



Stereotactic radiosurgery for patients with breast cancer brain oligometastases — molecular subtypes and clinical outcomes

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ABSTRACT

Background: We sought to determine the clinical outcomes of patients with breast cancer (BC) who had undergone stereotactic radiosurgery (SRS) for a limited number of brain metastases (BM) and to identify factors influencing overall survival (OS) and local control.

Materials and methods: The records of 45 patients who underwent SRS for 72 brain lesions were retrospectively evaluated. Statistics included the chi-squared test, Kaplan-Meier method, and the multivariate Cox model.

Results: The median number of treated BM was 2 (range 1–10). Median OS from BM diagnosis and post-SRS were 27.6 [95% confidence interval (CI): 14.8–40.5] and 18.5 months (95% CI: 11.1–25.8), respectively. One-year and two-year survival rates after BM diagnosis were 55% and 41%, respectively. In a univariate analysis, the Luminal-B-human-epidermal-growth-receptor-positive (HER2+) subtype had the longest median OS at 39.1 months (95% CI: 34.1–44.1, $p = 0.004$). In an adjusted analysis, grade 2 [hazard ratio (HR): 0.1; 95% CI: 0.1–0.6, $p = 0.005$], craniotomy (HR: 0.3; 95% CI: 0.1–0.7; $p = 0.006$), and ≥ 2 systemic therapies received (HR: 0.3; 95% CI: 0.1–0.9, $p = 0.028$) were associated with improved OS. One-year and two-year intracranial progression-free survival rates were 85% and 63%, respectively. Four factors for a higher risk of any intracranial recurrence remained significant in the adjusted analysis, as follows: age < 50 years (HR: 4.2; 95% CI: 1.3–36.3; $p = 0.014$), grade 3 (HR: 3.7; 95% CI: 1.1–13.2; $p = 0.038$), HER2+ (HR: 6.9; 95% CI: 1.3–36.3; $p = 0.023$), and whether the brain was the first metastatic site (HR: 4.7; 95% CI: 1.6–14.5; $p = 0.006$).

Conclusion: Intrinsic BC characteristics are important determinants for both survival and intracranial control for patients undergoing SRS for oligometastatic brain disease.

Key words: breast cancer; brain metastases; molecular subtype; stereotactic radiosurgery; radiation therapy

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Introduction

Patients with breast cancer (BC) frequently suffer from the development of distant metastasis, with bone, lung, liver, and brain metastasis (BM) being the most common [1]. The incidence proportion for the development of BM among a subset of metastatic BC at diagnosis is around 7–16% [2,

3] and approximately 17% during follow-up [3]. When different tumor subtypes are considered after a diagnosis of BM, the highest percentage was observed among patients with hormonal receptor-positive human epidermal growth receptor-negative (HR+/HER2–) primary BC, reaching 30–45%, followed by triple-negative (TNBC), HR+/HER2+, and HER2-positive subtypes with an incidence of

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17–25%, 20–24%, and 15–21%, respectively [3–6]. In autopsy studies, up to 35% of patients with BC are found to have BM, not all of which had been clinically relevant in the lifetime of the patients [7]. The combination of new systemic treatment options, which have resulted in improved survival for metastatic BC and implementation of sensitive diagnostic imaging in clinical practice, have contributed to a higher overall detection of brain metastasis [8].

Local management of BM involves surgery, either single fraction or hypofractionated radiosurgery (SRS), and/or whole-brain radiotherapy (WBRT). Two large randomized studies comparing SRS alone versus SRS and WBRT found higher intracranial failure rates with SRS alone without compromising overall survival (OS) [9, 10]. Studies also demonstrated significantly worse learning and memory functions with the SRS and WBRT combination compared to SRS alone, which made the latter a first-choice treatment, particularly for limited brain metastatic disease and, increasingly, for patients with four or more BM [11, 12]. Patients with diffuse brain involvement or large metastases are typically offered WBRT without or with hippocampal sparing to preserve the neurocognitive function [11, 13].

