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BREAST CANCER (B OVERMOYER, SECTION EDITOR)

The Current and Evolving Role of Radiation Therapy for Central Nervous System Metastases from Breast Cancer

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Abstract

Purpose of Review For patients with breast cancer who develop brain metastases, radiation therapy (RT) provides local control. Here, we review the current role for central nervous system RT, particularly focusing on the evolving role for stereotactic radiosurgery (SRS).

Recent Findings SRS treats only known CNS disease as opposed to whole-brain radiation therapy (WBRT), which treats the entire brain parenchyma. SRS has been found to cause less neurocognitive decline than WBRT. SRS is currently utilized in patients with four or fewer brain metastases, but several ongoing trials are examining the use of SRS for greater than four metastases. For patients requiring WBRT, hippocampal avoidance WBRT and memantine concurrent with and adjuvant to WBRT have been found to reduce the risk of neurocognitive decline.

Summary Both SRS and WBRT are used as a local therapy for brain metastases. SRS is increasingly preferred given fewer long-term neurocognitive side effects.

Keywords Whole-brain radiation · Radiosurgery · Stereotactic radiation · SRS · Brain metastases · Central nervous system metastases · Breast cancer · Side effects · Neurocognition · Radiation therapy

Introduction

Breast cancer represents the second leading cause of brain metastases in the United States [1]. The incidence of brain metastases among women with breast cancer is increasing in the modern era, likely due to advances in systemic therapy and imaging technologies [2]. Nonetheless, the overall incidence proportion of brain metastases among women with breast cancer has been estimated to be as low as 5.1%, and current guidelines including those by the National Comprehensive Cancer Network (NCCN) do not support routine surveillance brain MRI in neurologically asymptomatic women with breast cancer [3]. As such, the vast majority of patients with breast cancer who are diagnosed with brain metastases present with neurologic symptoms prompting brain imaging.

In practice, however, the natural history of breast cancer and propensity for brain metastases is variable and based on certain clinical and pathologic tumor features, particularly tumor subtype. One study suggests the 15-year incidence of brain metastases in women with early-stage breast cancer is 2.2% for women with luminal A (estrogen receptor–positive and/or progesterone-positive and Ki-67 < 14%) breast cancer and 14.3% for women with human epidermal growth factor receptor 2 (HER2)-positive (HER2+), estrogen receptor negative, and progesterone receptor negative tumors [4]. In patients with metastatic HER2+ breast cancer treated with trastuzumab, the incidence of brain metastases is between 21 and 34% [5–7]. Patients with inflammatory breast cancer also have a relatively high risk of developing brain metastases; the incidence at two years can approach 25–34% in women with metastatic disease [8, 9]. A more nuanced understanding of this heterogenous propensity for brain metastases may consider specific biological differences among cell types utilizing specific pro-metastatic signaling pathways including NOTCH3, c-MET XIST, and a multitude of other factors [10–12].

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Accordingly, the management of brain metastases in patients with breast cancer in the modern era has become increasingly nuanced, with specific attention to a variety of patient factors, local therapy options, and an evolving landscape of breast cancer subtype-specific systemic therapies. In this review, we will outline principles for the approach to breast cancer brain metastases with specific attention to radiation therapy options including stereotactic radiosurgery (SRS) and whole-brain radiation therapy (WBRT) in the context of emerging systemic therapies that may impact current practice.

Management Principles of Breast Cancer Brain Metastases

Brain metastases in breast cancer, as is the case in most solid tumors, are often managed uniquely from extracranial disease due to the limitations of traditional systemic therapies in this setting. The brain is enshrouded by a distinct microvascular network lined by non-fenestrated endothelium with tight junctions and limited vesicle transport [13]. This "blood–brain barrier" (BBB) acts to limit the transit of circulating macromolecules from entering the brain parenchyma. Furthermore, the brain lacks a lymphatic system, for which it is considered an immunologically privileged site [14]. These factors limit the effectiveness of traditional chemotherapies, certain targeted therapies, antibody therapies, and potentially certain immunotherapies in the brain.

