

Managing Brain Metastases in Patients with Advanced Breast Cancer

Brain metastases are an increasingly important cause of morbidity and mortality among patients with metastatic breast cancer (MBC). This clinical situation represents a therapeutic challenge for the treating physician and an emotionally and physically debilitating experience for the patient. While significant advances have been achieved in the treatment of MBC, more research is necessary to determine appropriate protocols for early diagnosis, proper surveillance, and effective treatments for MBC that has spread to the brain.

Brain metastases are the most common brain tumors seen in clinical practice today, comprising well over half of all brain tumors. The annual incidence of brain metastases in the United States is nearly 170,000 cases, compared with only 17,000 for primary brain tumors.ⁱ The risk of developing brain metastases varies according to primary tumor type. Approximately 15 percent of the brain tumor cases treated each year are the result of metastatic breast cancer (MBC). In fact, up to twenty percent of all breast cancer patients will experience a brain metastasis.

It is speculated that the annual incidence is rising for several reasons, better treatment of systemic disease, and the improved ability of imaging modalities, such as magnetic resonance imaging (MRI), to detect smaller metastases in asymptomatic patients.ⁱⁱ

A significant portion of women diagnosed with breast cancer has what is called HER2-positive breast cancer. Patients with HER2-positive breast cancer have cancer that over expresses the human epidermal growth factor receptor-2 (HER2).

Extra copies of the HER2 gene (commonly referred to as gene amplification) result in overproduction of the HER2 receptor, which is found on the outside of cancer cells. Patients whose tumors have an excess amount of these receptors are referred to as HER2-positive.

All women with breast cancer should undergo testing to determine if their cancer is HER2-positive.ⁱⁱⁱ Targeted therapies such as Herceptin[®], a monoclonal antibody, are highly effective at stopping the spread of cancer cells that overexpress HER2. Herceptin[®] is currently approved for the treatment of HER2-positive, metastatic breast cancer in combination with the chemotherapy agent Taxol[®] (paclitaxel, or as a single agent in women whose breast cancer has recurred following previous therapy).^{iv}

The natural history of breast cancer as a systemic disease has changed with the addition of Herceptin[®] and other treatments to control the disease or prevent recurrence. “While these therapies have made breast cancer more chronically survivable, we are seeing increased relapse at the Central Nervous

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System (CNS) when other sites are controlled,” says Dr. Frank Liebermann, director of the adult neuro-oncology program at The University of Pittsburgh Medical Center. “There appears to be a predilection for CNS metastatic sites in patients with HER2 metastatic breast cancer.”

“It is true that treatments for MBC have improved dramatically over the past 10 to 15 years,” says Dr. Eric Winer, Director of the Breast Oncology Center at the Dana Farber Cancer Institute in Boston. Previously, MBC patients were not often surviving long enough to develop brain tumors. Now we know that a significant percentage of MBC patients will be faced with a brain metastases. The risk is even greater for the HER2-positive patient population. By general estimates, 25 to 40 percent of HER2-positive patients will develop brain metastases in the first two years after they are diagnosed with metastatic disease” Dr. Winer says.

“The chemotherapy agents we have today are very effective in the body, but because of the blood brain barrier (BBB) they have not proven effective in the brain,” says Dr. Leonard Cerullo, neurosurgeon and founding member of the Chicago Institute of Neurosurgery and Neuroresearch. The importance of considering potential brain metastases early on in patients with MBC cannot be overstated. For patients with systemic disease that has a high propensity to metastasize to the brain, an MRI scan should be performed as a routine part of the initial diagnosis and during follow-up,” says Dr. Cerullo.

Classically, scanning the brain has not been considered part of the routine protocols that oncologists follow when managing a patient with metastatic disease. Typically, CT scans of the chest, abdomen and pelvis are performed. Only after neurologic symptoms occur, such as seizure, cerebral hemorrhage, or focal neurological deficit, would an imaging study of the brain be performed.

“In patients with MBC, the idea that early detection of brain metastases could have a positive impact on outcomes is an attractive paradigm,” says Dr. Frank Liebermann, director of the adult neurooncology program at The University of Pittsburgh Medical Center. “One could argue that by identifying asymptomatic metastases early we can increase survival and improve quality of life, but we don’t know that for sure. More research is needed. There is hope that if we can identify the subgroups within high risk

populations like MBC, we can develop preventative and surveillance strategies to diagnose and treat before the disease becomes metastatic.”