Roughly, 50% of patients with BC with BM will die from intracranial progression [3]. HER2-positive disease is more frequently associated with intracranial recurrence after brain-directed radiotherapy for BM, compared to HR+/HER2-primary BC molecular subtypes [6]. In contrast, patients with TNBC disease demonstrated higher rates of new brain lesions and shorter time to salvage SRS or WBRT [6].

The purpose of this retrospective study was to assess the clinical outcomes of BC patients with a limited number of BM who had undergone SRS for BM at the Institute of Oncology Ljubljana, and to identify clinical and pathohistological characteristics affecting their survival and local recurrence patterns.

Materials and methods

The study was approved by the institutional review board committee (approval number ERID-KSOPKR-0074/2020). We retrospectively reviewed the medical files of patients with metastatic BC

who were consecutively treated with SRS for BM between April 2010 and December 2019. Brain disease was assessed by contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI). All patients were presented at a multidisciplinary conference (MDT), consisting of a radiation oncologist, a medical oncologist, a radiologist, and an oncology surgeon. A neurosurgeon was consulted when required. The decision to treat BM with SRS was confirmed by the MDT. Patients underwent SRS with or without WBRT. Radiotherapy dose fractionation was left to the discretion of the treating radiation oncologist.

For most of the patients, a dedicated contrast-enhanced planning brain CT was acquired, with a slice thickness of 1 mm, using the BrainLAB (BrainLAB AG, Munich, Germany) thermoplastic mask and a frameless system for localization. The planning CT was co-registered with a post-gadolinium contrast-enhanced T1 weighted MRI. The use of contrast for the planning CT and the co-registered MRI improved the accuracy of image fusion. The gross tumor volume (GTV) was defined as the enhancing lesion on the post-gadolinium T1 weighted MRI. For postoperative cases, the GTV was defined as the resection bed plus any residual enhancement. The planning target volume (PTV) was defined as the GTV plus a 2 mm isotropic margin. For tumor < 3 cm a single fraction was delivered using RTOG 9005 protocol guidelines [14]. Single fractionated stereotactic radiosurgery was typically prescribed to a dose of 18–25 Gy. For larger tumors, particularly for tumors in eloquent areas, we used hypofractionated stereotactic radiosurgery in five fractions from 28–30 Gy. The dose was normalized so the 100% isodose line encompassed nearly all (> 95%) of the PTV. All treatment plans were reviewed and approved by the treating radiation oncologist and physicist. SRS was performed using the True Beam TX Novalis Radiosurgery linear accelerator (Varian Medical Systems, inc.) with ExacTrac® X-ray 6D robotic image guidance. WBRT was performed as two-dimensional radiotherapy using a 6-MV photon beam by two laterally opposed standard fields or as a three-dimensional conformal radiotherapy technique.

Data were collected on general patient demographics, pathohistological and clinical characteristics of the primary BC tumor, systemic therapy (chemotherapy, endocrine treatment, or targeted therapy) used in both the adjuvant and metastatic

settings. Local treatment details were reviewed including surgical notes and data regarding radiotherapy treatment. For the purpose of this study, patients' disease stage was classified using medical records, according to the seventh edition of the *TNM Classification of Malignant Tumors* [15]. The modified breast prognostic index (MB-GPA) was calculated for each patient [16]. Intrinsic BC subtypes were defined as Luminal A (ER+, HER2-, low Ki67, high PR+), Luminal B HER2- (ER+, HER2-, high Ki67 or low PR+), Luminal B HER2+ (ER+, HER2+, any PR, any Ki67), HER2+ (HER2+, PR-, ER-), and "Basal-like" (ER-, PR-, HER2-) [17]. "Basal-like" tumors were grouped with TNBC in our study. The study was approved by the local institutional review board committee.

