Treatment of breast cancer brain metastases: radiotherapy and emerging preclinical approaches

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Abstract

The breast is one of the common primary sites of brain metastases (BM). Radiotherapy for BM from breast cancer may include whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and stereotactic radiotherapy (SRT), but a consensus is difficult to reach because of the wide and varied protocols, indications, and outcomes of these interventions. Overall, dissemination of disease, patient functional status, and tumor size are all important factors in the decision of treatment with WBRT or SRS. Thus far, previous studies indicate that WBRT can improve tumor control compared to SRS, but increase side effects, however no randomized trials have compared the efficacy of these therapies in BM from breast cancer. Therapies targeting long non-coding RNAs and transcription factors, such as MALAT1, HOTAIR, lnc-BM, TGL1, and ATF3, have the potential to both prevent metastatic spread and treat BM with improved radiosensitivity. Given the propensity for HER2+ breast cancer to develop BM, the above-mentioned cell lines may represent an important target for future investigations, and the development of everolimus and pyrotinib are equally important.

Keywords

Stereotactic radiosurgery; whole-brain radiation therapy; breast cancer; brain metastasis

Introduction

Brain metastasis (BM) is the most common intracranial tumor, with over 200,000 new cases of BM diagnosed each year [1], of which the most common primary tumor site is the lung followed by the breast [2]. Of patients with breast cancer, 5-30% are likely to develop brain metastasis during the course of their disease [3,4], having a major impact on quality of life and mortality. Breast cancer subtypes vary in their propensity to develop BM, with triple negative and hormone receptor negative (HR−)/human epidermal growth factor receptor 2

positive (HER2+) cancer being most likely to develop brain metastasis when compared with HR+/HER2− and HR+/HER2+ breast cancer [5].

Breast cancer brain metastases (BCBMs) are thought to occur from hematogenous spread following the epithelial-mesenchymal transition (EMT) [6]. In the EMT model, primary cancer cells undergo a transition where they lose their adhesive properties and gain mobility as mesenchymal cells. These cells eventually invade through the vasculature and may contain stem-like properties allowing them to malign into metastatic tumor cells.

These metastases have a known preference for watershed territories, commonly at the gray-white junction. Probably, the small size of distal vasculature facilitates cell adhesion and invasion through the vascular layers [7-11] (Figure. 1). In addition to vessel size, vascular anatomy plays a role in intracranial seeding due to both blood flow magnitude and distinct anatomic pathways from the primary cancer site to the metastatic destination [12,13]. Another cause behind the high rate of BCBM is the 'seed and soil' theory, which proposes that certain primary cancers have specific preferences for metastatic destinations based on the hospitality of the microenvironments within their tissue types [14,15].

Compared to BM from other primary cancers, breast cancer has previously shown a predilection for specific brain regions, occurring most commonly in the cerebellum, parietal lobe, and basal ganglia, and less likely occurring in the distribution of the posterior cerebral artery [16-20]. Compared to other breast cancer genetic subtypes, metastases from triple-negative breast cancer often occur in the frontal lobe, limbic region, and parietal lobe [21].

Treatment of brain metastases include neurosurgical resection, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), stereotactic radiotherapy (SRT), and medical management. In this review, we will focus on radiation therapies for patients with BM from breast cancer, comparing treatment protocols, indications, and outcomes among WBRT, SRS, and SRT. We will also discuss emerging pre-clinical treatment approaches for BM from breast cancer, including long non-coding RNAs and transcription factor targets to prevent BM and improve radiosensitivity.

Optimal treatment protocol and radiation dosing schemes for BCBMs

All radiation dosing schemes must balance tumor-minimizing therapeutic effect with toxicities associated with treatment. Acute toxicities include dermatitis, alopecia, and fatigue, while late toxicities include neurologic decline, leukoencephalopathy, and radiation necrosis [22]. The standard WBRT dose-fractionation schedule for BM remains at 30 Gy in 10 fractions or 20 Gy in 5 fractions [23], though several studies have explored alternate dosing schemes. A lengthened dose regimen of 37.5 Gy in 15 fractions was associated with more acute toxicity events but had no significant effects on overall survival (OS) or tumor control in a cohort of 194 patients with up to 3 BM (in which 5% of patients had BCBM) [24]. Similarly, larger dose regimens of 40 Gy in 20 fractions and 45 Gy in 15 fractions were associated with longer treatment times and increased cost, with no significant improvement in terms of OS or recurrence in a study of BM with 25% of tumors from BCBM [23].

A systematic review by Tsao et al. demonstrated that of eight alternative dose-fractionation schedules, none had a significant benefit on OS or symptom control for BM [25]. Taken together, these results support the standard-of-care dosing scheme of 30 Gy in 10 fractions or 20 Gy in 5 fractions.

