Review Article

The management of elderly patients with brain metastases from breast cancer

Henry Ruiz-Garcia[1,2], Lina Marenco-Hillembrand[2], Jennifer L. Peterson[1,2], Katherine Tzou[1], Timothy D. Malouff[1], Kaisorn L. Chaichana[2], Daniel M. Trifiletti[1,2], Laura Vallow[1]

[1]Department of Radiation Oncology, [2]Department of Neurological Surgery, Mayo Clinic, Jacksonville, Florida, USA

Contributions: (I) Conception and design: D Trifiletti, H Ruiz-Garcia; (II) Administrative support: D Trifiletti; (III) Provision of study materials or patients: H Ruiz-Garcia, L Marenco-Hillembrand; (IV) Collection and assembly of data: D Trifiletti, H Ruiz-Garcia; (V) Data analysis and interpretation: D Trifiletti, H Ruiz-Garcia; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Daniel M. Trifiletti, MD. Department of Radiation Oncology, Mayo Clinic, 4500 San Pablo Road South, Jacksonville, FL 32224, USA. Email: trifiletti.daniel@mayo.edu.

Abstract: Breast cancer is the most common type of malignancy diagnosed in women worldwide, as well as the second most common cause of metastatic brain lesions in the general population. Most breast cancer patients enrolled in clinical trials are relatively young. Elderly patients, as compared to their younger counterparts, pose unique clinical scenarios because there is limited data in this subpopulation of patients with brain metastases from breast cancer. Elderly patients are commonly treated with less aggressive therapies, perhaps due to comorbid conditions, patient preference, or other age-related concerns. Current treatment modalities offering more favorable toxicity profiles, along with more accurate prognosis, can represent an opportunity to offer improved care for this patient population. From the few efforts studying brain metastatic disease in the elderly, it is be possible to infer that age alone may not play an independent role in treatment selection and that a patient-specific evaluation and ultimate clinical judgment should guide clinical decision-making.

Keywords: Brain metastases; breast cancer; elderly; management; radiotherapy; radiation

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Introduction

Breast cancer is the most common type of malignancy diagnosed in women worldwide. An estimate of 271,270 new cases of breast carcinoma will be diagnosed in the United States in 2019 with 42,260 predicted deaths (1). Increasing age remains an important risk factor for the development of breast cancer, with an estimated incidence of 403.8 new patients per 100,000 women ≥65 years old versus only 82.2 per 100,000 women aged less than 65 years (2). Brain metastases (BM) represent an important cause of mortality in elderly population, where 40% of women older than 80 years old at diagnosis will die from breast cancer (3).

Statistics show that survival for breast carcinoma has improved through the years, which is attributed to better screening tests and treatment modalities (4). With an increase in survival, a higher incidence of metastatic breast cancer has been reported (5). Metastatic breast cancer to the brain is the second most common source of brain metastases, after metastases originating from the lung (6). Ten to 30% of women with breast cancer will develop brain metastases through the course of their disease, and as much as 5% of them will have presented with a brain metastatic lesion at diagnosis (7). Once diagnosed with metastatic disease, the prognosis can be limited, mostly due to the ultimate resistance of chemotherapy and radiotherapy, with an average survival of 12 months after the diagnosis of a brain metastasis (8).

Different therapeutic modalities have been directed towards prolonging the survival in these patients. These

Table 1 Prevalence of brain metastasis according to breast cancer subtype

Molecular subtype	Frequency/prevalence of brain metastasis	Overall survival (months) (16)
Percentage of brain metastasis due to breast cancer	10–30% (5,7)	
Luminal	5% (11)	A: 23.1, B: 15.0
HER2 positive	15–29% (14)	12.5
TNBC	22–46% (11,14-15)	6.4

Overall survival measured from initial treatment of brain metastases to death. HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.

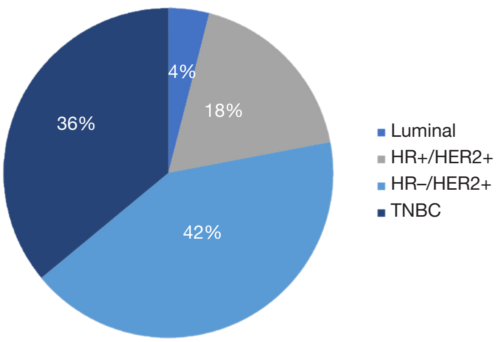

Figure 1 Prevalence of CNS metastasis according to breast cancer subtype.

include surgical resection, radiotherapy and systemic therapies. For young patients who possess good functional statuses, there is a fairly clear standard of care. However, due to the underrepresentation of the elderly population in clinical trials, there exists a gap of knowledge regarding the best treatment for this group of patients, especially when dealing with radiotherapy. In this review, we aim to critically analyze the literature and describe the current treatment options for patients ≥65 years old with metastatic breast cancer to the brain.