Brain metastases are also unique from extracranial disease in their capacity to cause significant neurologic and functional compromise with even modest local progression. As such, local therapy with surgery and/or radiation therapy is typically prioritized in the initial or early management of brain metastases. Neurosurgical resection may be favored to establish pathologic diagnosis or for large (> 3 cm), urgently symptomatic, or solitary brain metastases. Radiation therapy is a non-invasive alternative to neurosurgery for smaller, asymptomatic, unresectable tumors, and/or for patients with significant competing risks prohibiting neurosurgical resection.

Prognosis

Optimal management of breast cancer brain metastases necessitates a thorough assessment of patient factors including competing risks and overall prognosis. Although patients with brain metastases historically carried a grim prognosis with a median survival time of 6 months [15, 16], modern series of breast cancer brain metastases in the era of more effective systemic therapies including trastuzumab suggest more optimistic median survival estimates of 14.4 months overall and 23.1 months for those with HER2+ breast cancer [17]. Patient-specific prognostic factors include performance status, age, primary tumor site, and the presence of extracranial metastases, as identified through recursive partitioning analysis (RPA) of 1200 patients from three Radiation Therapy Oncology Group (RTOG) trials [18] and validated in a cohort of breast cancer patients treated with WBRT [19]. A more contemporary breast cancer-specific graded prognostic assessment (GPA) has also identified breast cancer subtype as a powerful prognostic factor which can in part be used to stratify patients into prognostic estimates of 3, 8, 15, and 25 months [20]. As such, any approach to management would be well supported by an improved prognostic estimate, so as to better weigh the intended benefits and risks of various treatments within a patient's expected lifetime.

Whole-Brain Radiation Therapy

For most patients with brain metastases, cranial radiation remains a key component of therapy, either as monotherapy or in combination with systemic therapy or surgery (Fig. 1). Patients with multifocal or urgently symptomatic brain metastases are commonly offered whole-brain radiation (WBRT), which remains a well-established and standard treatment option. The basis for utilization of WBRT stems from a study by Patchell et al. randomizing patients with a single brain metastasis to WBRT or observation after surgical resection [21]. The additional of WBRT significantly decreased in-brain recurrence both at the original site of disease and elsewhere in the brain. However, WBRT did not improve median survival, although it did decrease the risk of death from neurologic causes. Based on these data among others [22, 23], WBRT became a standard of care for patients with brain metastases. WBRT is typically delivered over 2 to 3 weeks to the entire brain parenchyma.

The use of WBRT for all patients with brain metastases has come into question given multiple studies demonstrating a neurocognitive detriment to WBRT. Brown et al. randomized patients with one to three brain metastases to receive SRS with or without WBRT with a primary endpoint of cognitive deterioration 3 months following treatment [24••]. Secondary endpoints included time to intracranial failure, quality of life, functional independence, long-term cognitive status, and overall survival. At 3 months, there was less cognitive deterioration (absolute difference between groups: 28.2%) and improved quality of life in patients who received SRS alone. There was no statistical difference in overall survival. For long-term survivors, the incidence of cognitive deterioration remained significantly less in the SRS alone group at 12 months. Chang et al. randomized patients with one to three brain metastases to SRS plus WBRT or SRS alone and similarly saw a cognitive decline with WBRT, as measured by the Hopkins Verbal Learning Test–Revised (HVLT-R) total recall at