Dr. Cerullo emphasizes that early diagnosis of brain metastases is critical to effective tumor management. “If we can make the diagnosis before the patient becomes symptomatic, we can obviate the symptoms before they become damaging or permanent,” Dr. Cerullo explains. There are treatment options for patients with metastatic disease that has spread to the brain. The earlier we catch it, the more treatment choices we have.”

PROMISING THERAPIES

More funding for research is needed to develop better treatments for MBC that has spread to the brain. “While a moderate amount of research has been done, I think the treatment of brain metastases has been understudied,” says Dr. Winer. He and his team are investigating Lapatinib, an epidermal growth factor receptor (EGFR) and ErbB-2 (HER2/neu) dual tyrosine kinase inhibitor. “Lapatinib inhibits HER1 and HER2 breast cancers. It’s promising because unlike Herceptin, Lapatinib is a small molecule and appears to penetrate the blood brain barrier.”

Researchers from Germany recently treated a breast cancer patient with Herceptin that was administered intrathecally. The woman was 39 years old and had HER2-positive, metastatic breast cancer. Her cancer spread to one site in the brain, and this one lesion was surgically removed. She then received the chemotherapy agent Xeloda® (capecitabine) plus intravenous Herceptin.

When her condition worsened, she was treated intrathecally with the chemotherapy agent methotrexate. Her condition continued to deteriorate, so her physicians administered Herceptin intrathecally. Within two weeks of therapy, she had improved significantly. Furthermore, clinical symptoms and results from magnetic resonance imaging (MRI) showed that her cancer did not progress for 11 months following diagnosis of CNS spread. Intrathecal administration with Herceptin was very well tolerated.

The researchers concluded that, although this case report included only one patient, intrathecal administration of Herceptin might provide substantial improvements in slowing disease progression that has spread to the CNS among HER2-positive breast cancer patients.

Although this approach still needs to be tested extensively in clinical trials, these results are promising. In the future, intrathecal administration of Herceptin may be used to prevent spread to the CNS among women with HER2-positive breast cancer.^v

PATHOPHYSIOLOGY OF BRAIN METASTASES

Because physical factors contribute to the distribution of tumor cells, the location of brain metastases generally occurs in proportion to blood flow. Thus, about 80 percent of metastases are located in the cerebral hemispheres, 15 percent in the cerebellum, and five percent in the brainstem. As a brain metastasis grows and edema forms, the majority of patients present with a progressive focal neurologic deficit such as hemiparesis, aphasia, or visual field defect. Other typical features include headache, seizure, and cognitive dysfunction. Notably about a third of brain metastases may escape detection during life.^{vi}

TREATMENT DECISIONS

When making treatment decisions regarding patients with brain metastases, one must consider the status of the systemic disease, tumor type, Karnofsky performance status (KPS), patient's neurologic status, number of lesions, and the presence or absence of leptomeningeal disease. It has been shown repeatedly that the status of primary cancer remains the most important factor influencing survival in patients undergoing surgical resection. In addition, even in highly selected and aggressively treated patients with brain metastases, up to 70% of such patients die as a result of progression of the primary cancer, rather than neurologic causes. Therefore, the results of treatment of patients with poorly controlled systemic disease are often disappointing.^{vii}

The patient's preoperative neurologic status also correlates well with the outcome: patients with severe neurologic deficits tend to have shorter survival. Most current studies use the Radiation Therapy Oncology Group's (RTOG) Recursive Partitioning Analysis (RPA) or prognostic factors to assign patients with brain metastases to one of three prognostic classes. Factors evaluated to determine the RPA class of a patient includes KPS, status of primary disease, presence of extracranial metastases, and age. RPA class 1, which has the best prognosis, includes

patients with KPS \geq 70, age younger than 65, primary disease control, and no extracranial metastases; this group of patients has a median survival rate of 7.1 months. Patients in RPA class 3 include those with KPS of at least 60 and the worst prognosis. All other patients are categorized as class 2. Other factors negatively influencing survival are presence of multiple metastases, infratentorial location, and leptomeningeal spread. Computed tomography (CT) era data suggest that brain metastases from solid tumors tend to be single or solitary in 50 percent of patients at diagnosis. However, more recent studies based on magnetic resonance imaging (MRI) suggest that less than one third of patients have a solitary or single brain metastasis at the time of diagnosis of brain metastasis. Such a considerable difference in sensitivity is an indicator of the inadequacy of CT in determining the number of brain metastases or in detecting small (millimeter size) metastases.^{viii}