Statistical analysis

Descriptive statistics were used to calculate typical measures in patients' demographic and clinical characteristics. Data were expressed as median with a range, and categorical data were expressed as counts and frequencies. A Pearson's chi-square test was used for comparing categorical variables between two groups. The primary endpoints were overall survival (OS) and local control. OS was calculated using the Kaplan-Meier method, measured from the time of BM diagnosis to the date of death or last follow-up. Progression-free survival (PFS) was defined as time to brain disease progression or development of new metastases (any brain recurrence) after the first local treatment. The log-rank test was used to compare OS between groups. All

tests were two-sided, and a statistical level of significance was set to $p < 0.05$. Univariate and multivariate Cox regressions were used to calculate the effect sizes [given as hazard ratios (HR), with 95% confidence intervals (CI)]. Statistical analyses were carried out using IBM SPSS Statistics software version 26 (Statistical package for the Social Sciences Statistical Software; SPSS Inc, IBM Corporation, Armonk, New York).

Results

The cohort included 45 patients with BC who received treatment with SRS for 72 brain lesions. The median age at BC diagnosis, metastatic BC diagnosis, and BM diagnosis was 50.2 (29.6–83.0), 52.7 (29.6–88.0), and 55.9 (30.8–88.0) years, respectively. The median time from initial BC diagnosis to development of BM was 32.8 months (8.9–224.4) and the median time from BM diagnosis to the first local treatment (surgery, SRS or WBRT) was 0.8 months (0–7.2). Patients for whom brain metastatic disease was the first sign of metastases were younger (53.3 years) and had a shorter median time from initial BC diagnosis to development of BM (19.3 months, range 8.9–178.0). In contrast, patients for whom extracranial disease spread was the first symptom of metastatic disease were older (56.7 years) and had a longer median time from initial BC diagnosis to development of BM (88.1 months, range 14.4–224.4), although the observed differences were not statistically significant. Patients' clinical, pathohistological, and treatment characteristics are presented in Table 1. The median

Table 1. Patients' clinical and pathohistological characteristics

Characteristic		No. of patients	Percentage
KPS at BM diagnosis	100	9	20.0%
	80–90	28	62.2%
	60–70	8	17.8%
	≤ 50	0	0%
Histology	IDC	40	88.9%
	ILC	4	8.9%
	Other types	1	2.2%
Grade	G1	0	0%
	G2	15	33.3%
	G3	29	64.4%
	Missing values	1	2.2%

Table 1. Patients' clinical and pathohistological characteristics

Characteristic		No. of patients	Percentage
Hormonal receptor	ER-positive	24	53.3%
	ER-negative	21	46.7%
	PR-positive	20	44.4%
	PR-negative	25	55.6%
HER2	HER2-positive	26	57.8%
	HER2-negative	17	37.8%
	HER2-unknown	2	4.4%
Molecular subtype	TNBC	9	20.0%
	Luminal A	4	8.9%
	Luminal B HER2-	6	13.3%
	Luminal B HER2+	14	31.1%
	HER2+	12	26.7%
Stage at BC diagnosis	I	4	8.9%
	II	13	28.9%
	III	25	55.6%
	IV	3	6.7%
No. of BM	1	18	40.0%
	2	16	35.6%
	3	9	20.0%
	> 3	2	4.4%
Extracranial disease	Yes	29	64.4%
	No	16	35.6%
	Bone only	3	6.7%
	Visceral* and bone	15	33.3%
	Visceral* only	11	24.4%
Timing of metastatic spread	Extracranial site first	24	53.3%
	Brain site first	21	46.7%
MB-GPA	Class 1	3	6.7%
	Class 2	12	26.6%
	Class 3	23	51.1%
	Class 4	7	15.6%
Hormonal therapy	Yes	15	66.7%
	No	30	33.3%
Chemotherapy	Yes	22	48.9%
	No	23	51.1%
Anti-HER2 therapy	Yes	22	48.8%
	No	23	51.2%

No — number; BC — breast cancer; BM — brain metastases; KPS — Karnofsky performance status; ER — estrogen receptor; PR — progesterone receptor; HER2 — human epidermal growth receptor 2; IDC — invasive ductal carcinoma; ILC — invasive lobular carcinoma; WBRT — whole brain radiation therapy; MB-GPA — modified breast graded prognostic assessment; *lung, liver, skin metastasis, other

number of systemic therapies received after BM diagnosis was 2 (range 0–6). The median number of treated BM was 2 (range 1–10). The total prescribed dose was 22 Gy (range 15–25) for single fraction-

ated and 25 Gy (range 25–28) for hypofractionated SRS. All patients were treated with SRS during the course of the metastatic brain disease; however, local treatment sequence differed. The frequency of