Widespread radiation dosing in WBRT is contrasted with localized radiation in SRS. Due to variance in SRS dosing by tumor size, maximum tolerable SRS doses were established in 2000 by the Radiation Therapy Oncology Group (RTOG) 90-05 dose escalation trial, which recommended no more than 24 Gy for tumors less than or equal to 20 mm in size, 18 Gy for tumors 21-30 mm, and 15 Gy for 31-40 mm tumors [26]. Though these guidelines remain the standard of care today, some work has found limited toxicity associated with SRS at these doses [27], suggesting that fractionated SRT may allow for higher cumulative doses. Indeed, SRT is less costly and more comfortable for patients [28] and has been reported to be associated with significantly better tumor control in patients with intracranial meningiomas [29]. Emerging studies have also suggested improved local control in SRT when compared to SRS for BM [30], which is currently being studied in an Alliance clinical trial [31].

The American Society for Radiation Oncology (ASTRO) guidelines in 2012 recommended several protocols for treatment of BM. Level 1 evidence suggests that patients with single BM ≤ 3-4 cm should be treated with surgery + WBRT, SRS + WBRT, or SRS alone, while patients with BM > 3-4 cm should be treated with surgery + WBRT [32]. However, according to the recently released ASCO-SNO-ASTRO guidelines, SRS alone is recommended for 1-4 unresected BM and for patients following resection of 1-2 BM [33]. Level 1 evidence also supports treatment of patients with unresectable single BM ≤ 3-4 cm with SRS + WBRT or SRS alone, while patients with multiple BM ≤ 3-4 cm may be treated with SRS + WBRT, SRS alone, or WBRT alone [32]. Some recent work even supports treatment of patients with more than 10 BM with SRS only [34]. In total, the majority of studies regarding radiation dosing schemes for BM involve BM from multiple primary sites, and there has been limited study on specific BCBM regimens.

Whole-brain radiation therapy versus stereotactic radiosurgery

Along with neurosurgical resection, SRS and WBRT form the cornerstone of treatment for most patients with BCBM (Table 1). However, given the rapid evolution of SRS and the lack of randomized controlled trials till date comparing these treatment options specifically for BCBM, there is some controversy in the literature regarding an optimal treatment algorithm. A myriad of other reviews [35-45] have detailed the state of current evidence and provided recommendations regarding when each modality is preferred; herein we summarize these findings with regard to the use of WBRT and SRS.

The number of metastases is the most common factor to decide whether to utilize WBRT or SRS. When deciding between radiation-based therapies for BCBM, SRS is preferred for oligometastatic disease (1-4 BM), while WBRT is often reserved for patients with more diffuse disease and more than 4 metastases [39,40,42]. Though traditionally used for oligometastatic BCBM [37], WBRT carries a risk of neurocognitive decline due to damage to healthy brain tissue, especially in the domains of memory, executive functioning, and

processing speed, and deficits are more pronounced over time [46]. The more targeted SRS can avoid this complication, though SRS is associated with a higher chance of recurrent BM in studies of BM from multiple primary tumor sites [47]. When WBRT is used, data suggest that hippocampal-avoidance WBRT (HA-WBRT) may provide similar outcomes with improved neurocognitive outcomes when compared to standard WBRT [45]. Despite the higher chance of recurrence of BM with SRS, several studies have demonstrated no significant difference in overall survival (OS) when comparing WBRT to SRS in BM from multiple primary tumor sites (with 4-30% of patients with BCBM) [47,48]. However, BCBM has previously been shown to be particularly sensitive to WBRT when compared to BM from other primary cancer types [49]. WBRT+SRS was found to be superior to WBRT alone in improving local control on magnetic resonance imaging for BM from multiple primary tumors, but the WBRT+SRS did not significantly improve OS [50] and has been shown to worsen cognitive outcomes [51]. Further, Yamamoto et al. [52] demonstrated the non-inferiority of SRS for 2-4 BM compared to the same therapy for 5-10 BM. A growing body of evidence regarding the efficacy of SRS for even high numbers of BM has led towards greater adoption of SRS over WBRT. Bailleux and colleagues argue that WBRT alone is a good option for patients with more than 10 BM that can not be treated locally or for patients with new metastases that are not amenable to SRS [53]. However, this trend is not universal, and currently WBRT still does play a role in treatment of BCBMs.