Prognosis in breast cancer and breast cancer brain metastases

Breast cancer is the second most common malignancy that metastasizes to the brain. It is estimated that 10–30% of patients diagnosed with breast cancer will develop brain metastases during the course of their disease (9). Survival can range anywhere from 3–25 months according to the molecular subtype (4) and several other factors affecting survival. The propensity for breast cancer to metastasize to the brain has been related to the tumor subtype. Patients harboring a triple negative breast cancer (TNBC) have the highest probability of developing a BM, followed by human epidermal growth factor receptor 2 positive (HER2+) breast cancer patients and finally, patients with luminal breast cancers (5,7,10-16) (*Table 1* and *Figure 1*). For instance, patients with HER2+ tumors have 2 to 4 times increased risk of developing a BM than patients with a HER2− tumor (17,18).

After the occurrence of brain metastasis, patients with estrogen receptor (ER) and progesterone receptor (PR) positive tumors have been reported to live significantly longer when compared to hormone receptor negative tumors; similar survival advantage is observed with HER2+ tumors versus HER2− tumors (15). In HER2+ metastatic disease, trastuzumab plays an important role, prompting a median survival of 12.8 months versus only 4 months in patients without treatment (P=0.001) (15). The poor prognosis of TNBC patients typically occurs in the context of chemoresistant disease either from progressive extracranial disease, early recurrence of brain metastases, or both.

Age at diagnosis is another important factor when determining the prognosis of breast cancer patients. Studies have linked older age to a greater risk of developing brain metastases. Rotenberg *et al.* showed that the prevalence of metastatic disease significantly increases with older age from 3.9% to 23.4% (19). However; this increase in metastatic disease could potentially be related to the less aggressive therapeutic management offered to elderly patients. A large cohort study of 4,453 breast cancer patients showed that patients >80 years old had greater breast cancer specific mortality when compared to younger age groups (20). The increased mortality, found when stratifying patients according to age, can also be seen in the setting of metastatic disease. A retrospective analysis of the SEER database conducted by Chen *et al.* examined data regarding 4,932 patients with breast cancer metastases to sites including bone, lung liver and brain. The investigators concluded that when stratified by age, elderly patients (>69 years old) presented the worst overall survival (OS) (X^2=121.9, P<0.001) and worst breast cancer specific survival (BCSS) (X^2=69.8, P<0.001). Furthermore, after multivariable analysis, age at diagnosis was found to be associated with BCSS (P<0.05), defining age as an independent prognostic factor in distant metastatic breast cancer patients (21). While convincing, these results should be carefully analyzed as several non-evaluated factors could be playing a role in the reduced survival.

Prognosis of breast cancer patients can be evaluated through several prognostic indexes. These systems aid in determining and classifying patients with favorable or poor prognosis and ultimately, assist with decision-making. The most common prognostic scoring systems include the recursive partitioning analysis classification (RPA), the graded prognostic assessment (GPA) and disease-specific GPA (DS-GPA).

Patient selection: the role of prognostic scores in clinical decision making

Currently, there is controversy regarding the optimal management of patients with brain metastases. This is probably due to the heterogeneity of the data coming from a diverse group of patients, with different primary histologies, diverse genetic mutations, and other varied clinical features. This heterogeneous data has been generally taken together to drive conclusions about the universal standard of care for all BM patients (22-24). However, efforts have been made to combine these specific groups in order to obtain a more generalizable conclusion.

In the context where all patients with BM were considered a single group, Gaspar *et al.* published the first seminal paper evaluating the impact of patient selection on treatment outcomes (25). This study developed a RPA based on pretreatment variables such as tumor/patient characteristics as well as treatment variables. After analyzing a pool of 1,200 patients from three different Radiation Therapy Oncology Group (RTOG) trials conducted between 1979 and 1993, they found that pretreatment characteristics could define prognostic groups in BM patients. The group with best survival was integrated by patients with a Karnofsky performance status (KPS) ≥70, primary controlled disease, no extracranial metastases and age <65 years (RPA class 1: median survival of 7.1). The worst survival was found in the group of patients defined by a KPS <70. This study revealed the importance of the heterogeneity of patients with BM.

More than 20 years after the original work of Gaspar *et al.* (25) and upon the results of the RTOG-9508 trial, which supported the role of the number of BM as a potential prognostic factor (26), Sperduto *et al.* reevaluated the RTOG RPA classification system (27). The authors compared the RPA with a proposed updated version, the GPA, and found that the GPA was as good as RPA in regard to survival prognosis, but also the least subjective, most quantitative and easiest to use system. This new index did incorporate the number of BM into its four classification criteria: KPS, presence of extracranial disease, age (<50, 50–59, >60) and number of brain metastases (27).

