Opinion statement
Breast cancer metastases to the central nervous system (CNS) has devastating consequences for the individual. As treatment options for metastatic breast cancer expand and as quality of life and overall survival improve, researchers are targeting potential treatments for this sanctuary site. Attention is now being focused on defining the phenotype of breast cancer that has a propensity to metastasize to the CNS. Specific therapies that penetrate the blood brain barrier as well as adjuvant therapies that decrease recurrence in the CNS are currently being investigated. We will review current approaches to the diagnosis, evaluation, and treatment of CNS metastases in breast cancer patients.

Introduction
Breast cancer is the most common malignancy among women. In 2007, approximately 178,000 women will be diagnosed with invasive breast cancer in the U.S. Furthermore, 40,000 women die yearly of breast cancer metastasis, accounting for 15% of all estimated deaths among women with cancer (http://www.cancer.org). Though rare, the development of metastases to the central nervous system (CNS) is one of the most devastating consequences of tumor progression [1]. Clinically, apparent CNS metastases occur in approximately 10% to 16% of patients with metastatic breast cancer. Effective systemic treatments as well as improved technologies for detecting subclinical disease have resulted in an increase in the incidence of brain metastases [2]. Fortunately, the survival rates for patients diagnosed with metastatic breast cancer to the CNS have improved over the last several decades. Recent case series have reported a survival benefit for women diagnosed with breast cancer metastatic to the CNS with survival rates of 6–7 months in comparison to 3–4 months of survival reported two decades ago [3].

Breast cancer cells metastasize to the brain through the vasculature where they proliferate and subsequently invade the brain parenchyma, while most therapeutic agents with a high-molecular weight are excluded by the diffusion barrier [4]. The blood brain barrier (BBB) is the protective mechanism for the exclusion of toxic agents. The tight junctions of the BBB are composed of a three-part layer defined by a continuous endothelial cell layer sealed by tight junctions, a capillary layer with a
basement membrane, and astrocytes with foot processes. Astrocytes prevent passage and interfere with tumor treatment and also enhance metastasis by secreting cytokines that act as chemoattractants to recruit tumor cells [4].

Patients with parenchymal brain metastases frequently present with headache, seizures, focal weakness, ataxia, nausea, and vomiting. This classic clinical presentation of breast cancer CNS metastases is rare, and the actual prevalence of CNS involvement occurs more frequently than is clinically apparent. In autopsy studies, the rates of CNS involvement were as high as 30% [5••]. The CNS is rarely the site of first metastasis, and spread to the brain more commonly occurs after other visceral metastases have developed, including the lung, liver, and bone [6•].

The rate of occult brain metastases in breast cancer patients was recently elucidated in a series of four clinical trials evaluating antiangiogenic agents. Due to a concern for increased intracranial hemorrhage risk, each of the trials required screening neuroimaging on pretreated metastatic breast cancer patients [7••]. Across the four trials, the prevalence of occult CNS metastases was 14.8%. The clinical relevance of occult disease was unclear, as those patients with occult CNS metastases had a similar prognosis as a comparable group with systemic disease.

### Diagnosis

- Patients with symptoms suspicious for CNS metastases need a full neurological evaluation to determine physical and cognitive impairment. Cognitive testing suggests high rates of delayed memory, recall, and motor coordination impairment, independent of Karnofsky performance score (KPS) [8]. When CNS metastases is suspected, urgent evaluation is required. MRI is the preferred imaging modality due to the improved sensitivity compared with contrast-enhanced CT. One study found multiple brain metastases on MRI in 30% of patients with a single brain metastasis on contrast enhanced CT scan [9•]. Gadolinium enhancement detects small metastatic foci without edema. Therefore, the initial step is an MRI with gadolinium enhancement if a solitary metastasis is detected [10].

- The Radiation Therapy Oncology Group (RTOG) performed a retrospective recursive partitioning analysis of the outcomes of 1,200 patients with brain metastasis enrolled on three consecutive radiation therapy clinical trials. Three prognostic groups were identified, based on presenting clinical signs and symptoms. The first group included patients with a KPS of 70 or greater and were <65 years of age and who had controlled primary tumor without extracranial metastases. The second group included patients with a KPS of 70 or greater and were either older than 65 years of age or lacked primary tumor control. The third group included patients with a KPS of <70. The median survival was 7.1, 4.2, and 2.3 months for patient groups 1, 2, and 3, respectively [11••] (Fig. 1).

### Treatment

- Treatment modalities for the management of brain metastases from breast cancer include symptomatic management, surgery, radiation therapy, and chemotherapy. Whole-brain radiation with or without

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**RTOG RPA Class**

Class 1: patients with KPS ≥ 70, < 65 years of age with controlled primary and no extracranial metastasis; Class 3: KPS < 70; Class 2: all others

**Figure 1.** Prognostic classification for brain metastasis