Diagnosis and Management of Central Nervous System Metastases from Breast Cancer

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ABSTRACT

The brain, cranial nerves, leptomeninges, spinal cord, and eye compose the central nervous system (CNS) and are at risk for the development of metastases from breast cancer. Such metastases are diagnosed on the basis of clinical suspicion and substantiated by neuroimaging, resection when indicated, and sampling of cerebrospinal fluid when leptomeningeal metastasis (LM) is suspected. Treatment is aimed at palliation of symptoms and preservation of neurologic function. Historically, conventional radiation therapy has been the mainstay of palliative treatment for brain, cranial nerve, spinal cord, and ocular metastases. However, additional treatment options for brain metastases have been brought about by technological advances in surgery to resect brain metastases, and stereotactic radiosurgery (SRS) to focally irradiate metastases, both of which have been substantiated by data from randomized trials. Ongoing research is aimed at refining criteria to select which patients with brain metastases should undergo surgery and SRS and how these focal therapies should be optimally integrated with whole-brain radiotherapy. Therapy for LM must carefully balance the potential risks and perceived benefits associated with CNS-directed therapies. Despite advances in neuroimaging, surgery, and radiation therapy, novel treatments are needed to improve the effectiveness of treatments for CNS metastases, especially LM, while reducing attendant neurotoxicity.

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INTRODUCTION

The brain, cranial nerves, spinal cord, leptomeninges, and eyes compose the central nervous system (CNS) and can be at risk for developing metastases from breast cancer. Metastasis to the brain is diagnosed in patients with breast cancer at a rate of 10%-20%, making breast cancer the second most common...
source of brain metastases [1-3]; the true prevalence, however, as determined on the basis of autopsy data, could be as high as 30% [4]. Patients with breast cancer rarely present with manifestations of brain metastasis before detection of the primary breast cancer [5]. The median interval between the diagnoses of breast cancer and brain metastasis is 34 months [2]. Brain metastasis is usually associated with aggressive tumor behavior, a negative hormone-receptor status, relatively young age (premenopausal), and the presence of lung and liver metastases. In most series, no relationship has been found between the primary tumor size and number of positive lymph nodes and the development of brain metastases [6, 7].

The estimated frequencies of leptomeningeal metastasis (LM) in clinical and autopsy series of patients with breast cancer are 2%-5% and 3%-6%, respectively [8]. The incidence of epidural spinal cord compression in patients with breast cancer is reported to be 4% [9]. Breast cancer metastasizes to the eye at a higher rate than do other primary cancers [10].

**Diagnostic Considerations**

The diagnosis of brain metastasis is made on the basis of clinical suspicion that must be confirmed by contrast-enhanced computed tomography (CT) or, preferably, magnetic resonance imaging (MRI) of the brain. According to one series, patients with brain metastases from breast cancer presented with motor symptoms including deficit and gait disturbances (24%), seizures (23%), headaches (16%), cognitive dysfunction (14%), nausea and vomiting (11%), cranial nerve dysfunction (10%), cerebellar symptoms (2%), and speech disturbances (2%) [4].

MRI is the most sensitive method of detecting brain metastases. For brain metastases, the term ‘solitary’ indicates the absence of extracranial metastatic disease, whereas the term ‘single’ merely indicates the presence of one brain metastasis with no implication as to the status of extracranial disease [5].

In the case of solitary metastases, surgical resection should be performed if possible to firmly establish the diagnosis of brain metastasis because this is the first manifestation of metastatic disease. A brain lesion could represent an abscess, glioma, or even meningioma, since patients with breast cancer have a slightly higher incidence of meningioma than does the general population [11, 12]. It should be noted that a biopsy-proven false-positive rate of 11% for presumed single brain metastases was reported in patients undergoing screening for a randomized brain metastasis trial [13]. The management of single brain metastases, which constitute up to 50% of all brain metastases presentations, deserves special consideration. While surgical resection remains the gold standard for the treatment of single brain metastases, it is important to adequately stage the extent of metastatic brain disease preoperatively with MRI because occult metastases undetected on CT may render surgery inappropriate if multiple metastases are present [14]. For ambiguous single brain lesions suspected to be brain metastases but too small to resect, observation with serial MRI studies until tumor growth can be confirmed may be prudent [15, 16]. A treatment algorithm for the primary treatment of brain metastases is presented in Figure 1.