The number of metastatic lesions is not the only factor when deciding on therapeutic options. Notably, patient functional status, tumor size, age, time from primary to BM diagnosis, molecular subtype, prior radiation, primary and extracranial tumor control are other potentially important factors in deciding whether to adopt SRS or WBRT. Ideally, patients need to have a high functional status – Karnofsky Performance Score (KPS) of at least 70 – and a tumor diameter less than 6 cm [54] to be considered for SRS. Additionally, the presence of extracranial metastasis may classify the patient as "high risk". It has been proposed that this should prompt early treatment with WBRT rather than SRS. Further, OS is not the only important clinical outcome;

WBRT treatment has been reported to be associated with greater chances of appetite loss and general motor dysfunction compared to treating with SRS. These outcomes of poor quality of life are important to consider [55]. There is evidence that certain molecular subtypes may respond differentially to radiation with ER+/HER− having better outcomes, though further work is needed to determine a differential response between WBRT and SRS [56]. Additionally, evidence has shown that in SRS, factors such as smaller tumor volume and lack of prior WBRT have been shown to be associated with greater success in a study with 14% of patients with BCBM [57]. Given the possibility of greater recurrence after SRS, but the quality of life function is not affected compared to WBRT. This therapy may have higher utility with increasing age [47,55]. As evidence emerges in abundance, better selection of patients for optimal treatment will be possible. In sum, a comprehensive and individualized approach to treatment selection is necessary, and machine learning algorithms that are capable of processing individual patient factors to predict outcomes after WBRT or SRS may become valuable tools. A list of significant prognostic indicators as evidenced by the literature are provided in Table 1 [58].

The controversy of WBRT and SRS also exists in in the treatment of leptomeningeal metastasis (LM). LM is a rare sequela of breast cancer and carries a substantially poor prognosis, with a median survival of 4 months [59]. Standard of care for LM generally relies on brain radiotherapy and intrathecal chemotherapy [60,61]. Concurrent radiotherapy and intrathecal methotrexate are thought to be associated with improved remission of symptoms and survival, as demonstrated in a prior study of patients with LM (18% of which had LM from breast cancer) [62]. Though some work has suggested an elevated incidence of LM following SRS when compared to WBRT [63], one study found that the only predictor of LM was active extracranial metastases from breast cancer that were present during SRS treatment [64]. Additionally, an increased risk of leptomeningeal dissemination after SRS has been observed with increasing number of BCBM [51]. Taken together, optimal management of LM is a poorly understood and controversial matter that requires further high-powered studies.

As mentioned previously, SRT is being investigated as an alternative local radiation treatment to the single-treatment of SRS, though the literature offers limited guidance as to the selection of one protocol rather than the other. Retrospective reviews comparing single fraction SRS to multifractionated SRT mostly show no difference in local control (in which 8-17% of patients had BCBM) [65-70] though etiology of tumor, tumor volume, and the biologically effective dose of radiation vary. Loo and colleagues [67] did find a slightly higher incidence of radionecrosis for patients who underwent SRT; the balance between the improved patient comfort and lower cost of SRT should be maintained. However, prospective randomized controlled trials (RCTs) comparing the two are necessary to provide level 1 evidence for better guidelines. Furthermore, although several studies have examined WBRT vs. SRS, there has been limited analysis on WBRT vs. SRT.

While there is an increasing trend towards greater adoption of SRS over WBRT, evidence to support this shift for BCBM is lacking. There are no randomized clinical trials comparing WBRT to SRS for treating patients with primary breast cancer, leading some to argue that WBRT remains as important as SRS in the treatment of most patients with BCBM [71]. Advances in medical therapy and combination of multiple forms of treatment may influence the preferred therapy. Finally, the preferred outcome likely differs among patients: those with worse prognosis and short life expectancy will most likely benefit more from palliative treatment, whereas patients in the early stages of disease may benefit from more aggressive treatments at the potential temporary expense of functional status. Future trials focused specifically on patients with BCBM.

Evaluating a range of outcomes will be instrumental in providing robust evidence that interdisciplinary teams including the patient can be used to select optimal care.

SRS Timing

SRS combined with neurosurgical resection can be delivered as either the initial treatment before surgery (neoadjuvant) or as a postoperative (adjuvant) treatment. Postoperative radiation to the tumor cavity was initially popularized as it was found to reduce the risk of recurrence after surgical resection. However, adjuvant SRS does have some associated risks. The size of the resection cavity may not be the same as the initial tumor volume,

and the size can further change over time, which can necessitate the expansion of target volume and risk damaging healthy brain parenchyma [70]. Further, since the recovery course from neurosurgical tumor resection may be variable, the timing of postoperative SRS may also vary, and some patients are at risk of loss to follow-up [72]. This is important because time for postoperative radiosurgery is associated with local recurrence of BM from multiple primary sites (18% of which were BCBM) [73]. Finally, compared with adjuvant WBRT, higher rates of leptomeningeal tumor spread (thought to occur iatrogenically during surgery) and symptomatic radiation necrosis have been observed in adjuvant SRS in BM from multiple primary sites (27% of which were from breast cancer) [74].

