Whole Brain Radiation Therapy (WBRT) vs. Stereotactic Radiosurgery (SRS): Round 20 in the War on Brain Mets

The end of September found me in Boston at ASTRO, the annual meeting of radiation oncologists. MD Anderson Cancer Center presented their study on whole brain radiation vs. stereotactic radiation for 1-3 brain metastases as part of the plenary session, and I wanted to review it with you here and place it into a broader context of the issues and unknowns of how to best treat people with 1-3 brain mets.

The MDA study was designed to enroll 90 patients, but closed after it enrolled 58 because of safety signals (one arm looking convincingly superior to the other). The study took 7 years to enroll. It was closed early when there was worse neurocognitive decline (examining learning and memory at 4 months post treatment using a test to recall a list of 12 words) in patients receiving WBRT+SRS vs. SRS alone. There was a 49% decrease in function with WBRT+SRS vs. 23% in SRS alone. The patients in the WBRT arm received 30 Gy/12 fractions over 2 weeks, or 2.5 Gy/radiation treatment. The in-brain control rate was better in the WBRT arm (no in-brain disease recurrence at 1 year out from treatment) vs SRS (1/3 of patients had further tumor in their brain, though over half of patients never got WBRT within their remaining lives). Importantly, the overall survival of patients in the SRS arm was much better, a finding that is unexpected and unexplainable on the basis of the radiation treatment received for brain metastases.

So, the study adds more information to the debate on how to treat patients in this group. For a single met, few people would recommend WBRT, and for 4 or more mets, WBRT remains the standard of care. While this study appears internally consistent (following good statistical practices), the difference in survival based on brain radiation suggests some kind of imbalance of tumor burden between the two arms of the study, which may have just been a statistical fluke. What about external validity – i.e., do we believe the results relate to patients overall? Here several questions arise.

MDA is a massive cancer center, helping thousands of patients each year. For it to take 7 years to enroll a trial of 58 patients is worrisome. What that tells me is that there was probably unconscious bias at play in which patients were offered study treatment, though the study was randomized, which should have balanced this out. I would like to see what percentage of patients that were eligible for such a study chose to participate. I also cannot explain the worse overall survival with WBRT, and that again suggests that there may have been an imbalance between the two arms, in terms of extent of disease. The presentation did not indicate anything that was substantially different between the two groups of patients, but a more detailed look is worthwhile in my opinion. My skepticism partially arises because there are other studies – such as a Japanese study led by Dr. Aoyama (here) – that showed the reverse: patients with WBRT + SRS lived over twice as long as those with SRS alone (16.5 vs 7.6 months).

The MDA study also did not report on neurocognitive decline following in-brain recurrence, something that previous studies have noted does occur (see RTOG study 91-04, abstract here ). There can be some debate about whether the way that they measured neurocognitive
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Decline was the best test, but the difference between the groups is striking, suggesting that it is a real finding.

**Bottom line:** there is mounting evidence that going with SRS alone won't harm patients with 1-3 brain metastases, though they do need to be followed closely and accept that there is about a 1 in 3 chance that they will require more treatment for brain metastases. From a toxicity standpoint, as several people on this forum have noted, for some patients there is a substantial neurologic price to be paid for WBRT and risking that may make less sense if one can attend regular follow up and accept further treatment as needed. SRS is a highly technically complex treatment to deliver, so the quality of the facility and the number of SRS treatments they deliver each year is critical (the more the better).