3 mo, 46 [13%] within 3–6 mo, and 75 [21%] >6 mo). Best objective response and overall response generally improved as lapatinib was delivered closer to SRS, with a median best objective response of 77% for prior exposure (CR: 40%, PD: 7%), 100% for concurrent therapy (CR: 57%, PD: 11%), 100% for adjuvant therapy within 3 months (CR: 55%, PD: 14%), 78% for adjuvant therapy within 3–6 months (CR: 43%, PD: 15%), 85% for adjuvant therapy >6 months (CR: 48%, PD: 31%), and 54% for lesions never exposed to lapatinib (CR: 22%, PD: 23%). The 24-month actuarial cumulative incidence of local failure after SRS with or without concurrent lapatinib was 12% vs 19% ($P$ = 0.071; Fig. 2), similar to the crude incidence of PD.

Multivariable logistic and linear regression were performed to adjust for differences in confounding covariates for per-treatment CR rate and per-lesion best objective response between cohorts. After adjustment, concurrent lapatinib remained associated with an increased CR rate among treatment sessions with measurable disease (odds ratio 2.93, 95% CI: 1.50–5.74, $P$ = 0.002; Table 4). Among individual lesions, concurrent lapatinib remained statistically significantly associated with improved objective response (mean 11.52% decrease, 95% CI: 4.71–18.32%, $P$ < 0.001). This association remained significant after further adjusting by duration of radiographic follow-up (12.20% decrease, 95% CI: 5.39–19.00%, $P$ < 0.001). Concurrent trastuzumab with SRS was not associated with objective response rates.

We also investigated the efficacy of lapatinib in prevention of distant intracranial failure in patients receiving SRS. Among all patients, the 12-month cumulative incidences of distant intracranial failure after SRS were 48% (95% CI: 28–68%) with concurrent lapatinib compared with 49% (95% CI: 40–58%) without concurrent lapatinib ($P$ = 0.91). Among the 28 lesions (6%) that developed radiographic RN, 13 (46%) were grade 2 and 15 (54%) were grade 1 adverse events. Thirteen (46%) were diagnosed with serial MRI alone, 4 (14%) with MRI perfusion alone, 5 (18%) with MRI and PET, and 6 (22%) with MRI and biopsy or resection (which demonstrated necrotic tissue). The 12-month cumulative incidences of grade 2+ RN among patients treated with or without concurrent lapatinib were similar (1.0% [95% CI: 0.0–2.8%] vs 3.5% [95% CI: 0.2–5.4%], $P$ = 0.134). The 12-month cumulative incidence of grade 2+ RN generally increased with increasing lesion size (≤0.5 cm: 0.0%; 0.5–1.0 cm: 3.3%; 1.0–2.0 cm: 4.7%, >2.0 cm: 3.4%, $P$ = 0.177). Concurrent lapatinib was

**Table 3** Individual lesion objective response rates

| Characteristic | All Lesions | SRS + Concurrent Lapatinib | SRS Alone | $P$-Value |
|---|---|---|---|---|
| No. lesions | 487 | 132 (27) | 355 (73%) | |
| Best objective response (median [range]) | −78% [−100%, +125%] | −100% [−100%, +50%] | −70% [−100%, +125%] | <0.001 |
| Objective response categories | | | | <0.001 |
| Complete response | 209 (43) | 75 (57) | 134 (38) | |
| Partial response | 158 (32) | 38 (29) | 120 (34) | |
| Stable disease | 38 (8) | 4 (3) | 34 (9) | |
| Progressive disease | 82 (17) | 15 (11) | 67 (19) | |

Values are presented as percent change or as number (percent). No., number.