Table 2. Local treatment and median overall survival (OS) for patients treated with radiotherapy

		No. of patients (%)	Median OS (95% CI), in months	p-value
WBRT	Yes	34 (75.5)	26.2 (10.7–41.7)	0.360
	No	11 (24.4)	36.3 (13.6–58.9)	
WBRT	Before SRS	16 (35.6)	30.4 (5.5–55.3)	0.113
	After SRS	18 (40.0)	20.2 (5.7–34.7)	
	No WBRT	11 (24.4)	36.3 (13.6–58.9)	
Surgery	Yes	17 (37.8)	36.1 (25.9–46.3)	0.023
	No	28 (62.2)	15.9 (11.8–20.0)	
No. of local treatment modalities	2	23 (51.1)	15.9 (7.7–24.1)	0.130
	≥ 2	22 (48.8)	30.4 (20.9–39.9)	
Local treatment combinations	SRS only	5 (11.1)	36.3 (7.6–64.9)	0.094
	SRS + WBRT	23 (51.1)	15.6 (11.1–20.1)	
	SRS + WBRT + Surgery	11 (24.4)	36.1 (23.3–48.9)	
	SRS + Surgery	6 (13.3)	33.6 (0–69.2)	

No. — number, OS — overall survival; WBRT — whole brain radiation therapy; SRS — stereotactic radiosurgery

the first local treatment following BM detection was as follows: 24 (53.3%) patients received SRS, 12 (26.7%) received craniotomy (metastasectomy) and 9 (20.0%) patients received SRS. Median time to SRS treatment since BM diagnosis was 1.6 months (range, 0.1–32.2). Other local treatment details are provided in Table 2.

Survival

The median follow-up time for the entire cohort was 20.2 months (range, 3.6–96.4). Median survivals from BM diagnosis and post-SRS were 27.6 months (95% CI: 14.8–40.5) and 18.5 months (95% CI: 11.1–25.8), respectively. The OS according to local treatment and BC intrinsic subtype is presented in Figure 1. Median one-year, two-year, and three-year survival rates were 55%, 41%, and 16%, respectively. At the time of study closeout date, 10 patients were still alive and 35 patients had died. Twenty-one (60%) patients died from progressive brain disease, nine (25.7%) from progressive extracranial disease, and one (2.8%) patient from both intracranial and extracranial disease progression. The cause of death for three patients could not be determined. In a univariate analysis, improved survival was associated with the following pre-treatment or treatment-related factors: grade two primary BC, hormonal-positive BC, HER2-positive BC, controlled extracranial disease, metastasectomy, MP-GPA Class ≥ 3, and receiving less than two lines of systemic therapy (Tab. 3). Upon

multivariate Cox analysis only grade 2 primary BC tumors, surgical therapy, and utilization of more than one systemic therapy were significantly associated with improved median OS (Tab. 4). Patients that were treated in the first 10 years (until the end of 2014) were more likely to have had HER2+ BC (19 vs. 7; $p = 0.001$) and less likely to be TNBC (1 vs. 8; $p = 0.004$) than patients treated in the last five years of the observation period (2015–2019).

Local control

Imaging data were available for 43 patients at follow-up. Identification of any intracranial progression (local or distant) occurred in 34 (75.6%) patients, nine patients did not have intracranial progression, and data for two patients were missing. The observed PFS for 43 patients was 29.3 months (range, 24.4–35.7) and varied according to HER2 status (HER2– vs. HER2+; 14.9 vs. 36.7 months; $p < 0.005$), ER status (ER– vs. ER+; 14.9 vs. 36.7 months; $p < 0.0005$), and SRS biological dose ($BED_{\alpha/\beta=10}$) (< 50 Gy vs. ≥ 50 Gy; 28.2 vs. 34.9 months; $p = 0.023$). There was a trend towards a longer PFS in patients who were treated initially with WBRT compared to patients who were treated with WBRT subsequently SRS or did not receive WBRT at all (38.7 vs. 27.1 months; $p = 0.054$). Median one-year, two-year, and three-year intracranial PFS rates were 85%, 63%, and 33%, respectively.