For these reasons, neoadjuvant SRS has recently become a relatively novel treatment paradigm for BCBM. Preoperatively, the tumor volume is well-defined and easily identified, allowing utilization of a more focused beam [75]. Since the treatment is delivered before surgery, timing, and loss to follow-up are not of concern. Patel and colleagues compared adjuvant to neoadjuvant SRS and found improvements in OS, leptomeningeal disease, and radiation necrosis in the neoadjuvant group but no significant difference in recurrence rates [74]. However, this was a retrospective study without matched cohorts; Randomized controlled trials (RCTs) comparing the two treatment paradigms are lacking in this study. Otherwise these trials will help to clarify more clearly on which patients may benefit more from neoadjuvant SRS.

Radiotherapy combined with systemic therapy

Although local interventions, like resection and radiation, are the standard of care for BCBMs, systemic therapies like ado-trastuzumab emtansine (TDM1), tucatinib, and liposomal irinotecan are being used to complement local strategies. Antibody-drug conjugates show promise for the treatment of patients with active HER2-positive brain metastases, with TDM1 displaying intracranial activity in preclinical models and multiple case series [81]. Tucatinib is a HER2-targeted tyrosine kinase inhibitor that has also shown intracranial and extracranial effectiveness. In a randomized trial, patients in the tucatinib-containing arm showed longer progression-free survival (PFS) and OS [82]. Liposomal irinotecan is a chemotherapeutic agent that has demonstrated both central nervous system (CNS) and extracranial responses in a cohort of patients with BCBM [83]. The combination of local therapies such as SRS with these systemic agents can improve outcomes but result in significant side effects. In a retrospective study of 45 patients, Stumpf et al. [84] found a strong correlation between the development of clinically significant radionecrosis after TDM1 and SRS therapy in patients with HER2-positive breast cancer, although the case series by Mills et al. did not note such a correlation [85]. The potential toxicities of systemic agents when used in combination with local therapies warrants prospective studies controlling for variations in radiation and medication dosing to further stratify risks and ameliorate toxicities.

Pre-clinical treatment targets

In addition to a number of patient-level prognostic factors for outcomes of radiotherapy that we previously described, there are a number of pre-clinical molecular targets that can enhance radiotherapy efficacy and improve treatment of BCBM. To this effect, a great

deal of preclinical literatures existed evaluate pathways underlying brain metastasis and radioresistance for the generation of targeted therapies. Novel pathways under investigation include targeting long non-coding RNAs or transcription factors that may drive breast cancer metastasis to the brain and reduce treatment efficacy. In addition, therapies focused on HER2+ breast cancer are also being trialed due to its propensity to metastasize to the brain.

Long non-coding RNAs (lncRNAs) and radioresistance

LncRNAs comprise a large and heterogenous group of RNA transcripts (greater than 200 nucleotides and incapable of direct translation) that are implicated in a variety of human diseases including breast cancer [86,87]. LncRNAs can carry out various functions such as gene expression regulation through multiple mechanisms including direct DNA binding or transcription factor modulation, RNA or protein modulation, interference with chromatin complexes and alternative splicing [88-92]. As a result, some lncRNAs may function as oncogenes, and others as tumor suppressors. One example of a tumor suppressor lncRNA is metastasis-associated lung adenocarcinoma transcript 1 (MALAT1).

when MALAT1 is inactivated in a transgenic mouse model of breast cancer, the metastasis is promoted [93]. Interestingly, MALAT1-knockout cells showed stronger migratory and invasive ability when compared to normal controls. Under video microscopy, MALAT1 knockout had increased speed of movement and metastatic colonization, which was completely reversed by restoration of MALAT1 expression. In addition, in esophageal squamous cell carcinoma, MALAT1 has been shown as a positive regulator for radioresistance by promting cyclin-dependent kinase subunit 1 (Cks1) expression. In vitro, silencing MALAT 1 and Cks1 improved radiosensitivity of cancer cells [94]. More investigation is required regarding MALAT1 activation and its opposing effects on cancer cell migration and radioresistance.

Conversely, oncogenic lncRNAs promote tumorigenesis and metastasis. For example, the HOX antisense intergenic RNA (HOTAIR) lncRNA has been shown to target polycomb repressive complex 2 (PRC2), a chromatin-modifying enzyme and transcriptional repressor [95]. In vitro, HOTAIR overexpression in breast cancer cell lines not only promotes colony growth, but also increases cell invasion through an extracellular matrix [96]. In breast cancer mice models, the same group demonstrated increased metastasis, preferentially to the lungs, in mice bearing HOTAIR+ primary tumors. Similar to MALAT1, HOTAIR expression has also shown increased radioresistance. Zhang et al. [97] found a positive correlation between HOTAIR lncRNA and heat shock protein family A member 1A (HSPA1A) levels in irradiated breast cancer cells, depicting a potential mechanism for lncRNA-mediated decreased radiosensitivity. HOTAIR was shown to sequester miR-449b-5p, a micro-RNA. One of the many tumor-suppressive effects of this microRNA is to inhibit HSPA1A transcription and allow for the overexpression of HSPA1A. Since HSPA1A is a major stress-inducible protein that facilitates protein folding, its overexpression decreases radiosensitivity.