**Management of CNS Brain Metastases**

**Medical Treatment**

Symptomatic therapy involving medical treatment is aimed at stabilizing the acute neurologic symptoms caused by peritumoral edema and controlling seizures. Headache,

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![Primary therapy for metastatic brain disease](image_url)

*Whether surgery or SRS is offered depends on the size and location of the tumor and the presence or absence of pressure effects. Lesions >3 cm are, in general, not suitable for SRS. Lesions causing significant pressure effects are best treated with surgery, if feasible. Lesions located in eloquent areas, such as the motor or speech cortex, may not be considered suitable for surgery.*
nausea, vomiting, and mental status changes are the most common signs and symptoms of elevated intracranial pressure. Dexamethasone should be given immediately to patients with these symptoms, typically with a loading dose of 10-20 mg followed by doses of 4 mg four times a day. An H$_2$-receptor antagonist, such as famotidine, should be given concurrently to protect against gastritis [17], and trimethoprim-sulfamethoxazole may help prevent Pneumocystis carinii pneumonia [5]. The treatment of patients presenting with seizures is straightforward and involves the use of standard anticonvulsants, such as phenytoin, carbamazepine, and sodium valproate [18].

Patients with brain metastases who receive anticonvulsant therapy have a greater incidence of allergic reactions, and clear evidence that anticonvulsant therapy reduces the incidence of seizures in patients who have never had a seizure is lacking. Therefore, routine prophylactic anticonvulsant therapy is probably unnecessary, except in cases of brain metastases located in the motor cortex and cases involving synchronous brain metastases and LM [5].

**Whole-Brain Radiotherapy for Brain Metastases**

Whole-brain radiotherapy (WBRT) is considered standard treatment for patients with brain metastases and may prevent or delay progression of neurologic deficits, restore function, and decrease steroid dependency [19-22]. On occasion, a robust radiographic response of multiple brain metastases from breast cancer also can be observed (Fig. 2).

A frequently prescribed WBRT regimen used in the U.S. to treat brain metastases is 30 Gy in 10 fractions, but the fractionation schedule should be tailored to patient prognosis so that late toxicity of WBRT can be minimized in long-term breast cancer survivors. The results of WBRT alone for brain metastases from breast cancer are shown in Table 1. Data from the Cleveland Clinic [23], Humboldt University in Berlin [24], and Karolinska Hospital in Stockholm [25] showed a median survival ranging from 4.2 to 6.5 months (26 weeks). The prognostic factors implicated are also shown in Table 1.

Dural-based metastases from breast cancer can be palliated with radiation therapy. If a dural lesion is isolated and less than 3 cm in diameter, it can be treated with stereotactic radiosurgery (SRS), otherwise focal techniques using conventional radiation may be used. If a dural lesion is accompanied by parenchymal metastases, WBRT can be used to treat both the dural and parenchymal brain metastases simultaneously. Similarly, isolated skull base lesions that are frequently associated with cranial nerve deficits are appropriately treated with limited-field irradiation encompassing the entire base of the skull. Care should be taken to allow for cranial irradiation

![Figure 2. Treatment response to WBRT in a patient with multiple brain metastases from breast cancer.](image_url)
Toxicity of WBRT

The acute toxicities of WBRT include headache, nausea, possible vomiting, blockage of ears, mild-to-moderate fatigue, hair loss, and mild scalp erythema leading to skin hyperpigmentation. Hair usually returns after 3-6 months, but occasionally hair loss may be permanent and may be due to dose ‘hot spots’ created by tangential radiation beams over the vertex of the head. Long-term survivors may be at risk for developing progressive dementia, ataxia, and even urinary incontinence. CT identified cortical atrophy and hypodense white-matter changes in one study [26]. Those changes were most likely due to demyelination secondary to irradiation of the brain [27]. Unusually large fractions of radiation (3-6 Gy) may have contributed to a greater incidence of late toxicities. On the basis of results from that study, fractionation schemes with smaller fraction sizes, such as 30 Gy in 12 fractions of 2.5 Gy/day or even 30 Gy in 15 fractions of 2 Gy/day, may need to be considered for patients with favorable prognostic factors.