Any brain recurrence was seen in 25%, 75%, 83.3%, 85.7%, and 90.1% patients with Luminal A,

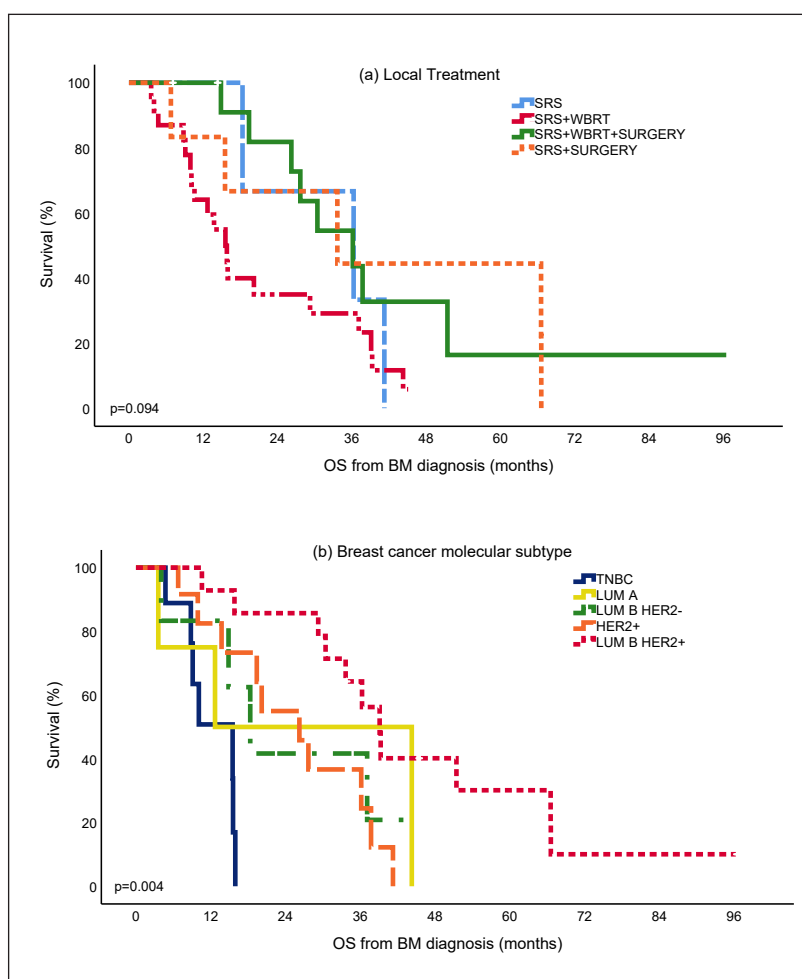


Figure 1. Overall survival from brain metastases diagnosis by **(A)** Local treatment and **(B)** Breast cancer molecular subtypes. OS — overall survival; BM — brain metastases; SRS — stereotactic radiosurgery, WBRT — whole brain radiation therapy; TNBC — triple negative breast cancer; LUM A — luminal A; LUM B — luminal B; HER2 — human epidermal growth receptor

Table 3. Prognostic factors influencing median overall survival (OS) times (univariate analysis)

Variables		Median OS (95% CI), in months	HR (95% CI)	p-value
Age at BM diagnosis	< 50	27.6 (12.2–43.1)	1.1 (0.5–2.3)	0.793
	≥ 50	33.6 (8.0–59.3)	Ref	
Grade	G2	39.3 (35.7–42.8)	Ref	0.004
	G3	15.9 (9.7–22.1)	3.1 (1.4–7.1)	
HER2	Positive	36.1 (27.5–44.7)	Ref	0.046
	Negative	15.5 (14.2–16.8)	2.1 (1.0–4.4)	
ER	Positive	37.1 (29.6–44.6)	Ref	0.002
	Negative	15.6 (8.2–22.9)	3.1 (1.5–6.6)	
Intrinsic BC subtype	Luminal B HER2+	39.1 (34.1–44.1)	Ref	0.004
	HER2+	26.2 (14.2–38.3)	3.1 (1.2–8.1)	
	Luminal A	12.7 (0–39.3)	2.5 (0.7–9.4)	
	Luminal B HER2–	18.3 (11.1–25.6)	2.2 (0.7–7.4)	
	TNBC	15.5 (7.8–23.2)	11.0 (3.3–37.2)	