Similarly, lncRNA associated with BCBM (lnc-BM) is a separate lncRNA showing preferential metastasis to the brain. Wang et al. [98] showed that the use of a nanoparticle encapsulated small interfering RNA targeting lnc-BM in BCBM-bearing mice significantly

reduces brain metastatic burden by week 4 and significantly prolonges survival rates when compared to untreated mice. Novel therapies that target oncogenic lncRNAs or increase expression of tumor suppressor lncRNAs are currently being investigated to inhibit brain metastases or increase radiosensitivity [99].

Transcription factors and radioresistance

The role of specific transcription factors in promoting breast cancer metastasis and radioresistance is also under investigation. Sirkisoon et al. [100] identified truncated glioma-associated oncogene homolog 1 (TGLI1) as a promoter of preferential breast cancer metastasis to the brain. In vivo, they also showed that TLGI1-expressing BCBMs are more invasive, vascularized, and proliferative when compared to controls. In essence, these tumors would be more difficult to eradicate unless specifically targeted. Accordingly, they showed that cells expressing TLGI1 are more radioresistant compared to other cell lines, and TGLI1 expression is significantly induced by radiation in a dose-dependent manner. They confirmed these findings by comparing tumor samples from patients with BCBMs who did have recurrence following radiosurgery (radioresistant) and from patients who did not (radiosensitive). As expected, radioresistant samples had significantly increased TLGI1 expression. The exact mechanism for radioresistance has yet to be identified. Antisense oligonucleotides were able to selectively inactivate TLGI1 and decrease brain metastases, but no change was observed in metastases to other organs. Targeting TLGI1 or the pathway through which it directs preferential metastasis to the brain and contributes to radioresistance may allow for increased treatment efficacy and prolonged survival.

Other transcription factors that may affect treatment efficacy have also been identified. Changes in activating transcription factor 3 (ATF3) activation have been shown to promote tumor metastasis via upregulation of genes involved in cell motility such as urokinase-type plasminogen activator, caveolin-1 and Slug [101]. More importantly, among breast cancer cell lines, ATF3+ cell lines demonstrated improved survival rates when exposed to radiation and survival rates were associated with degree of ATF3 expression. Mechanistically, radiation resistance is thought to occur through the modulation of the PI3K/Akt signaling pathway, as pAkt is a key radioresistance protein. Interestingly, cell lines with increased ATF3 expression also showed reduced caspase-3 activity and apoptosis rate [102]. In vivo, mice with silenced ATF3 show a significantly lower rate of tumor progression and higher sensitivity to irradiation [103]. Collectively, these data again point to a transcription factor that can reasonably and specifically treat and prevent BCBMs (Figure. 2).

Targeted therapies improve radiosensitivity for HER2+ breast cancer

Among breast cancer subtypes, HER2+ cancers have shown a high propensity for developing BM, in addition to triple negative and HR−/HER2+ [5,99,103]. Up to half of patients with HER2+ breast cancer develop tumor metastasis, while the brain is the main site of recurrence in these patients, and targeted therapies that inhibit cancer migration and proliferation are essential for a successful treatment [104]. Pyrotinib, an irreversible inhibitor of HER2 and its downstream signaling, has shown promising antitumor activity [105]. In a recent randomized phase 2 trial, women with HER2+ metastatic breast cancer treated with pyrotinib combined with chemotherapy yielded significantly better overall response

rate and PFS than those given lapatinib combined with chemotherapy [106]. This therapy can enhance cancer cell radiosensitivity, from which it is inferred that it may be particularly beneficial for patients undergoing radiotherapy for brain metastases [107,108]. This was shown in a study by Tian et al. [108] where patients with BCBMs were divided into two groups: radiotherapy with capecitabine or radiotherapy with pyrotinib and capecitabine. Patients in the pyrotinib group had shown the significantly increased overall treatment response rate, PFS, and the reduced response duration. The mechanism underlying this effect is currently under investigation but is thought to function via significantly inhibiting cell proliferation of cultured cells.