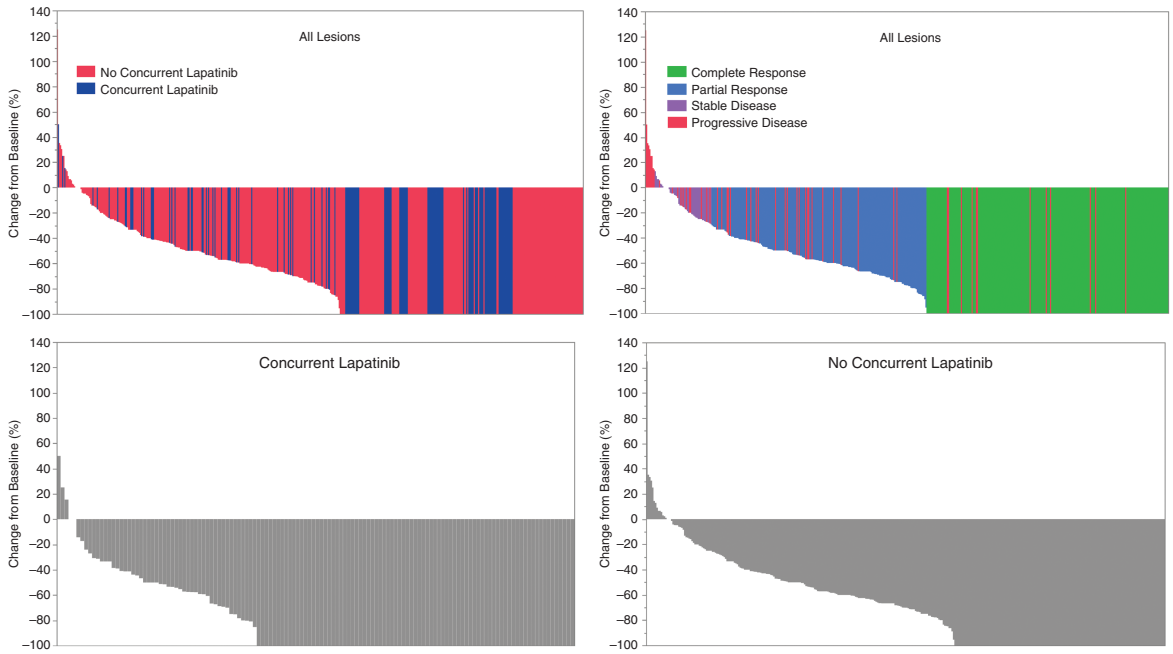


**Fig. 1** Waterfall plots depicting best objective response among the 487 treated lesions. (A) Best objective response, all 487 lesions, stratified by use of concurrent lapatinib (red = no concurrent lapatinib, blue = concurrent lapatinib). (B) Best objective response, all 487 lesions, stratified by overall response after full radiographic follow-up (green = complete response, blue = partial response, purple = stable disease, red = progressive disease). Note that lesions that ultimately developed progressive disease after a favorable best objective response (eg, –100%) are colored in red. (C) Best objective response among 132 lesions treated with SRS + concurrent lapatinib. (D) Best objective response among 355 lesions treated with SRS without concurrent lapatinib.

not associated with increased rates of RN among large (>1.5 cm) lesions (0.0% vs 4.5%, $P = 0.39$).

## Discussion

This retrospective institutional investigation sought to test the hypothesis that the addition of concurrent lapatinib to SRS improves the CR rate among *HER2*-positive breast cancer brain metastases. In support of our hypothesis, we observed a significantly higher rate of complete response among measurable lesions during radiographic follow-up, with lower rates of progressive disease and without higher rates of radiation necrosis. Moreover, a relationship was observed between timing of lapatinib and per-lesion best objective response, with poorer response rates among lesions exposed to lapatinib >3 months adjuvantly, previously exposed lesions, and lesions never exposed to this agent. Notably, similar outcomes were observed among lesions treated with either concurrent or early adjuvant lapatinib. These findings support previously published data reporting the intracranial efficacy of this agent, as well as the ongoing RTOG 1119 trial.[7]

Lapatinib is currently approved under narrow indications for patients with *HER2*-amplified disease previously treated with trastuzumab, or triple-positive patients alongside letrozole. Recently, the phase III ALTERNATIVE trial was reported, wherein the addition of lapatinib to trastuzumab and an aromatase inhibitor nearly doubled progression-free survival and objective response.[8] This trial supported a role for dual HER2 inhibition in the metastatic population. Previously, a multicenter phase II study reported modest efficacy of combination treatment with lapatinib and capecitabine against *HER2*-amplified brain metastases.[20] Moreover, in the phase II LANDSCAPE trial, the first-line use of combination lapatinib and capecitabine demonstrated 66% PR rate in WBRT-naïve patients, similar to the rates observed with the use of WBRT alone.[21] This suggested a potential role for lapatinib as a WBRT-sparing agent, thereby reducing the neurocognitive effects associated with WBRT. Although we did not observe improved distant intracranial control with lapatinib, our results indicate lower rates of PD with the addition of concurrent lapatinib to SRS. This may be related to the longer time at risk for distant intracranial failure in the lapatinib arm, or may reflect the relatively modest single-agent activity of lapatinib.[20,21]