Table 3. Prognostic factors influencing median overall survival (OS) times (univariate analysis)

Variables		Median OS (95% CI), in months	HR (95% CI)	p-value
KPS	≥ 80	33.6 (19.8–47.2)	Ref	0.094
	60–70	9.1 (0–21.6)	2.2 (0.9–5.1)	
Systemic therapy (number of lines)	≤ 1	13.7 (7.1–20.3)	2.2 (1.0–4.6)	0.042
	≥ 2	36.1 (24.7–47.5)	Ref	
Surgery	Yes	36.1 (25.9–46.3)	Ref	0.022
	No	15.9 (11.8–20.0)	2.3 (1.1–4.9)	
Number of BM	1 or 2	29.3 (14.7–43.7)	Ref	0.657
	3	26.2 (12.2–40.2)	1.2 (0.5–2.7)	
SRS BED _{α/β=10}	≥ 50 Gy	30.4 (12.3–48.5)	Ref	0.735
	< 50 Gy	27.6 (9.5–45.8)	1.2 (0.5–2.6)	
Extracranial disease control	Yes	87.9 (16.1–159.9)	Ref	0.033
	No	25.2 (14.0–36.3)	2.2 (1.1–4.5)	
Extracranial disease	No	19.4 (5.1–33.7)	Ref	0.749
	Bone only	36.3 (/)	1.0 (0.2–4.7)	
	Visceral* only	27.6 (5.2–50.1)	1.5 (0.6–3.7)	
	Visceral* and bone	29.2 (3.0–55.4)	0.9 (0.4–2.2)	
MB–GPA	Class 1 or 2	14.9 (10.3–19.4)	2.4 (1.1–5.0)	0.023
	Class 3 or 4	33.6 (25.4–41.9)	Ref	
Brain as the first metastatic site	No	36.1 (25.3–47.0)	Ref	0.533
	Yes	15.6 (9.1–22.1)	1.2 (0.6–2.4)	
Year of BM diagnosis	Before 2015	33.6 (22.8–44.4)	Ref	0.443
	2015 and after	15.9 (12.2–19.6)	1.3(0.6–2.7)	

G — grade; ER — estrogen receptor; HR — hazard ratio; OS — overall survival; BM — brain metastases; BC — breast cancer; TNBC — triple-negative breast cancer; KPS — Karnofsky Performance Status; HER2 — human epidermal growth receptor 2; MB-GPA — modified breast graded prognostic assessment; Gy — Gray; BED_{α/β=10} — biological dose, SRS — stereotactic radiosurgery; *lung, liver, skin metastasis, other

Table 4. Prognostic factors influencing median overall survival (OS) times (multivariate Cox analysis)

Variables	HR (95% CI)	p-value
MP–GPA Class ≥ 3	0.3 (0.1–1.3)	0.392
Grade 2	0.1 (0.1–0.6)	0.005
HER+ BC	0.5 (0.2–1.7)	0.966
ER+ BC	0.8 (0.2–3.4)	0.529
Luminal B HER2+	0.7 (0–22.1)	0.661
≥ 2 systemic therapy lines received	0.3 (0.1–0.9)	0.028
Surgery	0.3 (0.1–0.7)	0.006
Extracranial disease controlled	0.5 (0.2–1.1)	0.138

HR — hazard ratio; OS — overall survival; BM — brain metastases; BC — breast cancer; KPS — Karnofsky Performance Status; HER2 — human epidermal growth receptor 2; ER — estrogen receptor; WBRT — whole brain radiation therapy

TNBC, Luminal B HER2–, Luminal B HER2+, and HER2+ molecular BC subtypes, respectively