After the acceptance of the GPA index (27), and with new data recommending the use of primary-specific prognostic systems (28), a subsequent study from the same group aimed to identify diagnosis-specific prognostic factors in order to develop a diagnosis-specific GPA (DS-GPA) (29). The authors found that patient stratification into different survival groups relies on different prognostic factors which vary according to specific primary sites. For instance, while classification of patients with brain metastatic lesions arising from non-small cell lung cancers (NSCLC) would depend on four prognostic factors (age, KPS, presence of extracranial disease, and number of BM), the DS-GPA classification for patients with brain metastases from breast cancer (breast-GPA) would solely depend on KPS score. Thus, as significant prognostic factors vary by diagnosis, DS-GPA indexes would also be particular for each primary site. The study also analyzed the effect of different therapeutic options on the survival of BM patients when classified according to these primary sites. Of note, there were different trends found in the analysis of potential treatments according to specific diagnoses. While WBRT alone presented as the best option for patients with BM from renal cell carcinoma, the same treatment suggested the less favorable outcomes for patients with BM arising from NSCLC or breast cancer. Overall, even with the retrospective nature of the study, the data suggested the urgent need to tailor BM patient's treatment, taking into consideration patient-specific characteristics as well as disease-specific biological features and its potential implication in their therapeutic responses.

Efforts to refine these predictive tools continued in a steadfast fashion. In 2012, Sperduto *et al.* (30) published a specific RPA analysis of patients treated for newly diagnosed BM arisen from breast cancer. The study incorporated

Table 2 Prognostic scores in brain metastatic breast cancer indicated by the Radiation Therapy Oncology Group (RTOG) Breast Cancer Graded Prognostic Analysis and the MD Anderson Cancer Centre (MDACC) Modification

Variable	Score				
	0	0.5	1.0	1.5	2.0
RTOG Breast Graded Prognostic Assessment (30)					
KPS	≤50	60	70–80	90–100	–
Phenotype	TNBC	–	HR + BC	HER2HN	HER2HP
Age (years)	≥60	<60	–	–	–
MDACC revalidation of RTOG Graded Prognostic Analysis (31)					
KPS	≤50	60	70–80	90–100	–
Phenotype	TNBC	HR+BC	HER2HN	HER2HP	–
Age (years)	>50	≤50	–	–	–
Number	>3	1-3	–	–	–

RTOG, Radiation Therapy Oncology Group; KPS, Karnofsky performance status; MDACC, MD Anderson Cancer Center; HR, hormone receptors; HER2HN, HER2-positive, hormone negative; HER2HP, HER2-poistive, hormone-positive.

two new variables into the original breast-GPA; "tumor subtype" and "age at diagnosis" were found to be independent prognostic factors and consequently and were incorporated in the new breast-GPA. A follow-up study by Subbiah *et al*. (31) in a large population of patients with BM from breast cancer, identified the role of the "number of brain metastases" as another variable of a newly proposed, modified-breast GPA. However, in the same track that "age at diagnosis", these two variables only have minor effects in the total score, whereas variables like KPS and tumor subtype were numerically the most important in defining the final GPA score (*Table 2*). The weight of these variables on the overall score was determined by the magnitude of their influence on survival. Furthermore, the RPA analysis showed that these two variables only define survival classes within subgroups of BM patients (32). For instance, "age at diagnosis" defined survival classes only in patients with KPS ≤50 but not in patients with higher KPS. These differences call for a holistic evaluation of each individual patient.

Overall, while prognostic indexes can be used as inclusion criteria for prospective studies or retrospectively to stratify patients for better group comparisons, all the previously described efforts have been made aiming to integrate simple but relevant patient characteristics to facilitate clinical decision making and individualize patient care. In this latter context, an important question arises: how accurate are these prognostic indexes for a specific patient? Although these prognostic indexes have been validated, it is clear that even the most accurate of them could potentially lead to overtreating patients who may actually have a really short survival, or even worse, undertreating patients because of an erroneously predicted unfavorable prognosis. As such, physician judgement should always be considered over any prognostic index alone.

Management of breast cancer brain metastases: a focus on elderly population geriatric assessment

Before the development of a treatment plan, all elderly individuals should undergo a comprehensive geriatric assessment. This should include the evaluation of functional, nutritional, and socioeconomic statuses, polypharmacy and comorbidities (33). Functional status can be assessed using the KPS scale, as it represents an effective proxy score for functional status in the elderly (34). When surgery represents a potential treatment option in elderly patients with BM, the Charlson comorbidity score could provide an insight about postsurgical outcomes such as risk of death, postoperative complication, and length of hospitalization stay, among others (35). Overall, this comprehensive evaluation provides important information used to evaluate the risk of future complications and death.

Healthy older adults who have no functional deficit and few comorbidities can be treated similarly to patients younger than 65 years old (33).

Treatment patterns in the elderly population

Local therapy has been the cornerstone in the management of patients harboring BM from breast cancer, where therapeutic options include surgical resection, whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS); and more recently, the use of systemic agents. The selection of one or more of these treatments is based principally on the number and location of the lesions, symptoms, prognosis of systemic disease, and the performance status of the patient. We will discuss the relevance of each of these elements in the following sections.

