REVIEW

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# LOCAL TREATMENT OF BREAST CANCER BRAIN METASTASES

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**Summary**

Breast cancer, along with lung cancer and melanoma, is one of the most common origins of central nervous system metastases. Due to improvement of systemic therapy options for primary disease and consequential prolonged survival, treatment of brain metastasis (BM) is presenting an evolving challenge. While new systemic therapy approaches for breast cancer brain metastasis are focusing on overcoming the blood brain and blood tumor barrier, as well as targeted therapies, local therapy remains the primary line of treatment. The decision of which local therapies to use, depends upon the number and volume of BM, their localization, patient's clinical status, previously used treatments, status of extracranial disease and patient's prognosis. In cases when an active approach, including surgery and/or radiotherapy, does not bring benefit to the patient's quality of life or overall survival, best supportive care is recommended.

KEYWORDS: *brain metastases; breast cancer; stereotactic radiosurgery; whole brain radiation therapy*

Breast cancer (BC), lung cancer and melanoma most common metastasize to the central nervous system (CNS)(1) with breast cancer being the number one solid tumor that causes leptomeningeal dissemination (LMD)(2). Several predictive factors for developing brain metastases (BM) have been recognized, including HER2+/ER- subtype, node positive disease, younger age, high histological grade and tumor larger than 2 cm(3). According to the recent study from Darlix, BM occur in about one quarter of BC patients (7.2% at the time of metastatic BC diagnosis)(4). After diagnosing breast cancer BM, overall survival median (OS) is 7.9 months, and it is even shorter for HER2-/HR+ (7.1 months) and triple negative subtypes (4.4 months)(4). Since systemic therapy for BC is improving and results in prolongation of OS in BC patients, CNS metastases, as a characteristic of late stage disease, are becoming a more frequent cause of death. Bendell et al. observed HER2+ patients treated with trastuzumab and recorded median OS for HER2+/HR- of 13 months with 50% of patients dying because of CNS disease(5). Developing systemic therapies for BM are being customized considering histologic subtypes of breast cancer and are trying to overcome the blood brain barrier and blood tumor barrier. For now, active local therapy in patients with a better prognosis and best supportive care in those with poor prognosis remains the primary line of treatment. Mostly used active local therapies of BM include surgery and radiotherapy in the form of whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT).

Even though approximately 15% of metastatic BC patients have occult BM, their OS is similar to those with symptomatic BM and there is no

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preventive screening program for BM in breast cancer(6). Therapeutic approaches distinguish BM disease into three groups: limited, extensive BM and leptomeningeal metastases. NCCN guidelines recommend choosing the initial management of BM depending on the number and volume of BM, their localization, status of extracranial disease, patient's clinical status and prognosis(7).

## LIMITED BREAST CANCER BRAIN METASTASES

Yamamoto et al. define limited brain metastases as a case where SRS is equally effective and offers significant cognitive protection compared to WBRT. They analyzed treating BM smaller than 3 cm and with total cumulative volume less than 15 ml with SRS and found a similar percentage of treatment-related adverse events in groups of patients with two to four BM as in those with five to ten BM(8). The decision whether to choose surgery or SRS for limited BM in patients with a good prognosis is a complex one. Ewend et al. propose using surgery for surgically accessible lesions, single lesions or dominant lesions, tumors larger than 3 cm, lesions that are causing mass effect or obstructive hydrocephalus and in the need of tissue diagnosis(9). Operative treatment of limited BM in patients with disseminated systemic disease and poor systemic treatment options is not recommended by NCCN(7). Adding WBRT to initial SRS for limited BM does not show significant difference in OS, increases risk for cognitive impairment and it is not recommended(7,10).

In a multicenter, randomized, controlled Phase 3 trial, Brown et al. compared adjuvant WBRT to adjuvant SRS applied to the surgical cavity. They found that patients with adjuvant WBRT had better local control of the disease and worse cognitive function compared to the SRS group, without a significant difference in OS(10). ASTRO (American Society for Radiation Oncology) guidelines recommend adjuvant single or multiple fraction SRS after resection of limited brain metastases. For lesions larger than 4 cm and smaller than 6 cm, or those causing mass effect, that cannot be resected because the patient is not suitable for operation, multiple fraction SRS may be considered(11,12).