($p = 0.074$). Following SRS, local lesion progression was more prevalent in patients with HER2+ BC compared to HER2– BC (72.0% vs. 31.3%; $p = 0.022$), and there was a tendency towards less common distal brain disease progression (36% vs. 62.5%; $p = 0.097$). Metastases secondary to Luminal B HER2+ BC, in comparison to all other BC molecular subtypes, showed an increased rate for any brain recurrence (HR: 3.3 95% CI: 1.1–10.1; $p = 0.032$). However, in a multivariate analysis, after adjusting for SRS BED_{α/β=10}, systemic therapy received, ER status, and the use of WBRT or surgery, four factors remained significant for an increased risk of any intracranial recurrence, as follows: patients, younger than 50 years (HR: 4.2; 95% CI: 1.3–36.3; $p = 0.014$), grade 3 primary BC (HR: 3.7; 95% CI: 1.1–13.2; $p = 0.038$), HER2+ receptor status (HR: 6.9; 95% CI: 1.3–36.3; $p = 0.023$), and whether the brain was the first site of distant disease

spread (HR: 4.7; 95% CI: 1.6–14.5; $p = 0.006$). Local recurrence rates did not differ according to the year of treatment (before and after 2015; 76.2% vs. 81.8%; $p = 0.650$).

Seventeen (45.9%) patients developed radiographic leptomeningeal carcinomatosis (LMC) after SRS. The median time to LMC development after SRS was 11.5 months (range, 2.7–33.9). Out of 17 patients, whose follow-up imaging showed LMC, six had previous surgery and 11 were treated with radiation therapy only (35.3% vs. 64.7%; $p = 0.235$). LMC was more often seen in HER2-negative BC (66.6% vs. 31.8%; $p = 0.039$). The longest time interval from SRS to LMC development was observed in patients who were initially treated with WBRT compared to patients who were treated with WBRT post-SRS or did not receive WBRT (22.8 vs. 8.3 months; $p = 0.036$).

Discussion

Metastases spreading from the primary BC tumor to the brain indicate a poor prognosis and represent a treatment challenge, despite recent systemic and local treatment innovations. In our study, we retrospectively explored our database and evaluated treatment outcomes for all patients with BC, who were consecutively treated with SRS for BM.

Median survival rates after BM diagnosis and post-SRS treatment (single fractionated or hypofractionated) were 27.6 and 18.5 months, respectively. Our results compare favorably with analogous studies, reporting OS after BM diagnosis in the range of 12–26 months [18–21] and post-SRS in the range of 15–19 months [22–24]. In a univariate analysis, improved survival was associated with grade 2 primary BC, HR+ and HER2+ BC, controlled extracranial disease, metastasectomy, MP-GPA Class ≥ 3 , and receiving more than two lines of systemic therapy. We have found out that patients with Luminal B HER2+ molecular subtype had the longest median OS. Due to bias in patient selection and a small study sample, our findings may not be truly representative. Nevertheless, our results demonstrated that patients with BM and HER2+ HR+ primary BC have longer median OS compared to patients with HER- HR+ subtype and data are well in line with previous studies evaluating larger subsets of patients with BC BM [3–5]. One study also found that survival after BM was

dependent on the HER2 status and not on the HR status; and was longer with HER2+ BC; suggesting the effect of novel anti-HER2 therapies [4]. In a multivariate Cox analysis, improved survival rates remained significant in moderately differentiated primary BC, when surgery was part of the local treatment and when patients received at least two lines of systemic treatment. The importance of craniotomy was likewise demonstrated in a recent study, showing that longer survival rates might be achieved with surgery performed before receiving SRS [18]. In our study, WBRT, performed pre- or post-SRS did not influence OS rates, which is consistent with previous studies [9, 25]. Other positive factors of improved OS following SRS, as described elsewhere in the literature, such as HER2+ [18, 23, 24, 26, 27], HR+ disease [23, 24, 26], younger age of the patients [26] or extracranial disease control [23], were not associated with improved OS in our adjusted analysis, most probably due to small size of the study cohort and patient selection bias.