Additional targets have been identified for more sustained responses. Hyperactivation of the phosphoinositide-3-kinase (PI3K)/ mammalian target of rapamycin (mTOR) pathway is a primary driver of metastasis in HER2+ breast cancer and treatment resistance [109]. Everolimus is an inhibitor of this pathway. Two recent phase two trials evaluating everolimus in BCBMs patients have demonstrated therapeutic efficacy and survival outcomes, like current standard of care and low toxicity [110,111]. Although patients with brain metastases have not been tested with the combination of everolimus and radiotherapy, the literature postulates that it may have increased the efficacy. This is thought to be due in part to increased radiosensitization caused by RAS inhibition [112]. Su et al. [113] did demonstrate everolimus' radiosensitizing effects primarily through an autophagy-driven pathway (Table 3).

Conclusions

Overall, number of brain metastases, dissemination of disease, patient functional status, age, and tumor size are all important factors in treatment decisions between WBRT and SRS. Although WBRT improves tumor control compared to SRS, it increased side effects. No randomized trial has specifically compared these therapies in BCBM. Although SRS is traditionally applicable to patients with less than 5 metastases, some studies have shown that the more metastases, the more effective, but the risk of recurrence and leptomeningeal dissemination may also increase. Future trials and prospective studies can help predict metastatic zones and tailor radiotherapies accordingly in order to improve the risk profile of radiation and avoid low-risk metastasis areas [114]. Evidence for treatment guidelines of leptomeningeal disease is currently limited, though treatment conventionally consists of concurrent radiotherapy and intrathecal medical therapy. Prime areas for future investigation include BCBM-specific studies across different molecular subtypes,management of leptomeningeal disease, combination therapies, radiation timing (adjuvant vs. neoadjuvant) and management of patients with an intermediate number of metastases of 5-10 tumors. Furthermore, radiotherapy efficacy can be further improved using therapies targeting unique lncRNAs and transcription factors.

By analyzing the propensity of HER2+ breast cancer for forming BM, future studies can use these cell lines to identify additional treatment targets including the HER2 receptor and PI3k/mTOR pathways, and the function of pyrotinib and everolimus also require further validation. Future studies should evaluate further mechanisms and targets of radiosensitivity in order to improve outcomes after WBRT or SRS.