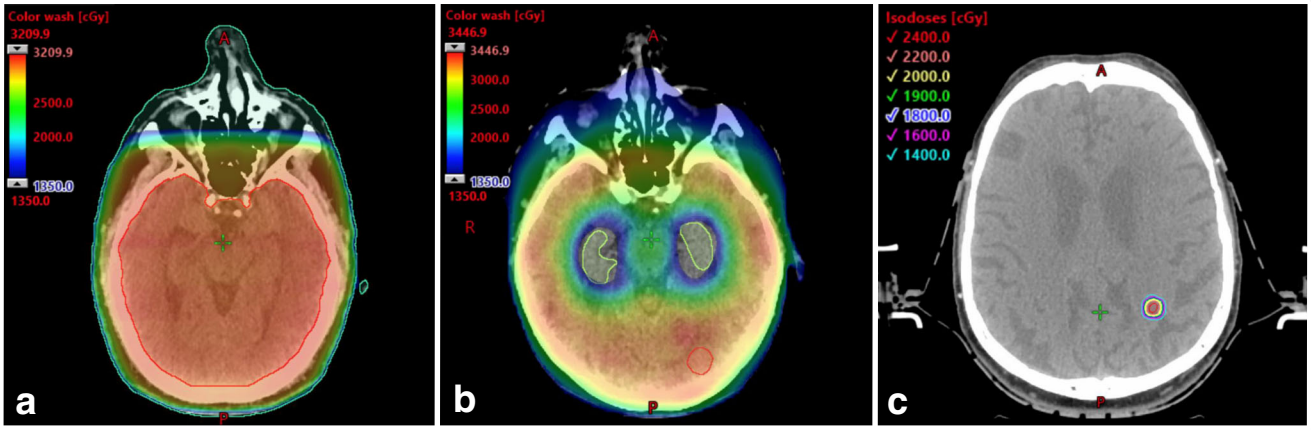

Fig. 1 Cranial radiation modalities. **a** Conventional whole-brain radiation therapy delivered with lateral opposed fields designed to deliver 30 Gy in 10 fractions to the entire brain parenchyma. **b** Hippocampal-avoidance whole-brain radiation therapy using volumetric modulated arc therapy (VMAT) and intensity-modulated radiation therapy (IMRT) treatment planning, designed to deliver 30 Gy is 10 fractions to the brain parenchyma while sparing a 5-mm avoidance region around the bilateral hippocampi. **c** Linear accelerator-based stereotactic radiosurgery using VMAT and IMRT treatment planning, designed to deliver 20 Gy in a single fraction to a single brain metastasis plus 1-mm margin

4 months [25]. However, those patients receiving SRS plus WBRT had a higher freedom from central nervous system (CNS) recurrence at 1 year (73% vs 27%; $p = 0.0003$).

Given the data demonstrating a neurocognitive detriment with WBRT, efforts have been made to investigate therapies by which to mitigate these deleterious effects. Radiation-induced neurocognitive decline is thought to be a result of injury to the neural stem–cell compartment of the hippocampal dentate gyrus [26–28]. Based on these data, investigators designed RTOG 0933, a single-arm phase II study examining the impact of hippocampal-avoidance WBRT (HA-WBRT) on cognitive function and quality of life [29]. The primary endpoint was the HVLT-R Delayed Recall (DR) at 4 months. When compared to a historic control, which demonstrated a 30% mean relative HVLT-R DR decline at 4 months [30], the mean relative decline in patients receiving HA-WRBT was 7.0% and there was no evidence of declining quality of life scores. These data provided the background for NRG-CC001, a randomized phase III trial of memantine and WBRT with or without hippocampal avoidance in patients with brain metastases. The primary outcome of this trial was time to cognitive function failure. Data presented in abstract form demonstrate that HA-WBRT prolonged the time to cognitive function failure, with those patients receiving HA-WBRT showing a 6-month incidence of neurocognitive failure of 59.5% versus 68.2% ($p = 0.03$) with standard WBRT, with differences noted starting around 3 months [31•]. There was a similar benefit demonstrated across all age groups. These data support the role for HA-WBRT in appropriately selected patients.

However, questions arise regarding the use of HA-WBRT in patients with poor prognoses given that the neurocognitive benefits of HA-WBRT over standard whole-brain radiation were not demonstrated until at least 3 months after completion of therapy. Additionally, HA-WBRT requires technical expertise for treatment planning and delivery, which may not be available at all radiation oncology facilities. HA-WBRT may also not be recommended in patients requiring urgent treatment as the time to treatment due to more technical radiation planning and quality assurance are usually longer than 1 week as compared to fewer than 2 days for standard WBRT. The cost of HA-WBRT is higher than standard WBRT so there may be a financial burden to patients with utilization of this approach. Lastly, this technique may not be appropriate for patients with brain metastases in the hippocampal avoidance region.