When analyzing local control outcomes, we observed worse intracranial control in patients with poorly differentiated and HER2+ primary BC tumors, in patients who were younger than 50 years of age and for whom BM occurred as the first symptom of metastatic disease, denoting aggressive tumor biology. Specifically, we found that HER2+ tumors more frequently recur locally and less often distally in the brain. Our observation is supported by findings in a similar study performed by Cagney et al. who found that HER2+ BC displayed poorer local control, whereas TNBC were more likely to recur distantly in the brain [6]. We did not find any differences in local or distant brain relapse according to the intrinsic BC subtype, which is most probably due to the low number of included cases. Grubb et al. found a considerable variation in the response to SRS on a per lesion basis when stratified by the BC subtype. Compared to luminal lesions (48%), none of the HER2+ lesions exhibited a complete response at an average follow up time of six months, and only some of the TNBC lesions (35%) responded. On the other hand, the authors did not find any differences in local lesion progression according to the BC subtype [27]. SRS dose escalation, boosting a tumor subvolume, the use of novel radiosensitizers and the development of new systemic therapies for BM, have all been suggested to improve local control for patients with BM [6, 28,

29]. However, more research is needed to prospectively investigate individualized SRS dose depending on BC molecular subtypes.

Interestingly, compared to HER2- tumors, we observed a statistically longer median time to brain disease progression after the first local treatment (absolute difference 19.8 months) in HER2+ disease. This observation can be explained by the effect of newer HER2-directed therapies, suggesting intracranial activity, which could prolong both the time to the development of BM and time to intracranial progression of BM, following local treatment [30–32]. Parsai et al. showed that in patients with HER2+ BC subtypes, the use of lapatinib concurrently with SRS improved local control of BM, without increasing the rate of adverse events [32]. In our study, 22 out of 26 patients with the HER2+ BC subtype received anti-HER2 therapy in conjunction with SRS. The number of patients receiving lapatinib was too small to make any relevant analysis. A phase 2 study of WBRT/SRS with or without lapatinib in HER2+ BC subtype in patients with ≤ 10 BM is ongoing to explore this topic further (ClinicalTrials.gov Identifier Number NCT01622868). Additional research, including both local radiation treatment strategies and systemic therapy, is warranted for all BC subtypes to identify therapies to optimize local control [33].

In our series, 45.9% of patients developed LMC post local treatment. The risk of LMC in patients with BM, treated with SRS was described previously, especially after BM resection [34]. WBRT or focal cranial radiotherapy might help to lower the LMC risk [35]. In our study, three-quarters of patients received WBRT, either upfront or following SRS. The addition of WBRT did not influence LMC, local lesion, or distant brain recurrence rates. Nevertheless, upfront WBRT prolonged time to develop any intracranial recurrence, but there was no difference in OS. The new tendency in the management of brain metastases is to avoid WBRT due to the toxicity and neurological deterioration [11]. However, this topic is still open to scientific debate.

We acknowledge downsides to our study, which might have influenced our results: retrospective data collection, small and unbalanced sample size, and not all medical charts were fully available at the time of study data collection. Furthermore, we did not systematically assess the neurological outcomes

of our patients, which would improve the reporting of the treatment outcomes. However, our results, especially regarding improved OS rates, imply the cautious selection of BC patients throughout the observation period. In the future, multicentric prospective studies are warranted to further explore the use of SRS in patients with BC.

Conclusions

In this single-institutional retrospective study, evaluating patients with BC, who underwent SRS for oligometastatic brain lesions, we observed improved survival rates. All patients were carefully evaluated and selected for SRS treatment by the multidisciplinary neurooncology team, which might partially contribute to the results. According to the intrinsic BC subtype, patients with Luminal B HER2+ BC had the longest estimated median OS, which exceeded three years. On the other hand, HER2+ local brain lesions were more likely to recur locally post-SRS and at the same time, the interval after first local brain treatment and brain lesion progression was the longest in patients with HER2+ tumors. SRS is a noninvasive and effective treatment modality and should be considered in all patients with BC who have BM and particularly in patients with HER2+ BC subtypes because of their long-expected OS and duration of local treatment benefit. Our findings, supported by other investigators, warrant further explorations.

Conflict of interest

None declared.

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