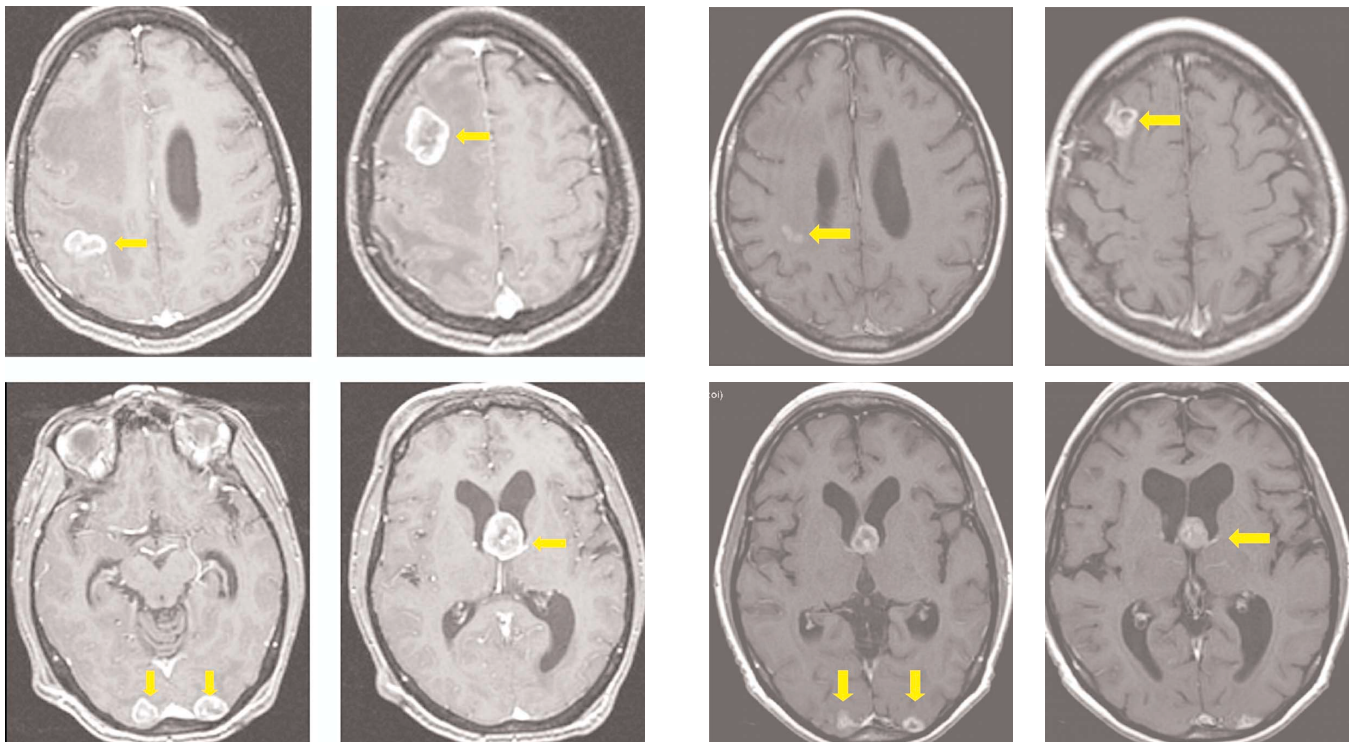
TREATMENT GOALS AND OPTIONS

Depending on the patient's age, functional status, extent of systemic disease, number of metastases, median survival ranges from 2.3 to 13.5 months. Management consists of supportive care and definitive therapy. Supportive care addresses brain edema, seizures, deep venous thrombosis, gastrointestinal complaints, psychiatric complications, and side effects from treatment.^{ix}