Another proposed approach to limiting the neurocognitive side effects of WBRT is prescribing memantine for patients receiving this therapy. Memantine is an *N*-methyl-D-aspartate receptor antagonist utilized in patients with vascular dementia. In two phase III trials, memantine was found to be well-tolerated and effective in improving cognition in treated vascular dementia [32, 33]. Based upon these data, RTOG 0614 randomized patients with brain metastases to receive placebo or memantine (20 mg/day for 24 weeks with escalating doses over the first 4 weeks) concurrent with and adjuvant to whole-brain radiation therapy for a total of 24 weeks [34]. The primary endpoint of the trial was preservation of cognitive function at 24 weeks as assessed by HVLT-R DR. There was less decline in HVLT-R DR for those patients receiving memantine, with a median decline of zero in this group compared to the placebo arm, which showed a median decline of − 0.90. There also appeared to be a benefit with memantine for other cognitive tests, including time to cognitive failure and

mini-mental state examination scores. There were no reported differences in grade 3–4 toxicities between the treatment arms, but side effects of memantine have been reported in other studies which include dizziness, confusion, headache, hypertension, and gastrointestinal problems.

Based upon these data, both memantine and/or HA-WBRT are considered in patients for whom WBRT is recommended. As above, there are a variety of considerations when selecting appropriate patients to receive HA-WBRT. Memantine is often considered for patients receiving WBRT but may not be recommended in patients already experiencing dizziness or borderline hypotension and may need to be discontinued due to intolerance.

Stereotactic Radiosurgery

Alternatively, patients with limited intracranial disease or patients who are ineligible for WBRT are increasingly offered more focal radiation options including stereotactic radiosurgery (SRS). SRS delivers relatively large doses of radiation to small, well-defined targets using a highly precise and accurate setup, often with complex distribution of dose. SRS typically refers a single-fraction of high dose radiation, but such treatments may also be divided into a very limited number of treatments, generally referred to as stereotactic radiotherapy (SRT) or stereotactic body radiotherapy (SBRT). In this way, SRS/SRT aims to intensify dose to effectively overcome mechanisms of radioresistance including DNA repair, hypoxia, and cell-cycle-dependent effects.

The basis for SRS draws from several randomized studies comparing SRS monotherapy with WBRT with SRS for the initial management of patients with limited (one to four) brain metastases [23, 24••, 25, 35]. EORTC 22952 [23] represents the largest of these studies, in which 359 patients with 1–3 newly diagnosed brain metastases were randomized to focal therapy (with either SRS or surgery per treating physicians) with or without WBRT. Although the addition of WBRT to SRS reduced the rates of 2-year progression at the initial site(s) of intracranial disease (31% vs. 19%, $P = 0.040$) and elsewhere in the brain (48% vs. 33%, $P = 0.023$), these benefits did not translate into an overall survival benefit, possibly related to the high rates of extracranial progression seen in this study (65%).

More recent studies have affirmed that while WBRT reduces the risk of local and regional intracranial disease progression relative to SRS alone, these benefits come at the cost of increased neurocognitive toxicity without improved survival. NCCTG N0574 [24••] randomized 213 patients with 1–3 newly diagnosed brain metastases to SRS alone vs. SRS plus WBRT and showed significantly higher rates of neurocognitive decline at 3 months as assessed by a battery of 6 tests (92% vs. 64%, $P < 0.001$), oddly with a trend for worse survival with WBRT (7.4 months vs. 10.4 months, $P = 0.92$).

For patients with resected brain metastases, post-operative SRS/SRT similarly appears to further reduce the risk of local disease recurrence within the surgical cavity. In practice, post-operative cavities may be treated in 1–5 fractions to a 0 to 10-mm margin around the tumor cavity [36•]. Mahajan et al. reported a randomized trial of post-operative cavity SRS vs. observation after brain tumor resection, in which SRS improved the 1-year freedom from local failure (72% vs. 43%, $P = 0.015$) [37••]. Additionally, a multi-institutional randomized trial of WBRT vs. cavity SRS for patients with 1–4 brain metastases after resection of one tumor showed that WBRT was associated with improved local control (80.6% vs. 60.5%, $P < 0.001$) and intracranial control (78.6% vs. 54.7% at 12 months, $P < 0.001$), but no differences in survival. There were higher rates of cognitive deterioration at 6 months with WBRT, particularly within the domains of immediate/delayed recall and processing speed [38].