Surgery

The first randomized controlled trial (RCT) presenting survival benefits from surgical intervention in the treatment of patients with single metastatic brain disease came from Patchell *et al*. (36). This phase III RCT randomized patients into "surgery + WBRT" versus "biopsy only + WBRT"; surgery was found to improve local control, preserve functional status and most importantly, improve OS compared to WBRT alone. Another phase III RCTs from Vecht *et al*. (37) confirmed the OS benefit of surgical resection. However; Mintz *et al*. (38) failed to prove this previously described benefit. This fact could be related to a higher percentage of patients with active extracranial disease (80% *vs*. 30–40%) and a lower KPS. An extension of the benefit from surgical intervention to patients with two to three metastatic brain lesions has been described for the those who are in good neurological condition and possess a well-controlled systemic disease (39). Furthermore, none of these RCTs were disease-specific studies and the ER/PR/HER2 status was not described in patients with BM from breast cancer (*Table 3*). Evidence supporting the benefit of surgery for metastatic breast cancer patients is an extrapolation from results obtained from a heterogenous population of BM patients.

Retrospective studies have highlighted the role of surgical resection in the treatment of breast cancer patients with CNS metastasis, pinpointing that surgical resection was associated with better outcomes when compared to WBRT alone (46). However, patients who undergo neurosurgical resection are usually individuals with a single brain metastasis, favorable KPS, and controlled extracranial disease, consistent with the aforementioned RCT. The role of resection in patients with multiple brain metastases is controversial.

Technical aspects of neurosurgical interventions have improved over time, and it is currently more feasible to perform maximal surgical resection with minimal morbidity. The use of intraoperative navigation, cortical mapping and minimal invasive approaches have increased the chances of achieving gross total resection and obtaining tumor tissue for pathology and molecular analysis (47-50). Patel *et al*. reported on the role of the surgical technique on patient's outcomes. They found that en bloc resection of single metastatic lesions was associated with better local control when compared to piecemeal resection, without increase the rates of complications even in patients with large or eloquent-located lesions (51,52).

In general, resection should be considered in elderly patients with large tumors (generally >3 cm), particularly if they are causing edema and/or if neurologic symptoms are refractory to medical management. Surgical decompression remains the optimal approach to improve neurological function, reduce seizures and taper steroids. SRS or WBRT can be used as adjuvant therapies (25,26,53).

Whole brain radiotherapy

Whole brain radiotherapy has played a historical role in the management of BM patients for more than 60 years. While still the mainstay in the palliative treatment of patients with multiple symptomatic brain metastatic lesions not amenable to surgical resection or SRS or in cases with leptomeningeal involvement, its neurotoxicity profile has led to preferential selection of other radiation modalities such as SRS.

A second RCT from Patchell *et al*. (40) published in 1998, analyzed whether the addition of WBRT to surgery was beneficial in patients with single lesions. The study showed that the "surgery + WBRT" arm was superior to the "surgery + observation" arm in regard to local and distal intracranial tumor control as well as in the ability to decrease neurologic death rates; however, there was no improvement in OS. More than one decade later, Kocher *et al*. (41) published similar results adding WBRT to surgical treatment for patients with 1 to 3 lesions as part of the EORTC 22952-26001 study. This phase III RCT also evaluated the addition of WBRT to SRS, where the rates and grades of reported neurotoxicities were equivalent in both groups (surgery and SRS) (*Table 3*).

Short-term adverse effects of WBRT include headaches, nausea, vomiting, hair loss and increased fatigue, which can appear during treatment and last up to 2 to 6 months after

Table 3 Randomized controlled clinical trials evaluating different treatment combinations for patients carrying limited brain metastases