In contrast to the aforementioned trials, the phase III EMILIA trial demonstrated that the use of T-DM1 leads to reduced toxicity and superior progression-free survival relative to combination lapatinib and capecitabine in *HER2*-positive patients.[22] A secondary analysis also showed superior overall survival with the use of T-DM1 among patients with stable or treated brain metastases at baseline without a corresponding progression-free survival benefit, suggesting that the survival benefit of T-DM1 is driven primarily by the control of extracranial disease. Further, the CEREBEL trial showed no difference between lapatinib

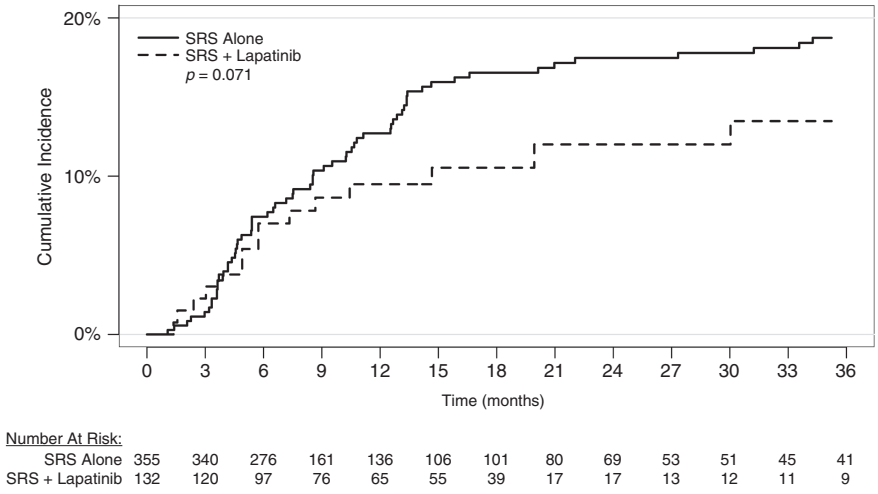


**Fig. 2** Cumulative incidence plots of local failure after SRS with concurrent lapatinib vs SRS without concurrent lapatinib, with death as a competing risk.

and capecitabine versus trastuzumab and capecitabine in the incidence of CNS metastases among *HER2*-positive metastatic breast cancer patients.[23] These results suggest that for patients with extracranial disease progression, the use of T-DM1 may be of greater benefit than lapatinib. Nevertheless, with the advent of dual HER2-blockade in the ALTERNATIVE trial, lapatinib may serve a role in therapy alongside SRS, primarily for its intracranial efficacy.

Smaller studies have reported the efficacy of lapatinib against metastatic breast cancer in combination with local therapies. In a phase 0 study of 12 patients reported by Morikawa et al, 4 patients with breast cancer brain metastases received lapatinib in the days leading up to surgical resection of brain metastases. In the resected specimens, lapatinib was reproducibly detectable, and its tissue concentration was correlated to the number of preoperative doses of the agent.[24] These data provide evidence for the biological rationale for adding lapatinib to SRS. A separate single-institution retrospective cohort study of the effects of SRS and lapatinib on HER2-positive breast cancer brain metastases showed increased local control after treatment with SRS and lapatinib than without lapatinib.[25] Among 40 patients, 24 were treated with both SRS and lapatinib and demonstrated greater local control on serial imaging. Concurrent SRS and lapatinib has also shown no significant increase in rates of RN, the primary dose-limiting toxicity associated with SRS.[9] Taken together, these results suggest that the use of lapatinib and SRS may lead to favorable outcomes for patients with intracranial disease without an increase in toxicity.

The current study provides additional retrospective evidence that the addition of concurrent lapatinib to SRS may increase the rate of intracranial CR and augment best objective response. Given that a subset of patients with metastatic breast cancer die from CNS progression, this increase in intracranial response could improve clinical outcomes in this population.[5] However, until prospective evidence is available to confirm that concurrent lapatinib improves clinically meaningful outcomes in this population, routine use of concurrent lapatinib with SRS remains investigational.

The ongoing RTOG 1119 trial, a phase II randomized controlled study, is currently comparing the efficacy of WBRT/SRS with or without lapatinib among patients with *HER2*-positive breast cancer brain metastases.[26] The primary endpoint is complete response rate at 12 weeks after WBRT or SRS as determined by MRI, with secondary endpoints including CR at 4 weeks, objective response rates at 4 and 12 weeks, lesion-specific response rates at 4 and 12 weeks, CNS progression-free survival, and overall survival. The present study is timely and relevant, as it shares primary and secondary outcomes with this trial in a similar population.