Table 1. Brain metastases series representing breast cancer patients

<table>
<thead>
<tr>
<th>Institution</th>
<th>n of patients</th>
<th>Treatment</th>
<th>Survival duration</th>
<th>Prognostic factors</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.D. Anderson Cancer Center [33]</td>
<td>63</td>
<td>Surgery + WBRT</td>
<td>16 months</td>
<td>Menopause, WBRT, systemic disease, neurologic status, age</td>
<td>54 patients (86%) received WBRT; Surgery only in nine patients</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering Cancer</td>
<td>70</td>
<td>Surgery + WBRT</td>
<td>16.2 months</td>
<td>Estrogen-receptor status, WBRT, leptomeningeal disease</td>
<td></td>
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<tr>
<td>Center [32]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SRS</td>
<td></td>
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</tr>
<tr>
<td>Miami Neuroscience Center [101]</td>
<td>68</td>
<td>Gamma knife radiosurgery + WBRT</td>
<td>7.8 months</td>
<td>Survival independent of number of lesions treated</td>
<td>38 patients previously received WBRT; average of eight lesions treated per patient</td>
</tr>
<tr>
<td>University of Pittsburgh [102]</td>
<td>30</td>
<td>Gamma knife radiosurgery + WBRT</td>
<td>13 months</td>
<td>Solitary metastasis</td>
<td>Tumor control 93%</td>
</tr>
<tr>
<td>WBRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleveland Clinic [23]</td>
<td>116</td>
<td>WBRT</td>
<td>4.2 months</td>
<td>KPS</td>
<td>Patients treated with WBRT alone</td>
</tr>
<tr>
<td>Humboldt University, Berlin [24]</td>
<td>162</td>
<td>WBRT</td>
<td>26 weeks</td>
<td>KPS, primary tumor size, dose, solitary</td>
<td>WBRT, 30 Gy in 15 fractions</td>
</tr>
<tr>
<td>Karolinska Hospital, Stockholm [25]</td>
<td>99</td>
<td>WBRT</td>
<td>5 months</td>
<td>Extracranial disease</td>
<td>Median time from breast cancer diagnosis to brain metastasis was 33 months</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian Oncology Group [103]</td>
<td>56</td>
<td>Front-line chemotherapy: platinum, etoposide, median 3 cycles, (range 1-8)</td>
<td>31 weeks</td>
<td>—</td>
<td>Post-chemotherapy WBRT may have confounded results</td>
</tr>
</tbody>
</table>

to be given at a future date in case brain metastases develop. This can be accomplished by giving 10 2.5-Gy fractions of radiation to the base of skull, allowing for a subsequent course of 10 3-Gy fractions of cranial irradiation to be given. The optic chiasm should be appropriately blocked to avoid optic neuropathy.

Surgery for Brain Metastases

The goals of surgery in the management of brain metastases are to obtain immediate symptom relief, gain local control of the metastasis, and confirm the diagnosis histologically [28]. Most lesions are surgically accessible due to improvements in stereotactic techniques, cortical mapping, and the use of ultrasonography [29]. For the general population of patients with brain metastases, a landmark randomized trial demonstrated that selected patients with resectable single brain metastases randomized to undergo resection and WBRT survived longer than did those who received biopsies and WBRT alone [30]. This randomized trial and a confirmatory trial have established surgery and postoperative irradiation as
the standard approach for such patients [31]. Retrospective data from the Memorial Sloan-Kettering Cancer Center [32] and the M.D. Anderson Cancer Center [33] on the surgical treatment of brain metastases from breast cancer showed median survival times of approximately 16 months (Table 1).