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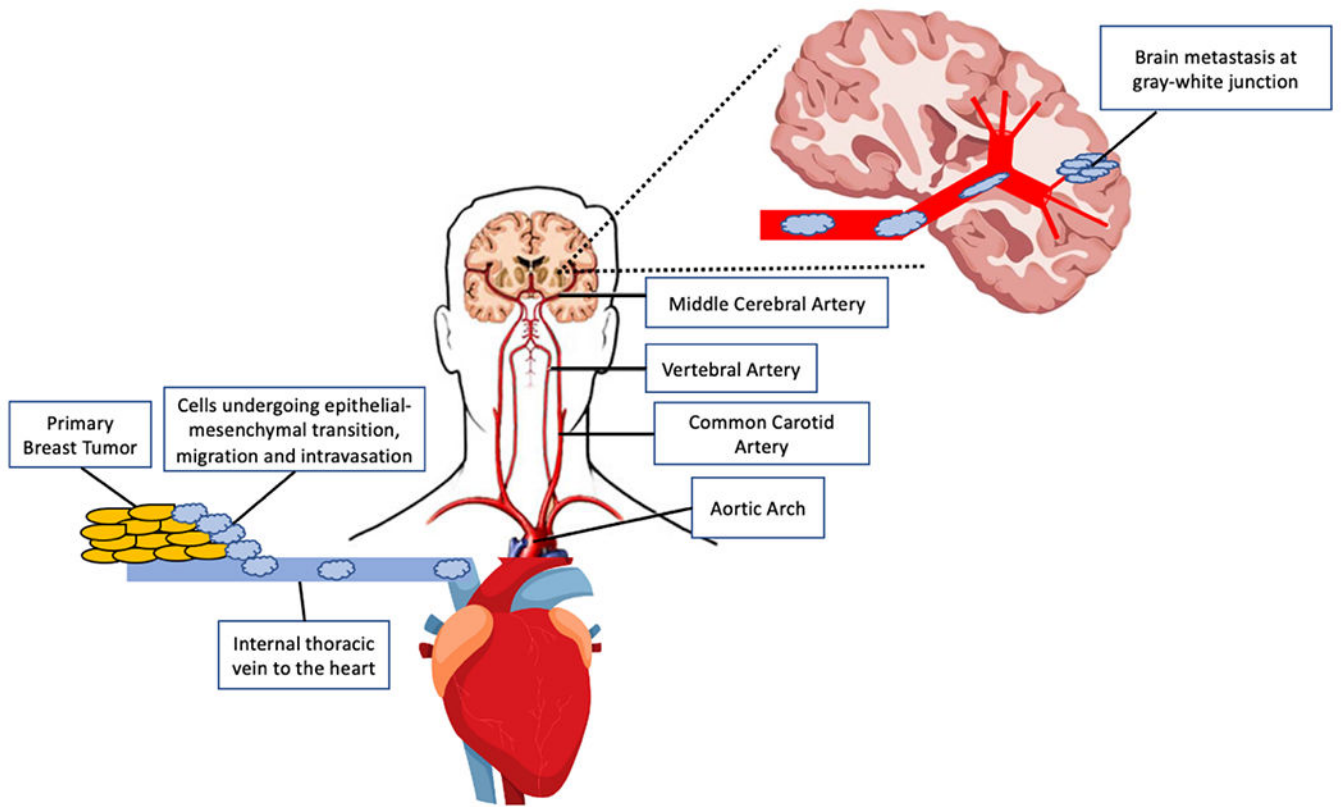
Figure 1.
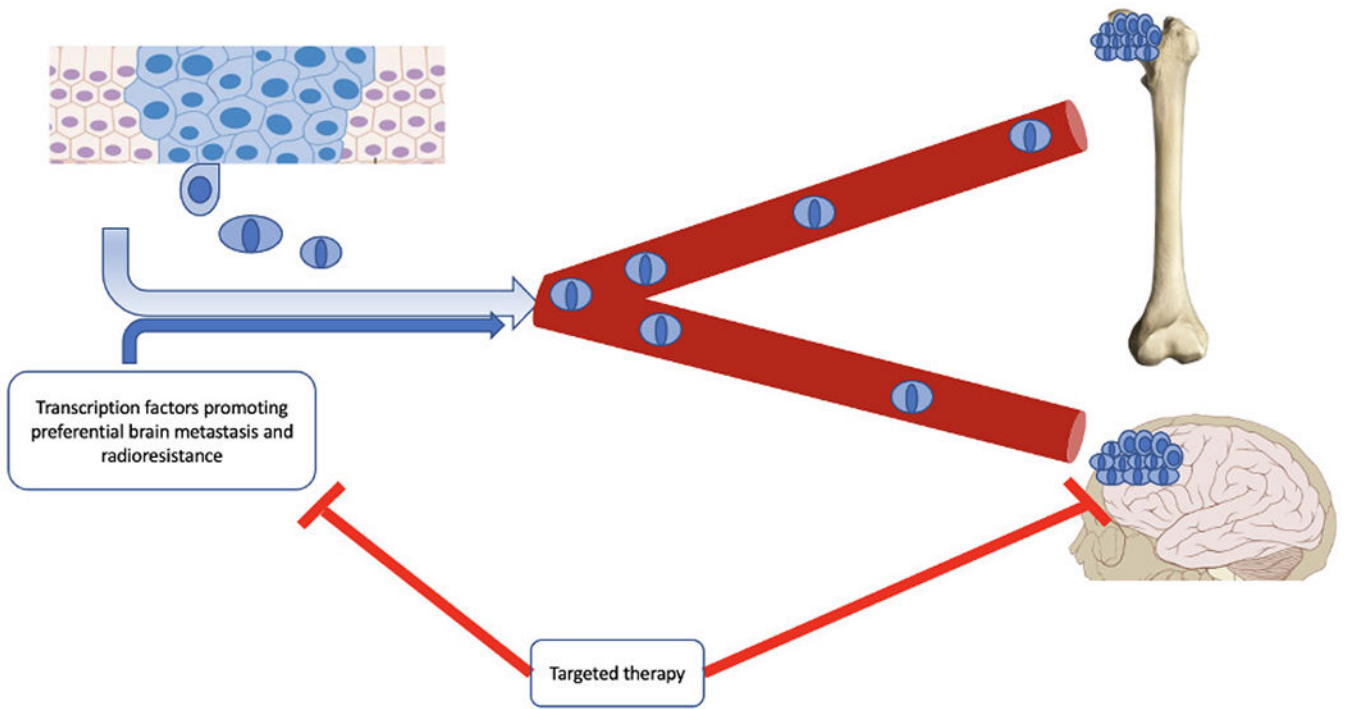Vascular routes from a breast cancer primary tumor to a cerebral metastasis

Figure. 2.
Targeted therapies to both prevent and treat metastatic spread

Table 1.

Proposed factors to predict outcome after WBRT or SRS using a machine learning algorithm.

Variable	Prior Study Demonstrating Prognostic Significance
Age	[47,55]
ER, PR, and HER2 status	[56]
Functional Status (KPS score)	[53]
Tumor Size	[53]
Control of Primary and Extracranial Metastatic Disease	[64]
Number of BM	[51]
Time from primary cancer diagnosis to BM diagnosis	[66]
Prior Radiation	[57]

Table 2.