In cases with recurrent limited BM possible treatment options include surgery and postoperative SRS or radiotherapy to the surgical bed and single-dose or fractionated SRT, according to NCCN. The NCCN guidelines also include WBRT, with or without hippocampal avoidance, but it may only be considered if it has not been administered before. SRT for a local site recurrence is also a treatment option in cases of a good response to previous SRS (progression free period longer than 6 months) and with no radiologic signs of necrosis(7). A newer method, laser interstitial thermal (LITT) ablation, is finding its place in treating recurrent tumors and radionecrosis (RN) in patients with stable systemic disease, especially in treating RN where LITT achieved up to 100% lesion control(7,13). In patients with poor performance status, with limited or extensive BM, and a progressing systemic disease with no promising systemic therapy options, ASTRO guidelines favor steroid therapy over WBRT, if the BM symptoms can be efficiently controlled(12).

## EXTENSIVE BREAST CANCER BRAIN METASTASES

Until recent years, the term *extensive* BM has been considered status over 4 BM, but with developing radiotherapy and surgery techniques, the terms *limited* and *extensive* BM disease are becoming susceptible to change. New studies are emerging, treating up to 10 or 15 BM with SRS, a modality usually reserved for limited BM(8,14). Extensive BM, if left untreated, have a median survival of 1 month(15) and with supportive care using steroids OS can be prolonged up to 2 months(16). WBRT alone can prolong life up to 5 months(17). In patients with a very poor prognosis and bad performance status, even with limited BM, supportive care is also a valuable treatment option according to NCCN (7). For determining patient's prognosis with BC BM, a new prognostic index (Breast-Graded Prognostic Assessment (GPA) was developed by Sperduto et al. and it includes several previously used prognostic factors: Karnofsky prognostic score (KPS) <70%, age, number of BM, tumor subtype and extra-cranial disease(18).

Conventional treatment for extensive BM would include WBRT with considering surgery prior to WBRT for dominant lesions causing

symptoms due to its localization(9). Adjuvant WBRT is known to improve local control and reduce distal brain recurrence. In a study done by Patchell et al., WBRT after surgical treatment of a solitary BM, prevented recurrence locally (10% versus 46% without adjuvant WBRT) and in distant parts of the brain (14% versus 37%)(19). In patients with extensive BM, adjuvant WBRT after resection of BM larger than 4 cm or those causing mass effect is not the only therapeutic option. Depending on the size of the lesions and patient's performance status, single fraction SRS or multiple fraction SRS, may also be considered(12). In order to decrease cognitive impairment accompanying WBRT and improve quality of life (QoL), hippocampal avoidance and memantine provide best results when applied together(20). This combination is recommended for patients with stable systemic disease, favorable prognosis and BM further than 5 mm from the hippocampus(7,20).

Although adding WBRT to surgery is known as a gold-standard in reducing local recurrence (LC) and distal brain failure(19), adding SRS to surgery has been analyzed in desire to find new ways to avoid cognitive impairment following WBRT. Garsa et al. made a systematic review of studies comparing adjuvant WBRT to adjuvant SRS and found higher QoL accompanying SRS (effect was measurable only 3 months after treatment, but not after 6 months) with no significant difference in OS(21). In this systematic review, the authors have not found any benefit in OS comparing adjuvant radiotherapy to surgery alone. Adjuvant SRS, compared to adjuvant WBRT, is associated with a higher risk of radionecrosis and LMD(22). Using preoperative SRS decreases risk of LMD (16.6% vs 3.2%, P = 0.010) and radionecrosis (16.4% vs 4.9%, P = 0.010), compared to postoperative SRS, with similar OS and local recurrence(23).