**Stereotactic Radiosurgery for Brain Metastases**

The hallmark of SRS is the rapid dose fall-off at the target edges, permitting a clinically significant dose to be given to the target while a clinically insignificant dose is delivered to the surrounding brain [28]. The combined experience from multiple institutions using SRS for single brain metastases considered eligible for resection showed that SRS and WBRT for a single brain metastasis produced a median survival of 56 weeks [34]. The advantages of SRS include lower risks for hemorrhage, infection, and tumor seeding, as well as lower costs from not requiring hospitalization. On the other hand, surgery immediately relieves the mass effects, provides a pathologic diagnosis, and has no risk of radiation necrosis [35]. In the Radiation Therapy Oncology Group (RTOG) 95-08 trial, patients with one to three brain metastases were randomized to receive WBRT either alone or with SRS. The results showed a survival benefit associated with SRS for patients with single metastases [36, 37]. It was also noted that patients in the WBRT plus SRS group were more likely to have stable or improved performance statuses than were members of the WBRT alone group.

**Adjuvant WBRT**

The role of postoperative radiation therapy for brain metastases not exclusive to breast cancer has been examined by several retrospective studies, most of which did not demonstrate any survival benefit associated with postoperative WBRT [26, 38-42]. The only prospective randomized study included mostly patients with lung cancer but also included nine patients with single brain metastases from breast cancer who were treated with complete surgical resection and then randomized to undergo either postoperative WBRT or observation. Recurrence was significantly less frequent in the WBRT group (18%) than in the observation group (70%) (p < 0.001). The incidence of neurologic death was also lower in the postoperative WBRT group (14% versus 44%, p = 0.003). Overall survival did not differ significantly between the two groups. The investigators in that trial concluded, on the basis of a demonstrable lower number of neurologic deaths, that postoperative WBRT should be given routinely [43], but this point is highly controversial in the neurooncology community.

The role of adjuvant WBRT in the setting of radiosurgery has been retrospectively investigated, and the outcomes were reported from 106 patients with single or multiple brain metastases who were managed initially with SRS or with SRS followed by WBRT [44]. In both treatment groups, the median survival was on the order of 11 months. The group treated with SRS alone had a significantly higher rate of tumor progression in the brain at 1 year (69%) than the group receiving SRS plus WBRT (28%). A multi-institutional study retrospectively analyzing 569 evaluable patients treated with SRS either alone or with WBRT for brain metastases resulted in a conclusion that the omission of up-front WBRT did not seem to compromise length of survival in patients treated with SRS for newly diagnosed brain metastases [45].

**Intracavitary and Interstitial Brain Irradiation**

The GliaSite® Radiation Therapy System (RTS) (Proxima Therapeutics; Alpharetta, GA; http://www.gliasite.com) has been approved by the U.S. Food and Drug Administration for delivering intracavitary radiation for the treatment of brain tumors. Evaluation of the GliaSite® RTS for the treatment of resected solitary brain metastases is ongoing in a multicenter prospective phase II study. It is a single-applicator system that is used to deliver a conformal dose of 60 Gy of radiation to a depth 10 mm beyond the resection cavity at risk for recurrence. The radiation source consists of Iotrex® (125I radiotherapy solution) infused through the GliaSite® RTS catheter, which has a dual silicone balloon configuration at the distal end. The inner balloon acts as a reservoir for the Iotrex®, while the outer balloon acts as a backup reservoir in case the integrity of the inner balloon is compromised. The primary end point of that study is the 1-year local control rate of a resected solitary metastasis treated with GliaSite® RTS.

Cosgrove, et al. reported the use of a novel SRS device for interstitial irradiation of malignant brain tumors. Fourteen patients with cerebral lesions less than 3.5 cm in greatest diameter were treated with 12.5 Gy of radiation. Local control was obtained in 10 of the 13 patients with tumors, with a mean follow-up of 12 months. However, the use of this system has not been popularized [46].