Study	Randomization	n	Criteria	Primary end point	Breast cancer, n (%)	Elderly†, n (%)	Tumor control		Survival
							Local control	Distal control	
Evaluating the addition of surgery to WBRT									
Patchell *et al.* [1990] (36)	WBRT + surgery	25	1 lesion	NR	2 (8.0)	NR	77% (1 year)	80%	36% (1 year)
	WBRT + biopsy	23	No RT		1 (4.3)		14% (1 year)	87% (P=0.52)	5% (1 year)*
Vecht *et al.* [1993] (37)	WBRT + surgery	32	1 lesion	Overall survival	6 (18.8)	NR	NR	NR	41% (1 year)
	WBRT	31			6 (19.4)				23% (1 year)*
Mintz *et al.* [1996] (38)	WBRT + surgery	41	1 lesion	Overall survival	2 (4.9)	NR	NR	NR	13% (1 year)
	WBRT	43			8 (18.6)				31% (1 year)
Evaluating the addition WBRT to surgery									
Patchell *et al.* [1998] (40)	Surgery + WBRT	49	1 lesion	Local control	5 (10.2)	NR	87% (1 year)	93% (1 year)	NS
	Surgery	46			4 (8.7)		37% (1 year)	49% (1 year)	
Kocher *et al.* [2011][a] (41)	Surgery + WBRT	81	1 to 3 lesions	OS with FI	NR	NR	75% (1 year)	83% (1 year)	46% (1 year)
	Surgery	79					46% (1 year)*	62% (1 year)*	46% (1 year)*
Evaluating the addition of SRS to WBRT									
Kondziolka *et al.* [1999] (42)	WBRT + SRS	13	2 to 4 lesions	Local control	2 (15.4)	NR	92% (1 year)	34 m**	46% (1 year)
	WBRT	14	<2.5 cm		2 (14.3)		0% (1 year)	5 m (P<0.002)	20% (1 year)
Andrews *et al.* [2004] (26)	WBRT + SRS	164	1 to 3 lesions	Overall survival	15 (9.0)	55 (34.0)	82%	NR	21% (1 year)
	WBRT	167	<4 cm		19 (11.0)	66 (40.0)	71% (P=0.01)	NR	11% (1 year)***
Evaluating the addition of WBRT to SRS									
Aoyama *et al.* [2006] (43)	SRS + WBRT	65	1 to 4 lesions	Overall survival	43 (66.0)	33 (51.0)	88.7%	41.5%	7.5 m
	SRS	67	Each <3 cm		45 (67.0)	33 (49.0)	72.5% (P=0.02)	63.7% (P<0.003)	8 m (P=0.42)
Kocher *et al.* [2011][b] (41)	SRS + WBRT	99	1 to 3 lesions	OS with FI	NR	NR	81%	67%	10.7
	SRS	100					69% (P=0.04)	52% (P<0.02)	10.9 (P=0.89)
Chang *et al.* [2009] (44)	SRS + WBRT	28	1 to 3 lesions	Cognitive outcomes	4 (14.0)	NR	100%	73%	63%
	SRS	30			4 (13.0)		67% (P=0.012)	45% (P=0.02)	21% (P<0.003)
Brown *et al.* [2016] (45)	SRS + WBRT	102	1 to 3 lesions	Cognitive outcomes	7 (6.9)	58 (56.9)†	90%	92.3%	34% (1 year)
	SRS	111	<3 cm		11 (9.9)	58 (52.3)†	73% (P<0.003)	69.9% (P<0.001)	37% (1 year)*

*, values obtained indirectly from Kaplan-Meier curves using PlotDigitizer®; **, time to any brain failure; ***, survival time for patients with single metastasis; [a,b] are part of the same RCT (EORTC 22952-26001); †, elderly classified as >60 years old. WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; Sx, surgery; NR, not reported; NS, not significant; LC, local control; OS, overall survival; FI, functional independence, CP, cognitive preservation.

therapy completion, especially in elderly patients. Long-term side effects, specifically cognitive decline has been associated with a consequent decreased quality of life (QoL). The most detrimental symptom in this setting is typically short-term memory decline (44,45,54,55).

The use of radiotherapy as a treatment of choice for breast cancer patients with CNS metastasis has increased through the years. This trend is evident in the study conducted by Leone *et al.* (56), where the investigators analyzed treatment patterns in patients >65 years old with CNS metastases from breast carcinoma. In this study, data was acquired and analyzed from 5,969 patients who received treatment for breast cancer metastases from 1992 to 2012. Findings revealed that 42.2% of patients did not receive any treatment; after palliative care, radiotherapy was the second most common treatment modality (27.1%). The authors demonstrated that the use of radiotherapy significantly increased over time (P=0.03), and when comparing radiotherapy to no treatment, the odds ratio (OR) of mortality was 0.83 (95% CI: 0.79–0.88). Furthermore, when therapeutic efforts were not limited in this elderly population, the administration of a combination of ≥2 therapies was associated with a significantly improved survival over time (P<0.05).

Frisk *et al*. analyzed a cohort of 241 patients with breast cancer BM receiving WBRT. For this cohort, the median OS for WBRT was 2.9 months. Patients over the age of 50 years old had an increased mortality; however, this association was no longer significant when adjusting for performance status, which at the same time was the strongest predictor of survival in the cohort. Interestingly, similar to the findings from Leone *et al*., mortality after WBRT was significantly better in those patients receiving transtuzumab or chemotherapy before radiation (57).

SRS in the definitive setting

SRS has challenged the role of WBRT as gold standard radiation modality in the treatment of BM patients. SRS involves the delivery of highly precise, ablative radiation to a well-defined area of disease while sparing normal brain parenchyma (58,59). Thus, SRS diminishes the risk of radiation-induced injury and safeguards patients from the detrimental effect of WBRT on neurocognition and QoL.

SRS has risen as one of the most effective therapeutic options for the management of metastatic brain disease. In general, SRS does not compromise patient survival and represents a lower risk of cognitive decline when compared to WBRT in patients with 1 to 4 brain metastases (45,60).