In this context, definitive or post-operative SRS/SRT is being increasingly utilized for patients with limited brain metastases with a view of limiting or delaying the long-term neurocognitive impacts from WBRT. While the available data support initial SRS for patients with one to four brain metastases, there is considerable practice variation in selection criteria for SRS. Retrospective studies of SRS for ≥ 4 metastases from the US demonstrate reasonable survival with expected rates of distant intracranial control concordant with the above studies [39]. A prospective non-randomized study of SRS for up to 10 brain metastases from Japan shows comparable survival outcomes among those with 2–4 tumors and 5–10 tumors (10.8 months, P[non-inferiority] < 0.78) without an increase in SRS-induced complications [40]. There are currently no available randomized data to compare the efficacy and toxicity of SRS for multiple (> 4) brain metastases in a single radiation plan to WBRT. Data are also limited regarding the efficacy and toxicity of serial SRS over multiple courses targeting > 4 intracranial metastases. There are currently several studies that are actively investigating these questions with regard to efficacy and neurocognitive outcomes (clinicaltrials.gov, NCT03075072, NCT01592968, NCT02353000). Furthermore, the direct applicability of these available trial data to patients with breast cancer, for whom prognostic considerations, systemic therapy options, and competing risks may be unique, remains a limitation to current practice.

Leptomeningeal Disease

Patients with leptomeningeal rather than parenchymal CNS metastases represent a unique patient population. Due to the

significant morbidity of craniospinal irradiation, radiation in these patients is directed at symptomatic sites of disease. WBRT is often utilized in patients with obstructive hydrocephalus and/or cranial neuropathies. Radiation can also be used in patients with involvement of their lumbosacral spine causing symptoms such as lower extremity weakness or bowel or bladder dysfunction. Due to the multifocal involvement of the leptomeninges and concerns over rapid disseminated intracranial progression, a more focused, stereotactic approach is generally not recommended for these patients. However, retrospective data do suggest a more protracted natural history of leptomeningeal disease among patients with breast cancer relative to other solid tumors [41], potentially challenging our view and approach to carefully select patients with expectation for positive outcomes.

Role for Systemic Therapy in Conjunction With Brain Radiation

Traditionally, systemic therapies for breast cancer have played a more limited role in the treatment of breast cancer brain metastases. Although CNS activity has been reported for various endocrine therapies for both parenchymal and leptomeningeal metastases from breast cancer [42–44], this effect appears to be limited and less efficacious than CNS-directed local therapies. Conventional cytotoxic chemotherapies (i.e., cyclophosphamide, 5-FU, methotrexate, doxorubicin) likely have limited penetration beyond the intact BBB, but several reports do suggest higher than expected activity of these agents, possibly related to disruptions of BBB related to tumor vasculature [45]. Several studies have investigated capecitabine, temozolomide, etoposide, and platinum either alone or in combination for breast cancer brain metastases with some efficacy [46–49], and other studies are ongoing investigating newer agents like GRN1005, a paclitaxel-angiopep-2 conjugate designed to maximize CNS penetration (clinicaltrials.gov, NCT01679743) and anthracycline derivatives. The combination of platinum chemotherapy with bevacizumab also appears to have promising CNS response (77.1%) in early studies of patients with metastatic breast cancer [50], with additional studies currently underway (clinicaltrials.gov, NCT01004172). However, caution should be made with the interpretation of CNS response with anti-angiogenic therapies such as bevacizumab as these therapies alter the vascular permeability and resultant contrast enhancement of such tumors, but the radiographic changes may not actually correlate with biologic tumor response.