**Repeat Cranial Irradiation**

Of the two types of repeat irradiation (SRS and WBRT), SRS is preferable if it can be done, because it can spare normal brain from being irradiated. Repeat WBRT should be reserved for patients with greater than three recurrent lesions who have limited systemic disease, good performance status, and a controlled primary. Not infrequently, the radiation oncologist may be called upon to consider reirradiation in cases in which patients who have already received WBRT develop new or progressive brain metastases. The results of a study examining reirradiation with SRS in the context of
prior WBRT were reported [47]. That study involved 18 patients with 21 recurrent or persistent brain metastases treated with SRS. Patient eligibility requirements for treatment were Karnofsky Performance Score (KPS) ≥70 and stable systemic disease. With a reported median follow-up of 9 months, all tumors treated were controlled and no cases of symptomatic radiation necrosis occurred. Breneman et al. reported a series of 84 patients (79 of whom had recurrent brain metastases and prior WBRT) with brain metastases treated with SRS [48]. The median survival time and median time to failure were 43 weeks and 35 weeks, respectively. Noel et al. reported a 2-year local control rate of 84%, a 2-year brain control rate of 57%, and a 2-year overall survival of 28% for 54 patients treated with SRS for recurrent brain metastases [49].

The RTOG 90-05 study was initiated to study the maximum tolerable dose of single-fraction SRS in patients with previously irradiated primary brain tumors or brain metastases [50]. Multivariate analysis showed that maximum tumor diameter was associated with a significantly greater risk of grade 3, 4, or 5 neurotoxicity. The following dose recommendations were made: 24 Gy for tumors ≤2 cm, 18 Gy for tumors 2-3 cm, and 15 Gy for tumors 3-4 cm in maximum diameter [51].

When recurrences following WBRT are too numerous to treat with SRS, carefully evaluated reirradiation with WBRT can be considered. The largest published series on external beam reirradiation of brain metastases involved 86 patients from the Mayo Clinic [52]. The median survival following reirradiation was 4 months. There was complete symptom resolution in 27%, partial resolution in 43%, and no change or worsening of neurologic symptoms in 29% of patients. No significant toxicity related to reirradiation in the majority of patients was reported. The absence of extracranial disease was associated with greater survival on multivariate analysis. A treatment algorithm for recurrent metastatic brain disease based on our own practice is presented in Figure 3.

**Radiation Sensitization for Brain Metastases**

RSR13 (efaproxiral; Allos Therapeutics; Westminster, CO; http://www.allos.com) is an allosteric modifier of hemoglobin that decreases the affinity of hemoglobin binding to oxygen, permitting greater oxygenation of hypoxic tumor cells to theoretically enhance radiation cell killing. A multicenter, randomized, open-label phase III study was completed, involving 538 patients, 107 of whom were prestratified breast cancer patients, demonstrating a doubling in median survival time among eligible patients with metastatic breast cancer who received WBRT plus RSR13 versus WBRT alone (9 months versus 4.47 months, \( p = 0.002 \)). Preliminary results will be reported at a scientific meeting and are available online [53]. A confirmatory trial focused on brain metastases from breast cancer is currently planned.

**Chemotherapy for Brain Metastases**

The role of chemotherapy for the treatment of brain metastases has not been defined [5]. Because of the blood-brain barrier, chemotherapy is rarely used as part of the treatment plan for brain metastases. A study was conducted by Rosner et al., who treated 100 patients with brain metastases from breast cancer [54]. Fifty percent of patients had an objective response (10% complete response and 40% partial response), whereas 9% had stable disease. The median duration of remission was 10 months for those who had a complete response and 7 months for those who had a partial response. The most common regimens used were CFP (cyclophosphamide, 5-fluorouracil, and prednisone) and CFPMV (CFP plus methotrexate and vincristine). Rosner et al. used the same regimens and added cyclophosphamide and doxorubicin for an additional 26 patients with progressive brain metastases from breast cancer. The median survival time in that study was 12 months for responders but only 2.4 months for nonresponders [55].