Choosing between surgery or SRS alone in cases of solitary or oligometastatic brain disease can still be controversial given the lack of solid RCT. In this setting, every patient should be evaluated on an individual basis, weighing all the aforementioned factors (like the need for symptomatic debulking) as well as the need for obtaining diagnostic tissue during decision making. Anecdotical reports like the study from Bindal *et al*., where SRS was compared to surgery alone in patients with lesions <3 cm treated between 1991 and 1994, support the superiority of surgery over SRS in terms of survival and local control. This led the authors to suggest that SRS should be reserved for lesions not amenable to surgery or for patients in poor medical conditions (61).

Muacevic *et al*. presented the results of a phase III RCT that was required to stop early due to poor accrual. The authors randomized 64 patients with single lesions <3 cm into "surgery + WBRT" or "SRS alone". Similar median OS (9.5 *vs*. 10.8 months, P=0.8), local control (82% *vs*. 96%, P=0.06) and neurological death rates (29% *vs*. 11%, P=0.3) were reported (62). Furthermore, the addition of SRS to WBRT was studied in two RCTs from Kondziolka *et al*. and Andrews at al. The authors showed that SRS could add significant benefit in terms of LC and OS in patients with oligometastatic brain disease (26,42). Similarly, when the addition of WBRT to SRS was studied, combined therapy resulted in improved CNS endpoints like LC and DC when compared to SRS alone (41,43-45) (*Table 3*).

Studies have sought to compare SRS and WBRT as treatment modalities in the elderly. Minniti *et al*. evaluated the role of SRS in this population. Their findings suggest that initial management with SRS offer a good neurotoxicity profile while still associated with a survival benefit in patients older than 70 years old, with outcomes similar to those reported in historical series of SRS for younger patients (63).

Chen *et al*. (64) evaluated the toxicity associated with upfront SRS and WBRT in the elderly population with BM. This retrospective analysis included a cohort of elderly (70–79 years old) and very elderly (≥80 years old) patients with metastatic solid malignancies. The study accrued a total of 119 patients and found that WBRT was associated with worse OS [hazard ratio (HR) 3.7, 95% CI: 1.9–7.0, P<0.0001] and higher CNS toxicity profile when compared with SRS in multivariate analysis. However, even when patients undergoing urgent WBRT and WBRT for leptomeningeal disease were excluded from the analysis, the WBRT cohort still had worse KPS, higher tumor burden and more cases of uncontrolled systemic disease. Interestingly, being older than 80 years old was not associated with reduced OS nor higher risk of toxicities, which suggests that age alone could be a less important factor during treatment decisions. Finally, the authors advocate the consideration of SRS for the treatment of BM in the elderly or poor prognosis patients.

SRS in the pre or postoperative setting

The use of SRS to the surgical resection cavity has been

Table 4 Randomized controlled trials evaluating postoperative stereotactic radiosurgery to resection cavities in patients with brain metastases

Study	Randomization	n	Criteria	Primary end point	Breast Ca, N (%)	Elderly, N (%)	Tumor control		Survival
							Local control	Distal control	
Brennan *et al*., 2014, phase II (65) (MSKCC)	Surgery + SRS	49	1 to 2 lesions >18 yo, PTV = cavity + 2 mm	LC at 12 m	9 (18)	NR	85%	44% 50% (P=0.08)*	14.7 m
Mahajan *et al*., 2017, phase III (66)	Surgery + SRS Surgery + Obs	63 65	1 to 3 lesions >3 yo, PTV = cavity + 1 mm	LC	9 (14.0) 14 (22.0)	18 (29.0) 18 (28.0)	72% 43% (P=0.015)	42% 33% (P=0.35)	17 m 18 m (P=0.24)
Brown *et al*. 2017, phase III (67)	Surgery + SRS Surgery + WBRT	98 96	1 lesion, >18 yo <5 cm, PTV = cavity + 2 mm	OS and CDFS	NR	59 (60.0)† 59 (61.0)†	61% 81% (P<0.0007)	64.70% 89.2% (P<0.0005)	12.2 11.6 (P=0.7)

*, based on competing risk analysis including patients who completing postsurgical SRS and those who did not received SRS (n=40 and n=10 respectively); †, elderly classified as >60 years old. WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; NR, not reported; LC, local control; OS, overall survival; CDFS, cognitive deterioration free survival; PTV, planning target volume.

studied in three different phase II and phase III RCTs in the general population (*Table 4*) (65-67). The findings support the benefit of boosting the post-surgical cavity with SRS in terms of local tumor control (66). When SRS was compared with WBRT as adjuvant treatment, the surgery + WBRT arm showed higher rates of LC and DC, but no differences in OS were described. Given SRS could improve local control with minimal complications, SRS was recommended over WBRT as a less toxic alternative in this group of patients (68).

Preoperative SRS is a novel modality of radiation delivery that has been gaining increased attention in the treatment of BM. It represents several advantages over postoperative SRS including decreased rates of radiation necrosis and leptomeningeal disease (69-71). Additionally, no compromise of local or distal control has been reported with this approach but several randomized trials are underway (70,72-74). Similar research is being conducted to determine the benefit of fractionated SRS (75).