Definitive therapy for brain metastases is intended to restore neurologic function, improve quality of life, and extend survival. Therapeutic modalities that may be used singly or in combination include surgical resection, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), and more recently chemotherapy agents with some degree of central nervous system activity. The role of each of these modalities alone or in combination remains a frequent topic of discussion.^x

SURGICAL RESECTION

The current availability of other therapeutic modalities has clearly narrowed the indications for surgical resection. However, better imaging techniques and improved intraoperative navigation methods have contributed to improve the results of resection for selected patients harboring a single, larger brain metastasis in an accessible location.^{xi} Complete surgical removal of a brain metastasis



62 year old female with history of breast CA; systemic disease stable. Symptoms at presentation: memory difficulties, change in vision, headaches. Treated five metastases with Gamma Knife resulting in decrease in size of all tumors, decrease in edema and symptomatic improvement.

leads to immediate elimination of a mass compressing surrounding brain structures or causing blockage of the Cerebrospinal Fluid (CSF) flow, and removal of the source of perifocal edema. Surgery is particularly useful for patients with large (≥ 3 cm) lesions, especially those in the posterior fossa. Surgical patients may also benefit from a taper of steroids in the postoperative period, thereby reducing the risk of potential complications associated with their use.^{xii}

Surgical resection of metastases is also valuable to confirm or define the diagnosis. Even in an era of widespread use of novel imaging techniques (e.g., magnetic resonance spectroscopy, positron emission tomography), surgery remains the only treatment modality that provides actual tissue diagnosis.^{xiii}

Van der Ree et al^{xiv} reported that surgical resection of brain metastases, particularly in the posterior fossa, may cause leptomeningeal dissemination of the tumor. In their series, 33 percent of patients developed leptomeningeal metastasis two to 13 months after surgery. This included six of the nine patients operated on for posterior fossa metastasis. Some authors, therefore, suggest an en bloc removal of metastatic lesions.^{xv}

The justification for the use of surgical resection for the treatment of multiple brain metastases is less clear than it is

for single or solitary brain metastasis. Uncontrolled, retrospective studies suggest that patients with multiple brain metastases did not benefit from surgery, compared with the historical results with WBRT alone. These studies included patients with advanced disease or patients in whom only a fraction of the total number of metastases was treated with surgery. A significantly longer survival rate was found in patients in whom at least one lesion was not resected (14 v 6 months).^{xvi}

STEREOTACTIC RADIOSURGERY (SRS)

Increasing numbers of patients harboring brain metastases are undergoing stereotactic radiosurgery. This minimally invasive strategy can be performed either with the Leksell Gamma Knife[®] (Elekta, Inc., Atlanta, Georgia) or with a linear accelerator (linac). Current evidence shows that radiosurgery provides high local tumor control rates. It can be used to treat multiple brain tumors in a single session and can be repeated in the instance of local or remote recurrent disease. Numerous advantages exist to radiosurgery compared with WBRT or resection, including less invasiveness, patient preference, reduced incidence of short-term and long-term memory loss, and less depression and fatigue.^{xvii}

Radiosurgery provides better local control rates compared with WBRT alone and similar or better control rates than those reported for surgical resection followed by WBRT. At the same time, radiosurgery allows treatment of patients with multiple tumors while limiting brain irradiation. Stereotactic radiosurgery is performed as a single session procedure, so the patient can start with or continue to receive other systemic disease therapies allowing concomitant management of extracranial cancer. Radiosurgery-related morbidity is low, and mortality is close to zero.

Both safety and efficacy have been documented after radiosurgery alone. Many investigators now question the role of WBRT in the initial care of patients with brain metastases regardless of their RPA class. After stereotactic radiosurgery, patients can still undergo WBRT if follow-up images warrant this therapy because current doses used for radiosurgery have not been shown to be associated with higher risk of adverse radiation effects when added to conventional radiation therapy.