![Salvage therapy](image)

**Figure 3. Treatment algorithm for recurrent brain metastases.**
More recently, temozolamide has been investigated. It is an agent with a good safety profile that crosses the blood-brain barrier and has shown activity against many solid tumors. Early data showed that the drug was safe and well tolerated and demonstrated antitumor activity [56]. A phase II trial showed partial response and disease stabilization rates of 4% and 17%, respectively, in heavily pretreated patients with brain metastases from solid tumors (four of 27 patients had breast cancer) [57]. Another phase II trial showed 6% and 44% partial response and disease stabilization rates for patients with recurrent or progressive brain metastases [58]. The median survival was 6.6 months. Clinical activity against brain metastases from breast cancer was shown for capecitabine in one case report [59].

**MANIFESTATIONS OF CNS METASTASES OTHER THAN BRAIN**

**LM**

LM is an increasingly common complication of breast cancer [8, 60], and breast cancer accounts for the largest number of patients in most large series evaluating LM [61]. Both clinical and autopsy series confirm the propensity of lobular carcinoma to spread to the leptomeninges, although the reason for this propensity is not known [62-64]. The occurrence of LM can range from weeks to more than 15 years from the initial breast cancer diagnosis [65, 66]. Although patients with cancers other than breast tend to have widespread metastatic disease when LM is diagnosed, patients with breast cancer may develop LM even when systemic disease is under control or absent [67]. A diagnostic MRI showing LM enhancement of the brain can be seen in Figure 4.

Spinal symptoms, particularly leg weakness, constitute the most frequent presentation of LM and are often accompanied by paresthesia. The simultaneous occurrence of multifocal abnormalities at more than one level of the neuraxis, from cerebrum, cranial nerve, or spine, is highly suggestive of LM [68]. The obstruction of cerebrospinal fluid (CSF) flow can lead to headache, changes in mentation manifested as lethargy, confusion, and memory loss, nausea, vomiting, and ataxia. Seizures are rarely the presenting symptom. Mental status changes are the most common finding of cerebral dysfunction. Diplopia, facial weakness, and diminished hearing are the most frequent cranial nerve findings [65, 66].

The demonstration of malignant cells in the CSF by lumbar puncture is the definitive method for diagnosing LM. The success of obtaining malignant cells depends on the amount of CSF available for analysis and increases with additional spinal taps. An elevated CSF protein level and a mononuclear pleocytosis are commonly present. Less frequently, a pathologically abnormal CSF glucose level <70% of the serum glucose level is discovered. The CSF carcinoembryonic antigen (CEA) level is elevated in some cases of breast carcinoma metastatic to the leptomeninges, but must be compared with the serum CEA level because CEA can cross the blood-brain barrier. Elevated CEA levels in CSF may be a result of elevated serum CEA levels [69]. Neuroimaging is necessary to help diagnose and define the extent of disease, which may be as low as the cauda equina (Fig. 5), and to determine whether parenchymal brain metastases exist. Patients with LM require MRI of the entire brain and spine to identify bulk disease. Radiation therapy is focally directed to bulky or symptomatic sites of disease along the craniospinal neuraxis. Intrathecal chemotherapy administration follows radiation therapy. Cerebrospinal fluid flow studies are needed for patients with normal imaging to show flow abnormalities that may interfere with the delivery of intrathecal chemotherapy and that may be relieved with focal irradiation [70]. The preferred route of administration of chemotherapy is intraventricular, to assure steady therapeutic levels into the CSF. The standard agents administered intrathecally are limited to methotrexate, thiopeta to a lesser extent, and rarely cytarabine, except in the form of a DepoCyt® (SkyePharma; London, UK; http://www.skye pharma.com), a recently available slow-release preparation.
that can be administered once every 2 weeks. A randomized trial comparing DepoCyt® with intrathecal methotrexate in patients with neoplastic meningitis showed similar response rates and a significantly greater time to neurological progression (58 days versus 30 days) [71]. Although a number of agents, including mafosfamide (a derivative of cyclophosphamide), busulfan, topotecan, diaziquinone, interferon, monoclonal antibodies, and interleukin-2, as well as gene therapy, are under active investigation, these are limited to use in the setting of experimental protocols and are not widely available [72]. There is no agreed upon standard regarding the best therapy. Therefore, expected complications may be the overriding factor in deciding whether or not to give treatment that may have a profoundly negative effect on the quality of life of patients with short-term life expectancies [70].