There is a lack of studies specifically designed to evaluate these more recent radiation modalities in the elderly population. However, the previously described work from Chen *et al*. (64) included a high proportion of patients receiving SRS in the postoperative setting without describing any increased risk of toxicity. Forthcoming data from numerous RCTs will help to clarify the role SRS has in elderly population especially in the subgroup of patients harboring BM from breast cancer.

Overall, SRS remains an ideal treatment modality for the elderly population. It is an effective treatment option in BM from breast cancer and has a conservative toxicity profile for older patients, supporting its use in this patient population.

Systemic therapy

Prospective data to aid clinical decisions regarding the use of systemic agents are limited. This is due to the fact that patients with brain BM have been historically excluded from participating in clinical trials (76), probably because of concerns regarding blood-brain barrier (BBB) penetration, presence of transmembrane efflux pumps keeping the drug out of the CNS, drug interactions or intrinsic resistance to chemotherapy (77). This has led to missed opportunities in terms of collecting important data on CNS activity and potential efficacy endpoints. Nonetheless, there are some prospective and retrospective studies supporting the efficacy and/or activity of several agents in the brain. Relevant for treatment selection are the intriguing results showing differences in the expression of clinically-relevant genes in metastatic brain lesions when compared to their primary tumor, which could reflect the need for obtaining CNS tissue sample before treatment initiation (78).

The work from Leone *et al*. (56) showed that the use of a combination of ≥2 therapies was associated with a significant improvement in survival over time in patients >65 years old. Agents with proven effectivity in brain metastatic breast cancer include cytotoxic chemotherapies as well as novel targeted therapies. None of them should be excluded from the treatment of elderly population, geriatric assessment is warranted during the evaluation of these patients prior to the initiation of systemic treatment.

Different phase I and phase II trials have investigated the

Table 5 Summary of clinical trials evaluating cytotoxic chemotherapy in patients with brain metastases from breast cancer

Agent	Study	Regimen	Trial phase	Number of patients	CNS ORR
Platinum	Christodoulou *et al.* [2005] (80)	Cisplatin temozolomide	Phase II	15	40%
	Wu *et al.* [2015] (81)	Bevacizumab + etoposide + cisplatin	Pilot study	8*	60%
Anthracycline	Caraglia *et al.* [2006] (82)	Pegylated liposomal doxorubicin	Phase II	8	62%
Capecitabine	Rivera *et al.* [2006] (83)	Capecitabine + temozolomide	Phase I	24	18%
Irinotecan	Anders *et al.* [2014] (84)	Irinotecan + iniparib	Phase II	37	12%
Temozolomide	Christodoulou *et al.* [2001] (85)	Temozolomide	Phase II	4	0%
	Abrey *et al.* [2001] (86)	Temozolomide	Phase II	10	0%
	Trudeau *et al.* [2006] (87)	Temozolomide	Phase II	19	0%
	Iwamoto *et al.* [2008] (88)	Temozolomide	Phase II	11	0%
	Siena *et al.* [2010] (89)	Temozolomide	Phase II	51	4%

*, leptomeningeal carcinomatosis. CNS, central nervous system; ORR, objective response rate.

role of cytotoxic chemotherapy in the management of brain metastasis from breast cancer. However, to date, there are no FDA-approved systemic therapies for the treatment of CNS metastases originating from breast cancer (79). *Table 5* summarizes clinical trials that have examined the role of various cytotoxic chemotherapies in this population (80-89). Out of all of this studies, anthracyclines and cisplatin seem to have the greatest objective response rate (62% and 40% respectively) (80,82); however, this data varies when compared to case series or retrospective cohorts. As observed the role of temozolomide for the treatment of CNS metastases from breast is limited if not futile, with most trials finding no CNS response. Only one multicentric phase II trial conducted by Siena *et al.* in 2010 examined the efficacy of dose-dense temozolomide, resulting in a poor a response rate of 4% and a progression- free survival of only 2 months (89).

Currently, the only biological target in metastatic breast cancer is HER2. Even though trastuzumab is considered as first-line systemic treatment in patients with HER2+ metastatic cancer (90,91) and retrospective studies have reported benefit in BM (92-95), trastuzumab has failed in preventing CNS relapse (96,97). The survival benefit reported in a patient with CNS metastatic disease in the context of HER2+ breast cancer could be linked to extracranial response rather that truly therapeutic CNS activity (92).

The small molecule tyrosine kinase inhibitor (TKI) lapatinib has been tested as a single agent (98,99) and in combination (99-101), with better results found in the last setting for previously treated and untreated patients. The LANSCAPE study, reported improved intracranial outcomes when the combination of lapatinib plus capecitabine was studied in previously untreated patients. The therapy was proven to lead to a 66% CNS response rate, as defined by a 50% or greater volumetric reduction in brain metastatic lesions (100). Neratinib is the next promising TKI, an irreversible inhibitor of both HER1 and HER2. The Translational Breast Cancer Research Consortium (TBCRC) has published the results from two phase II trials evaluating neratinib for patients with previously treated BM from breast cancer. Neratinib plus capecitabine seems to achieve better CNS response than Neratinib alone (*Table 6*) (98-104).