In contrast, there appears to be a growing promise of HER2-directed therapies specifically for the treatment of HER2-positive breast cancer brain metastases. Monotherapy with lapatinib, an oral small molecule inhibitor of EGFR and HER2, has been studied prospectively with a limited objective response rate (2.6%) [51], but response rates may be augmented with the addition of capecitabine (20%) [52]. Similarly, combination therapy with neratinib, EGFR, ERB4, and HER-2 inhibitor, and capecitabine appears to show promising response rates (49% by volumetric, 24% by RANO-BM criteria) in early reports [53]. Trastuzumab-emtansine (T-DM1) similarly shows some promise in limited case reports. It may also have a possible synergistic effect with SRS, but conversely, it may potentially increase the risk of radionecrosis [54•, 55, 56]. Prospective data are needed to better characterize this effect. There are also several new "targeted therapies" under investigation including PARP inhibitors, HDAC inhibitors, next-generation small molecule inhibitors of HER2, and PI3K inhibitors. Lastly, there is growing interest in exploring immunotherapy (i.e., checkpoint inhibitors, CAR (chimeric antigen receptor)-T cells) for breast cancer brain metastases, particularly in light of the recently reported efficacy of atezolizumab for metastatic triple-negative breast cancer [57]. In addition, there may be several strategies to optimize the immune-stimulatory effects of radiation therapy with immunotherapy [58], but presently, the CNS activity of immunotherapy is largely underreported in breast cancer.

These active investigations of systemic therapies with CNS efficacy are likely to alter our traditional approaches to CNS-directed therapy, including WBRT and SRS. While improved CNS activity of upcoming systemic therapies may bring new emphasis to SRS over WBRT, the ideal sequencing of these treatments along with the relative toxicities of systemic therapy relative to radiotherapy options remains unclear and in need of deliberate investigation.

Future Directions

The role of radiation therapy in the management of patients with breast cancer and CNS metastases continues to evolve. Although guidelines do not currently support the routine use of brain MRI for neurologically asymptomatic women with breast cancer, routine screening in subgroups of patients at higher risk of brain metastases has been proposed [59]. Should this be adopted, it is more likely patients would be diagnosed with asymptomatic and smaller CNS metastases, facilitating the use of SRS as opposed to WBRT and/or systemic therapies with CNS penetrance.

As discussed above, there are several currently enrolling studies examining the efficacy and toxicity of SRS in patients with greater than four brain metastases. As these data mature, it is possible that the number of patients in whom SRS is recommended continues to grow. However, this raises questions regarding the acute and long-term side effects for patients who have a large volume of brain treated with SRS due to a larger number of metastases treated in one course or

over several sequential courses. As systemic therapies continue to improve the overall prognosis for patients with breast cancer, the longer-term toxicities of SRS become increasingly relevant and worthy of further research.

Future studies should also seek to better understand how to optimally sequence brain radiation, whether SRS or WBRT, with newer systemic therapies, including targeted therapies and immunotherapies, particularly those that have longer half-lives than traditional cytotoxic chemotherapies. There have been concerns raised about increased toxicity with targeted therapies and immunotherapies administered in conjunction with SRS, particularly related to radionecrosis [60–64]. However, with prolonged half-lives of systemic therapies, it may not prove practical or advisable to delay brain radiation or resumption of systemic therapy after brain radiation in an effort to avoid concurrent delivery. Additionally, combining immunotherapy with SRS in melanoma has shown promise with regard to a synergistic effect between the therapies [65–67], so potential added toxicity will need to be weighed against increased therapeutic efficacy. Although immunotherapy and targeted therapy are currently used with less frequency in patients with breast cancer than in patients with other primary malignancies, caution should be exercised, and further prospective research should be pursued as the role for these therapies and the role for SRS likely expands in the breast cancer population.

Conclusions

Increasingly, stereotactic approaches for patients with brain metastases are preferred over WBRT, given concerns about the toxicities with whole-brain radiation therapy, earlier identification of brain metastases, and improvements in overall prognosis in patients with breast cancer. For patients with a significant number of intracranial metastases and/or leptomeningeal disease, WBRT remains standard of care. Methods by which to limit the neurocognitive side effects of WBRT include memantine and hippocampal-avoidance radiation therapy. Further research will be necessary to understand to the optimal sequencing of systemic therapy and CNS-directed radiation therapy and the potential role for surveillance brain MRI in breast cancer patients at high risk of intracranial metastasis.

Compliance with Ethical Standards

Conflict of Interest Shyam Tanguturi and Laura E. G. Warren declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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