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Authors' reply: Whole-brain radiation therapy —concerns about neurotoxicity

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We thank Padovani and colleagues for their comments and interest in our article: Whole-brain radiation therapy in breast cancer patients with brain metastases. *Nat. Rev. Clin. Oncol.* **7**, 632–640[1] (Breast cancer—what about radiosurgery for brain metastasis? *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2010.119-c1).[2] As we previously described,[3] multidisciplinary discussion is mandatory before the choice of whole-brain radiation therapy (WBRT) and/or radiosurgery, especially in breast cancer patients. The neurotoxicity associated with WBRT is an important concern, in particular for patients whose survival will be long enough to experience delayed neurocognitive dysfunction; however, it has been insufficiently documented in the literature. Most studies used tests lacking both sensitivity and specificity; in addition, chemotherapeutic agents also carry a risk of neurological toxicity, making it difficult to distinguish WBRT-induced neurotoxicity from neurocognitive impairments caused by intracranial progression or decrease in general health status.[4] Despite these confounding issues, it was prospectively demonstrated that patients receiving radiosurgery plus WBRT exhibited a greater risk for learning and memory dysfunctions compared with those receiving radiosurgery alone as first-line treatment of their brain metastases.[5] We agree with Padovani *et al.*[2] that treatment with radiosurgery alone in conjunction with an accurate MRI-based surveillance is a good strategy for postponing WBRT, but a considerable number of patients cannot be offered radiosurgery because of progressive systemic disease, and/or the number or size of metastases. It is also difficult to draw definitive conclusions from trials that included patients with diverse primary tumors and various associated comorbidities that contribute to neurological toxicity.[1]

Breast cancer patients are a unique population with specific molecular subtypes that should be taken into account when deciding the optimal primary care of brain metastases. For example, HER2-positive breast cancers have a propensity to metastasize to the brain.[6] Intracranial progression outside the tumor bed is an important factor related to death and loss of autonomy in this population, encouraging new strategies for improving intracranial control.[7] Moreover, the neurocognitive effects of intracranial progression are not negligible. While the combination of WBRT and radiosurgery decreases brain relapse compared with radiosurgery alone,[8] new irradiation modalities combining WBRT, boosts to the tumor beds, and sparing of critical structures could ensure both good intracranial control and low neurotoxicity.[9] This should be prospectively confirmed. The place for targeted systemic therapies should also be further considered for improving patients' outcome.

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Competing interests
The authors declare no competing interests.

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