Several limitations must be considered when interpreting the results of this study. As a single institutional study, the generalizability of these results may be limited in other institutions. As a retrospective investigation, these results are susceptible to selection biases. The choice of systemic therapy in a nonrandomized population is influenced by prior therapy, performance status, toxicity profile, and extracranial disease, among other factors. This study also included only 2 patients who had received T-DM1 and no patients who received pertuzumab, which currently represent the first- and second-line therapies, respectively, against metastatic *HER2*-positive disease. Furthermore, the RECIST 1.1 criteria were used for response assessment, while the more recent Response Assessment in Neuro-Oncology–BM criteria were specifically designed for brain metastases.[27] The main strength of this study are the objective measurements made of each lesion serially through follow-up, and the analysis of local failure, distant failure, and survival in a large population.

**Table 4** Multivariate logistic and linear regressions

| Covariate | Per-Treatment Complete Response | | | | Per-Lesion Best Objective Response | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate | Multivariate | | | Univariate | Multivariate | | |
| | *P*-Value | OR | 95% CI | *P*-Value | *P*-Value | Est. | 95% CI | *P*-Value |
| Concurrent lapatinib | 0.008 | 2.93 | 1.50–5.74 | 0.002 | 0.001 | −11.52 | −18.32–−4.71 | <0.001 |
| Age | | | | | | | | |
| <50 | [ref] | — | — | — | [ref] | 0 | [ref] | [ref] |
| 50–59 | 0.634 | — | — | — | 0.008 | −12.95 | −19.86–−6.03 | <0.001 |
| ≥60 | 0.224 | — | — | — | 0.024 | −14.84 | −22.88–−6.80 | <0.001 |
| Extracranial metastasis | 0.254 | — | — | — | 0.934 | — | — | — |
| Karnofsky Performance Status | | | | | | | | |
| <70 | 0.186 | 2.67 | 0.13–56.07 | 0.527 | 0.001 | -26.07 | −40.46–−11.69 | <0.001 |
| 70–80 | 0.028 | 0.75 | 0.14–4.14 | 0.743 | 0.019 | 10.92 | 4.32–17.52 | 0.001 |
| 90–100 | [ref] | 1.00 | [ref] | [ref] | [ref] | 0 | [ref] | [ref] |
| Number of Brain Metastases | | | | | | | | |
| 1 | [ref] | — | — | — | [ref] | 0 | [ref] | [ref] |
| 2–3 | 0.218 | — | — | — | 0.038 | −12.77 | −21.81–−3.74 | 0.006 |
| >3 | 0.267 | — | — | — | 0.045 | −2.76 | −10.37–4.86 | 0.477 |
| Baseline maximum diameter (cm) | <0.001 | 0.34 | 0.17–0.68 | <0.001 | <0.001 | 15.86 | 12.36–19.35 | <0.001 |
| *ER+* | 0.499 | — | — | — | 0.917 | — | — | — |
| Supratentorial | — | — | — | — | 0.271 | — | — | — |
| WBRT with SRS boost | 0.030 | 2.47 | 0.27–23.03 | 0.425 | <0.001 | −9.42 | −19.86–1.02 | 0.077 |
| WBRT prior to SRS | 0.021 | 0.30 | 0.08–1.20 | 0.088 | 0.942 | — | — | — |
| Surgery with SRS boost | 0.229 | — | — | — | 0.085 | −11.26 | −37.99–15.48 | 0.409 |
| Surgery prior to SRS | 0.027 | 1.27 | 0.08–19.24 | 0.863 | 0.013 | 15.17 | −6.14–24.21 | 0.220 |
| Concurrent trastuzumab | 0.937 | — | — | — | 0.487 | — | — | — |
| Years into study period | 0.208 | — | — | — | <0.001 | −2.42 | −0.96–−3.88 | 0.001 |

*ER*, estrogen receptor; WBRT, whole-brain radiation therapy; OR, odds ratio; Est., parameter estimate; CI, confidence interval, [ref], reference.

## Conclusion

In this single institutional retrospective investigation, we observed higher complete response rates and superior best objective response among patients treated with concurrent SRS and lapatinib compared with patients treated with SRS alone. A temporal relationship was observed between objective response rate and the timing of concurrent versus adjuvant lapatinib. These data support ongoing clinical trials studying the safety and efficacy of lapatinib added to radiotherapy for HER2-positive breast cancer brain metastases.

## Keywords

brain metastasis | breast cancer | HER2 | lapatinib | stereotactic radiosurgery

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