Neurotoxicity from Treatment of LM

All CNS-directed therapies designed to treat LM are associated with high rates of complications [70]. The most serious potential delayed toxicity that can occur from cranial irradiation is leukoencephalopathy, which is diagnosed by MRI. Typical findings of leukoencephalopathy include periventricular white-matter hyperintensity on T2-weighted and fluid attenuated inversion recovery (FLAIR) images, brain atrophy, and ventricular dilatation. Symptoms include cognitive decline, behavioral changes, gait abnormalities, and seizures. The use of radiotherapy with chemotherapy, especially methotrexate, may enhance the likelihood of developing leukoencephalopathy but may not be clinically significant because of the very limited prognosis of patients with LM [73].

While the Ommaya reservoir provides a consistent means of achieving therapeutic drug levels, surgical complications from the Ommaya reservoir may arise in up to 10% of cases. A very high complication rate of about 70%, ranging from 37% to 84% in 14 series, has been reported on intra-CSF chemotherapy [70]. Severe and life-threatening complications account for 20%-45% of all complications, including neutropenia, sepsis, meningitis, decline in consciousness, and ascending myelopathy. Treatment-related deaths are reported to occur at a rate of about 5%. Aseptic meningitis is a frequently encountered complication directly related to intra-CSF injection and occurs at a rate of about 5%. Unrelated to any specific agent injected into the CSF, aseptic meningitis is marked by an abrupt onset of headache, stiff neck, nausea, vomiting, lethargy, and fever several hours after the injection and may last for 12 to 72 hours.

Focal radiation therapy is used to palliate symptomatic cranial neuropathies and bulky tumor deposits that may impair CSF flow and delivery of intrathecal drugs. Chemotherapy is used to treat the entire CSF compartment. Craniospinal irradiation is not indicated as a first-line therapy in the treatment of LM because it can cause severe myelosuppression, precluding subsequent chemotherapy. In our experience, craniospinal irradiation may be occasionally offered as palliation for increased symptoms related to LM as a last measure in the setting of intrathecal chemotherapy failure [74].

Spinal Metastases

Epidural metastases arise most commonly from the vertebral column (85% of cases) and less commonly from the paravertebral space, invading the epidural space through bone or the neuroforamen [75]. The vertebral column is the most common site for bone metastases, with incidences of 60% in patients with breast cancer [76] and up to 84% in those with advanced breast cancer (Fig. 5) [3]. Epidural spinal cord compression occurs with an incidence of 4% in patients with breast cancer [9]. Spinal cord damage results from direct compression of the spinal cord by the tumor rather than from compression of radicular arteries [3]. The median time from diagnosis of breast cancer to epidural spinal cord compression is 42 months [9]. The thoracic...
spine is most commonly involved in cases of spinal metastasis. The principal symptom of spinal metastasis is pain, which may be local, radicular, or referred, and precedes other symptoms by a mean of 6 weeks [77]. Isolated back pain without neurologic symptoms should be evaluated first with plain spine radiographs. If an abnormality is found, then further evaluation should be performed with spinal MRI. If the diagnosis still remains uncertain, bone scan and high-resolution CT of the vertebrae may also be performed to distinguish benign lesions, such as hemangioma, from bone metastases.

