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Breast cancer—what about radiosurgery for brain metastasis?

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We read with great interest the recently published Review by Chargari *et al.* in *Nature Reviews Clinical Oncology* (Whole-brain radiation therapy in breast cancer patients with brain metastases. *Nat. Rev. Clin. Oncol.* **7**, 632–640).[1] The authors discussed the challenges of treating brain metastases, the current strategies of treatment combination, and available radiation therapy techniques that improve efficacy and decrease or prevent neurological toxicity.

The article by Chargari *et al.*[1] focuses on strategies that include whole-brain radiation therapy (WBRT) because many patients with brain metastases from breast cancer are preferentially treated with WBRT.[2–4] In historical series, WBRT increased median overall survival time by 3–4 months versus 1 month without treatment and 2 months with corticosteroid alone.[5] The most common WBRT regimen is 30 Gy delivered in 10 fractions, which is proposed for patients in recursive partitioning analysis stage III (42% of patients with metastatic breast cancer).[6] Controversy still exists regarding therapeutic strategies and the impact of WBRT is still unclear. Patchell *et al.*[7] reported that withholding upfront WBRT was associated with a significantly higher risk of cranial distant recurrence. In three randomized controlled trials comparing upfront stereotactic radiation surgery (SRS) with or without WBRT, these results were confirmed and no significant difference was reported in overall survival rates.[8–10] Nevertheless, in the study conducted by Aoyama,[6] although WBRT reduced the brain recurrence rate at 6 months in the high-risk group (extracranial metastases or multiple brain metastases) from 57% to 21%, this difference was no longer observed at 12 months. For the low-risk group (no extracranial metastases and a single brain metastasis) two-thirds of the patients had no regional brain recurrence at 12 months when they are treated by radiosurgery alone.

As underlined by Chargari *et al.*,[1] WBRT induces severe neurotoxicity; however, this toxicity has not been comprehensively evaluated.[11] An indication of the severity of this toxicity was determined using mini-mental state examination; no significant difference was reported in neurological status between the two arms in the Aoyama study (SRS with or without WBRT).[8] Furthermore, a randomized controlled trial conducted by the MD Anderson Cancer Center assigned cognitive performance as a primary end point.[11] In patients with one to three brain metastases, a significant difference in memory decline at 4 months after treatment was reported; a larger proportion of patients who received SRS and upfront WBRT (49%) had a memory decline than those who received SRS alone (20%).[11]

The protection of organs at risk, such as the hippocampus, temporal lobes and frontal lobes, is one major challenge facing radio-oncologists. In this context, using upfront SRS alone could be proposed to remove the risk of late neurotoxicity from WBRT. In a series of patients with metastatic breast cancer with brain metastases, the median survival time was 17.1 months for the group treated with SRS alone versus 15.9 months for SRS and upfront WBRT. No significant difference was observed in terms of 1-year and 2-year new-brain-metastasis-free survival and median time-to-brain-metastasis-progression after salvage therapy.[12] Using a follow-up MRI scan of the brain, up to 80% of brain regional recurrence could be detected before the occurrence of clinical symtoms.[8] In this context MRI can be used to indicate the requirement for early treatment using radiosurgery and for delaying WBRT. We believe this point should have been discussed by Chargari *et al.*,[1] in particular with respect to patients in a favorable diagnosis-specific graded prognostic assessment group (median overall survival time 15–18 months).[13]

Finally, we are totally in agreement with Chargari *et al.*[1] that a multidisciplinary approach to integrate surgery, WBRT and radiosurgery, chemotherapy and targeted therapy offers the best way forward to preserve neurocognitive function and quality of life while maintaining treatment efficacy.

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Competing interests
The authors declare no competing interests.

1. Chargari, C. *et al.* Whole-brain radiation therapy in breast cancer patients with brain metastases. *Nat. Rev. Clin. Oncol.* **7**, 632–640 (2010).
2. Akyurek, S. *et al.* Stereotactic radiosurgical treatment of cerebral metastases arising from breast cancer. *Am. J. Clin. Oncol.* **30**, 310–314 (2007).
3. Liu, M. T. *et al.* Prognostic factors affecting the outcome of brain metastases from breast cancer. *Support. Care Cancer* **14**, 936–942 (2006).
4. Viani, G. A. *et al.* Whole brain radiotherapy for brain metastases from breast cancer: estimation of survival using two stratification systems. *BMC Cancer* **7**, 53 (2007).
5. Mehta, M. The dandelion effect: treat the whole lawn or weed selectively? *J. Clin. Oncol.* **29**, 121–124 (2011).
6. Aoyama, H. Radiation therapy for brain metastases in breast cancer patients. *Breast Cancer* doi:10.1007/s12282-010-0207-8.
7. Patchell, R. A. *et al.* Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* **280**, 1485–1489 (1998).
8. Aoyama, H. *et al.* Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* **295**, 2483–2491 (2006).
9. Kocher, M. *et al.* Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952–26001 study. *J. Clin. Oncol.* **29**, 134–141 (2011).
10. Muacevic, A., Kreth, F. W., Tonn, J. C. & Wowra, B. Stereotactic radiosurgery for multiple brain metastases from breast carcinoma. *Cancer* **100**, 1705–1711 (2004).

11. Chang, E. L. *et al.* Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. **10**, 1037–1044 (2009).

12. Kased, N. *et al.* Gamma Knife radiosurgery for brain metastases from primary breast cancer. *Int. J. Radiat. Oncol. Biol. Phys*. **75**, 1132–1140 (2009).

13. Sperduto, P. W. What is your patient's GPA and why does it matter? Managing brain metastases and the cost of hope. *Int. J. Radiat. Oncol. Biol. Phys*. **77**, 643–644 (2010).