WBRT still holds its place as initial radiation treatment of extensive BM, but a newer study shows that it is possible to treat even up to 15 BM with initial SRS (iSRS), with similar OS, and with similar need for salvage WBRT, as in a group of patients with 2 to 4 metastases treated with iSRS(10). Volumetric modulated arc therapy (VMAT) and its usage of one isocenter for the whole brain in treating extensive BM, can shorten the time of irradiation. For example, 2 hours for SRS Gamma knife using one isocenter for each BM was reduced, to only 20 minutes(24). Raman et al. noted a longer intracranial progression free period with initial WBRT (iWBRT) (12.8 months) than with iSRS (2.5 months)(25). Comparing initial radiotherapy treatment for BM in the USA from the year 2005 to 2010, Barbour et al. identified that the percentage of iSRS increased from 8.7% to 17.9% while iWBRT decreased from 27.8% to 23.5%(26).

For recurrent extensive BM disease along with progression of systemic disease, NCCN recommends best supportive care. In cases with stable systemic disease, operation, salvage SRS, reirradiation and systemic therapy are possible options(7).

## LEPTOMENINGEAL METASTASES

Leptomeningeal metastases (LM) occur in about 5% of BC patients(27) and indicate a poorer prognosis. Breast cancer histology of BM is a known risk factor of LM development. This was concluded by Atalar and al. comparing different types of BM, treated with stereotactic radiosurgery targeting the postoperative resection cavity(28).

Median OS slightly differs between subtypes of BC: 4.4 months for HER2+, 3.7 months for HER2-/HR+ and 2.2 months for TNBC(29). Systemic chemotherapy and intra-cerebrospinal fluid chemotherapy can be used in cases with a good prognosis (KPS >60, minimal systemic disease, absence of major neurological deficit)(7). A recent study compared clinical outcomes in patients treated with intrathecal (IT) trastuzumab (all patients in this group were HER2+), IT methotrexate (or thiotepa) or WBRT alone. The results showed craniospinal progression free survival (CS PFS) with 6 month rates of 44%, 18%, and 26% for IT trastuzumab, IT chemotherapy, and WBRT(30). In patients with good prognostic factors mentioned above, SRS or radiotherapy (involved-field radiotherapy and/or whole brain) can be used to treat bulky disease and symptomatic sites(7). For patients with a poor prognosis, besides best supportive care, radiotherapy of symptomatic sites is also an option(7).

## CONCLUSION

New therapeutic managements are being developed in order to improve local and systemic

treatment of one of the most common types of brain tumor. For now, radiotherapy and surgery remain the most often used methods of local treatment of BM. In everyday clinical practice, brain irradiation is usually associated with cognitive deterioration, but newer techniques, including HA-WBRT in combination with memantine, SRS or SRT, are trying to reduce that effect.

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Sažetak

## LOKALNO LIJEČENJE MOŽDANIH METASTAZA RAKA DOJKE

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Rak dojke, uz tumore pluća te melanom, najčešći je tumor koji metastazira u središnji živčani sustav. Uslijed razvitka sistemske terapije primarne bolesti, i posljedičnog produljenog preživljenja bolesnika, liječenje moždanih metastaza predstavlja sve veći izazov. Dok se novi pristupi sistemskoj terapiji moždanih presadnica tumora dojke fokusiraju na savladavanje prepreke krvno-moždane i krvno-tumorske barijere te na ciljanu terapiju, lokalna terapija ostaje primarna linija liječenja. Odluka o izboru metode liječenja ovisi o broju i volumenu moždanih presadnica, njihovoj lokalizaciji, kliničkom statusu bolesnika, prethodno korištenim metodama liječenja, stadiju uznapredovalosti osnovne bolesti te prognozi bolesnika. U slučajevima kada aktivni pristup liječenju, koji uključuje operaciju i/ili radioterapiju, ne pridonosi kvaliteti života ili ukupnom preživljenju bolesnika, preporuča se najbolja potporna njega.

KLJUČNE RIJEČI: *moždane metastaze; rak dojke; stereotaksijska radiokirurgija; radioterapija cijelog mozga*