Pain is usually worsened by lying supine, coughing, sneezing, or straining. Myelopathy can occur in the form of limb weakness, numbness, paresthesia, and alterations in bladder and bowel functions. Signs of myelopathy may include increased tone, clonus, hyperreflexia, bladder disinhibition, or an abnormal sensory level. In the setting of myelopathy, the entire spinal cord should be imaged with MRI. Left untreated, epidural spinal cord compression will inexorably lead to paraplegia or quadriplegia, depending upon the level of compression along the spine. Therefore, prompt evaluation is of the utmost importance when epidural spinal cord compression is suspected. Once epidural spinal cord compression is diagnosed, steroids should be instituted immediately, along with emergent radiation therapy. A randomized study showed that high-dose (100 mg loading dose) dexamethasone preceding radiotherapy resulted in a greater proportion of patients who were able to ambulate after treatment [78]. Patients whose MRI demonstrates epidural disease without cord compression can be given a lower loading dose of 10 mg dexamethasone. Maintenance dosing consists of 4 mg of dexamethasone every 6 hours and should be slowly tapered once radiation therapy has begun and symptoms have stabilized. Radiation therapy to the involved region is the treatment of choice for most patients with epidural spinal cord compression. For progressive or recurrent spinal cord compression in the previously irradiated spine, surgery is recommended because of the risk of radiation myelopathy from reirradiation. Laminectomy is not highly effective, because most epidural metastases are located in the anterolateral location, which is difficult to decompress using a posterior approach, and may further weaken the spine. Vertebral body resection and stabilization with methylmethacrylate cement has been used to overcome problems with laminectomy. Results from nonrandomized studies suggest that vertebral body resection restores ambulatory function better than does radiation therapy [79-82]. However, the highly selected patient population in those studies and the use of historical controls may limit the generalizability and validity of such results. For patients who are ambulatory prior to treatment, ambulation is preserved on the order of 80% of patients. However, in those who are paraplegic or quadriplegic, the rate is less than 10% [9, 83-85]. The median survival time in patients with breast cancer who develop spinal cord compression ranges from 4 to 13 months in those studies, yet ambulatory status following treatment is the most important prognostic factor for survival [9, 85].

Current research in the treatment of metastatic spinal disease is aimed at developing image-guided SRS procedures that may be used to safely treat paraspinal metastases [86, 87]. It is hoped that the metastasis control rates achieved with spinal SRS will be comparable with those achieved with intracranial SRS.

Ocular Metastases

The choroid is the most common site for ocular metastasis; among all cancers, breast cancer has the highest incidence (40%-70%) of ocular metastatic involvement [88-93]. Diagnosis should be made by indirect fundoscopic examination. After a diagnosis of ocular metastasis has been established, it is important to image the brain for metastatic involvement, because simultaneous metastatic involvement to the brain is common. The median time from diagnosis of breast cancer to development of choroidal metastasis is 4 years [94]. Presenting symptoms include worsened visual acuity, blind spot, diplopia, and image distortion. Fundoscopic examination may reveal retinal detachment and hemorrhage [95]. For progressive visual symptoms, patients should be referred for palliative radiation therapy. The target volume to be irradiated is the entire choroid posterior to the equator. For bilateral disease, both eyes should be treated. For patients with synchronous brain metastases, the field includes the entire cranial contents and the posterior halves of the globes. Fractionation schemes of 20 Gy in 2 weeks, 25 Gy in 1-2 weeks, 30 Gy in 2 weeks, and 50 Gy in 5 weeks have been described, with the majority demonstrating a response rate of greater than about 60% [96-99]. Reported complications include retinopathy, keratopathy, optic neuropathy, and glaucoma [100]. In a series of 42 breast cancer patients with choroid metastases treated with radiation therapy, the median survival time was 10 months [99].

CONCLUSION

The CNS remains a sanctuary site for metastases from breast cancer. The need for more effective CNS-directed treatments may become more pressing because improvements in systemic treatment for breast cancer could lead to a greater incidence of CNS metastases. Radiation therapy remains the mainstay of treatment for CNS metastases. Technological advances have enabled focal treatment,
such as surgery and SRS, to benefit patients with limited metastatic brain disease and good performance statuses. Similarly, it is hoped that focused treatments to the spine using spinal SRS, which are currently under active investigation, may be beneficial as well. The treatment of LM remains a significant challenge because of difficulties with neurotoxicity from combined intrathecal chemotherapy and radiotherapy. Future research should be directed at developing more effective agents for LM that have less neurotoxicity.

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