In a study evaluating long-term survival of patients treated with SRS for brain metastasis, Kondziolka et al^{xviii} reported that although the expected survival of patients with brain metastases may be limited, selected patients with effective intracranial and extracranial care for malignant disease can have prolonged, good-quality survival. Up to the year 2000, most patients received WBRT just before radiosurgery. However, Kondziolka and his team found that withholding initial WBRT might avoid short-term toxicity and longer-term cognitive problems in patients with limited brain disease. Because patients with fewer brain metastases and limited extracranial disease live longer, they are at risk for the development of new brain metastases with extended follow-up. For patients who have recurrent tumors after radiosurgery alone, later WBRT or repeat radiosurgery remain valuable options.^{xix}

WHOLE BRAIN RADIATION THERAPY (WBRT)

Whole brain radiation therapy has been used for decades as a mainstay of care for patients with brain metastases, increasing overall survival from two to six months from the time of brain tumor diagnosis. Different schemes (30–40Gy) and number of fractions (5–20 fractions) have been

evaluated by several Radiation Therapy Oncology Group (RTOG 69–01, RTOG 73–61, and RTOG79–61) studies, with no significant differences in survival detected.^{xx}

In patients who have brain metastases that impinge on eloquent areas, or are too large, numerous, or disseminated for surgery or radiosurgery, WBRT remains the treatment of choice and provides effective symptom relief in the majority of cases. Although response rates vary, complete or partial responses have been documented in more than 60 percent of patients in randomized controlled studies conducted by RTOG. The consensus of these studies is that differences in dose, timing, and fractionation have not significantly altered the median survival range of 2.4 to 4.8 months for patients treated with WBRT.^{xxi}

It is important to recognize that there are some arguments against the use of WBRT. Some question its ability to reverse neurologic symptoms and its use has been putatively associated with debilitating complications in long-term survivors. These data, however, are relatively weak, and WBRT remains the standard of care for patients with multiple brain metastases and for patients after radiosurgery or resection in the adjuvant setting.^{xxii}

SURGICAL RESECTION COMBINED WITH WBRT

Several investigators have examined whether WBRT is necessary after surgical resection of a brain metastasis. A retrospective review from the Mayo Clinic examined patients who had undergone surgical resection of a single brain metastasis followed by observation or WBRT. The authors found that 85 percent of the patients in the observation group subsequently experienced brain relapse (defined as local or distant tumor growth) whereas relapse occurred in only 21 percent of the patients treated with WBRT. Median survival was longer for the WBRT group as well (21 v 11.5 months).^{xxiii}

The benefit of surgery in the treatment of a single brain metastasis has been demonstrated in two prospective phase III studies. Patchell et al^{xxiv} prospectively randomly assigned 48 patients with a single brain metastasis to surgical resection followed by WBRT (WBRT; 36 Gy, 25 patients) or WBRT only (36 Gy, 23 patients). The median survival was prolonged significantly compared with the radiotherapy-only group (40 v 15 weeks; $P < .01$), as was

the length of functional independence (38 v 8 weeks; $P < .005$). Similarly, Vecht et al^{xxv} randomly assigned 63 patients to surgery and WBRT (40 Gy, 32 patients) versus WBRT only (40 Gy, 31 patients) and observed a significant prolongation in survival (10 v 6 months; $P = .04$) and a trend toward improved maintenance of functional independence (7.5 months v 3.5 months; $P = .06$).^{xxvi}

CONCLUSION

Management options for patients with brain metastases as well as the understanding of their related effects continue to evolve. Randomized studies in patients with multiple tumor types (not breast cancer exclusively) have shown an advantage of radiosurgery plus WBRT compared with WBRT alone in controlling tumors, improving quality of life, and prolonging survivals (in selected groups), so patients harboring four or fewer metastases at diagnosis should be considered for radiosurgery first. In patients with more than four metastases treated with WBRT and boost radiosurgery, further work is necessary to better define the roles of different options. It appears that the volume, rather than the number of tumors, is the defining variable.

Accessible larger lesions causing mass effect that fail to respond to steroid therapy should be resected followed by radiotherapy or radiosurgery.

Despite some element of nihilism to patients in poorer condition (RPA class), there are increasing numbers of reports showing benefit in improving survival and tumor control with multimodal management of brain metastases and extracranial cancer. A better understanding of the effects of interventions should result in improved patient care.^{xxvii}

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