Commonly utilized treatment protocols of whole-brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS)

Author	WBRT vs. SRS	Dose/Scheduling	Outcomes	Reference
Andrews et al.	WBRT vs	37.5 Gy / 15 fractions	WBRT+SRS improved survival and increased KPS at 6 months	[76]
	WBRT+SRS	WBRT: 37.5 Gy / 15 fractions; SRS: 24 Gy for 20 mm, 18 Gy for 21-30 mm, 15 Gy for 31-40 mm		
Brown et al.	SRS	24 Gy for < 20 mm, 20 Gy for 20-29 mm	In patients with 1-3 brain mets, lower cognitive decline at 3 and 12 months, higher quality of life at 3 months for SRS alone. Shorter time to intracranial failure with SRS alone but no significant difference in OS.	[50]
	SRS+WBRT	SRS: 22 Gy for < 20 mm 18 Gy for 20-29 mm; WBRT: 30 Gy / 12 fractions		
Brown et al.	Postoperative SRS vs WBRT	SRS: 12-20 Gy single fraction with dose determined by surgical cavity volume; WBRT: (30 Gy in ten daily fractions or 37.5 Gy in 15 daily fractions of 2.5 Gy	Cognitive deterioration at 6 months less in SRS group. No difference in survival.	[48]
Aoyama et al.	SRS	22-25 Gy for 20 mm; 18-20 Gy for > 20 mm	No difference in OS. 12 month recurrence rate and requirement for salvage therapy higher for SRS alone. No difference in functional preservation or radiation toxic effects	[47]
	SRS+WBRT	SRS: 15.4-17.5 Gy for 20 mm 12.6-14 Gy for > 20 mm; WBRT: 30 Gy / 10 fractions		
Li et al.	SRS	24 Gy for 20 mm, 18 Gy for 21-30 mm, 15 Gy for 31-40 mm	Reduced neurocognitive deterioration in SRS only without change in OSI for 4-15 non-melanoma BM	[77]
	WBRT	30 Gy / 10 fractions Mematine		
Salans et al.	SRS vs WBRT	N/A	WBRT associated with greater odds of appetite loss and motor dysfunction	[55]
Patel et al.	Neoadjuvant vs. Adjuvant SRS	24 Gy for 20 mm, 18 Gy for 21-30 mm, 15 Gy for 31-40 mm	Adjuvant SRS associated with significantly higher leptomeningeal disease and radiation necrosis	[74]
Mainwaring et al.	SRS vs WBRT		Longer survival for SRS	[78]
El Gantery et al.	SRS vs WBRT vs SRS+WBRT		In patients in 1-3 BM, greater local control with SRS+WBRT vs SRS alone or WBRT alone. No difference in OS, but patients with controlled primary tumor had greater survival with SRS+WBRT compared to SRS alone or WBRT alone.	[49]
Mahajan et al.	Postoperative SRS vs observation		Significantly lower recurrence in 12 months for SRS	[27]
Chang et al.	SRS vs SRS+WBRT		Greater decline in learning and memory in SRS+WBRT at 4 months. Greater CNS recurrence at 1 year in SRS alone.	[79]
Minniti et al.	SRS+WBRT vs. WBRT	WBRT: 30 Gy in 10 fractions	Longer survival in WBRT+SRS. Local and CNS control at 12 months greater in WBRT+SRS.	[70]

Author	WBRT vs. SRS	Dose/Scheduling	Outcomes	Reference
Muacevic et al.	SRS for breast cancer BM		Median OS: 10 months. 30% CNS recurrence rate. KPS > 70 associated with prolonged survival.	[80]

Table 3.

An summary of emerging pre-clinical targets and therapies for brain metastases from breast cancer

Target	Mechanism of action	Effects	References
MALAT1	LncRNA with positive regulation of Cks1, mechanism of metastasis is under investigation	Inhibits migratory and invasive ability, increases radioresistance	[93,94].
HOTAIR	LncRNA that leads to overexpression of HSPA1A and targets PRC2	Promotes proliferation, increases cell invasion through extracellular matrix, increases radioresistance	[95-97]
lnc-BM	LncRNA showing preferential metastasis to the brain, mechanism under investigation	Reduces metastatic burden, prolongs survival	[98]
TGLI1	Transcription factor that is significantly induced by radiation, mechanism under investigation	Promotes invasiveness, vascularization, and proliferation. Radioresistant breast cancer samples show elevated levels of TGLI1.	[100]
ATF3	Transcription factor that upregulates cell motility genes, modulates PI3K/Akt pathway, and reduces caspase-3 activity.	Promotes tumor metastasis, increases radioresistance, reduces apoptosis rate.	[101,102]
Pyrotinib (targeted therapy)	Irreversible HER2 inhibitor, mechanism related to reduced cell proliferation	Increased treatment response rates, increased progression-free survival	[105,108]
Everolimus (targeted therapy)	Inhibitor of the PI3k/mTOR pathway	Increased radiosensitization, progression-free survival, and low toxicity	[109,112,113]