A retrospective analysis of the EMILIA trial randomized 991 patients with metastatic HER2+ breast cancer into trastuzumab-emtansine (T-DM1) or capecitabine plus lapatinib, and revealed similar rates of CNS progression in patients without brain metastatic disease at baseline (2% with trastuzumab-emtansine; 0.7% with capecitabine plus lapatinib). Additionally, for those with asymptomatic brain metastases at baseline, whom had received WBRT and/or local treatment in around 70% of cases in both arms, TTDM-1 was associated with significantly improved OS (102). As these biologic agents are increasingly utilized, there is a greater need to determine their safety profile among patients treated with concurrent brain directed therapies, like SRS (105).

Around 5% of patients with luminal breast cancer will develop BM during the course of the disease. It is also

Table 6 Targeted therapy against HER2+ in breast cancer with CNS metastasis—clinical trials

Study	Number of patients	Prior BM Therapy	Regimen details	ORR% (CR + PR)	Disease control%	PFS (months[†])	Overall survival (months[†])
Lin *et al.* (98), phase II [2008]	39	100%; trastuzumab 95% WBRT and/or SRS	Lapatinib 750 mg BID	2.6 (0+2.6)	18*	3.0	NR
Lin *et al.* (99), phase II [2009]	242 L, 50 L + C[a,b]	95% WBRT; 26% SRS	Lapatinib 750 mg BID; lapatinib 1,250 mg QD + capecitabine 1 g/m^2 BID	6 (0+6); 20 (0+20)	43; 40**	2.4; 3.6	6.4; NR
Lin *et al.* (101), phase II [2011]	13 L + C[a], 9 L + T[a]	100% WBRT and trastuzumab; SRS in 1 case	Lapatinib + capecitabine; lapatinib + topotecan	38 (0+38); 0 (0+0)	84; 33	NR	NR
Bachelot *et al.* (100), multicenter phase II (LANDSCAPE) [2013]	44	0% WBRT or SRS	Lapatinib 1,250 mg ×21 d + capecitabine 2 g/m^2 d1–d14; per cycle	66 (0+66)	93***	5.5	17.0
Krop *et al.* (102), phase III (subgroup analysis of EMILIA) [2015]	45 T-DM1, 50 C + L	65% WBRT and/or local treatment; 70% WBRT and/or local treatment	T-DM1, capecitabine-lapatinib	NR	78****; 84****	5.9; 5.7	26.8; 12.9
Freedman *et al.* (103), multicentric phase II [2016]	40 with BM after CNS directed therapy	78% WBRT	Neratinib 240 mg QD	8 (0+8)	NR	1.9	8.7
Freedman *et al.* (104), multicentric phase II [2019]	49 total, 37 cohort 3A, 12 cohort 3B (prior lapatinib)	59% WBRT; 41% SRS; 82% trastuzumab	Neratinib 240 mg QD + capecitabine 750 mg/m^2; BID ×14 d then 7 d off	49; 33	NR	5.5; 3.1	13.3; 15.1

[†], incidence or median duration; *, free of any progression in both CNS and non-CNS lesions; **, % of patients with ≥20% reduction in volume CNS lesion; [a]combined therapy arm; [b]patients came from lapatinib alone arm; ***, subgroup analysis of 42 patient using RECIST criteria; ****, 100-disease progression. BM, brain metastasis; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; L, lapatinib; C, capecitabine; ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; disease control, CR + PR + SD; NR, not reported; CNS, central nervous system; HER-2, human epidermal growth factor receptor 2; KPS, Karnofsky performance score; PFS, progression free survival; BID, twice a day; QD, every day; T-DM1, ado-trastuzumab emtansine.

important to note that in almost 50% of these cases there is an overexpression of hormone receptors in the primary tumor while the metastatic lesion will not harbor receptor overexpression (106). Furthermore, even when receptor overexpression is still present, previous endocrine therapy could drive the emergence of mutations in the estrogen receptor gene 1 (ESR1) that confer constitutive expression, and potential resistance to hormonal therapy in metastatic lesions (107). In general, there is a good distribution of estrogen receptor antagonist within brain parenchyma and reports of prolonged survival and remission with tamoxifen, letrozole and megestrol acetate have been described in the literature (108).

Conclusions

Clinical decision making during the management of elderly patients with BM from breast cancer should be approached in a holistic way, particularly given the paucity of data among this patient population. Geriatric assessment including evaluation of comorbidities, functional status, and socioeconomic support should be warranted. Age, as an independent factor, does not seem to play a determinant role in treatment selection. The risks and benefits before initiation of any treatment should be weighed on an individual basis considering that the elderly represents a very heterogeneous population. Use of prognostic scores could aid in this endeavor; however, physician judgment is of utmost importance.

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