

'Sun Is Setting' on Whole-Brain Radiation for Mets

Nick Mulcahy | March 03, 2015

An era in the treatment of brain metastases with radiation is coming to an end, according to a trio of experts who published an editorial [online](#) today in *Lancet Oncology*.

Whole-brain radiation therapy (WBRT) should no longer be the reflexive treatment for patients with brain mets, say Arjun Sahgal, MD, from the University of Toronto, in Ontario, Canada, David Larson, MD, PhD, from the University of California, San Francisco, and Jonathan Knisely, MD, from Hofstra North Shore-LIJ School of Medicine, in New York.

They say that WBRT has been used "indiscriminately" in the past — and sometimes still is — for all patients with brain metastasis.

Another treatment, stereotactic radiosurgery (SRS), which is a more precise, less toxic, and more convenient method, is ready to take its place.

"Patients with limited brain metastases suitable for stereotactic radiosurgery should be treated upfront with organ sparing SRS," the editorialists write.

"The sun is setting on WBRT, and SRS alone is rising to be the standard of care," sing the trio.

The American Society for Radiation Oncology (ASTRO) recently recommended in their [second Choosing Wisely campaign](#) that oncologists should not routinely add adjuvant WBRT to SRS for limited brain metastases. In other words, SRS alone is enough for most of these patients in the first line.

The ASTRO declaration was "a major statement," in part because it did not specify the number of presenting lesions, say the editorialists.

The vagueness opens up the use of SRS for a wide range of patients with brain mets, they suggest.

"Metastasis counting is probably irrelevant if all tumors meet SRS criteria," write the editorialists.

"Whole brain radiation therapy will likely be a last-resort therapy, not an upfront therapy, if the patient is fit for radiosurgery," lead editorialist Dr Sahgal told *Medscape Medical News*.

Dr Sahgal and his coeditorialists point out that a landmark Japanese study of SRS alone for patients with one to 10 metastases showed that risk for distant brain failure rates and survival do not vary for patients with two to four versus five to ten lesion (*Lancet Oncol.* 2014;15: 387-395).

Dr Sahgal also pointed out that the National Comprehensive Cancer Network guidelines support SRS for multiple metastases as long as the patient is "fit and has a low volume of disease" and the guidelines "no longer stipulate a number of metastases."

Nonetheless, Dr Sahgal and his coeditorialists also say that, in recent years, clinician and patient preference has "largely driven" the choice of SRS alone, WBRT plus SRS, or WBRT alone because the different approaches have different virtues.

However, there is now a new meta-analysis of three randomized trials assessing SRS with or without WBRT that "has challenged our current understanding of the effect of adding WBRT," the editorialists assert.

First [presented](#) as a potentially practice-changing study at a conference in 2013, this meta-analysis was just published March 2 [online](#) in the *International Journal of Radiation Oncology, Biology, Physics*.

The meta-analysis, which used individual patient data, found a survival advantage for SRS alone in those patients with one to four metastases, Karnofsky performance status of 70 or higher, and age \leq 50 years.

Furthermore, in this group of patients, the expected reduction in the risk for new brain metastases with adjuvant WBRT was not noted, according to the international team of meta-analysis authors, led by Dr Sahgal.

Dr Sahgal has the unusual distinction of being the lead author of a meta-analysis published in a major journal one day (March 2) and the lead author of an editorial that comments on the very same meta-analysis in another major journal the next day (March 3).

In the meta-analysis, in older patients (aged > 50 years), WBRT decreased the risk for new brain metastasis, as expected, but without affecting survival.

This new study is important because the pluses and minuses of WBRT are well established, for the most part.

On the plus side, WBRT reduces the risks for both local and distant brain failure. On the minus side, it harms quality of life and cognition.

But there has been one area of murkiness: the effect of adjuvant WBRT on survival.

Now it looks like WBRT falls short of SRS in one group of patients (aged > 50 years) with respect to survival.

But another expert disagrees about this survival result, while agreeing that SRS is the ascendant technology.

"I agree that our field is moving away from reflexive whole brain radiotherapy for patients with a limited number of brain metastases," said Nils Arvold, MD, from Dana-Farber/Brigham and Women's Cancer Center, in Boston, Massachusetts, in an email to *Medscape Medical News*.

He also said that SRS alone is reasonable in many patients as first-line therapy because recurrences can typically be salvaged effectively with further SRS or WBRT.

But there are multiple limitations of the age-specific findings of the Sahgal meta-analysis that suggested SRS can provide improved survival, he also said.

Dr Arvold listed some of the shortcomings: the small number of patients who were aged 50 years or younger; the numerically higher rates of neurologic death in the SRS-alone group; the heterogeneity in systemic disease status and salvage therapy rates between groups; and the focus on overall survival in a group that typically dies from systemic and not-brain-related disease.

Dr Arvold further describes these limitations in an [editorial](#) that accompanies the new meta-analysis in *International Journal of Radiation Oncology, Biology, Physics*, which he coauthored with Paul Catalano, ScD, from Dana-Farber.

"The provocative subgroup findings for younger patients receiving SRS alone should be considered exploratory and hypothesis generating," the pair write.

In short, Drs Arvold and Catalano believe SRS is an "attractive approach" for treating a limited metastatic burden in the brain. But they are not ready to make conclusions about superior survival for SRS alone until top-level evidence supports it.

In addition, "the existing level 1 data so far demonstrate that WBRT alone is inappropriate [with regard to survival] only for the group of patients with one brain metastasis," Dr. Arvold said. In other words, while SRS and SRS plus WBRT have been shown to have equivalent survival in randomized trials, WBRT alone can still be justified for patients who have more than one brain met.

At Dana-Farber/Brigham and Women's Cancer Center, Dr Arvold and his colleagues "typically offer SRS alone for the majority of patients with limited brain metastases (3 or 4), but this is not an absolute recommendation for all such patients," he said.

Exceptions to this rule include patients who have rapid onset of new metastases shortly after a normal brain MRI and may have more extensive microscopic intracranial disease; they may be better served with WBRT in some cases, he said.

Also, among patients who have absent or controlled systemic disease but have several brain metastases, the highest-risk site for disease recurrence is the brain, said Dr Arvold. In those situations, "the reduction in distant intracranial recurrence risk afforded by WBRT can sometimes outweigh the potential WBRT side effects, and decisions need to be made on a case-by-case basis," he said.

More Meta-analysis Details

The meta-analysis comprised patient data on 364 patients from the three largest randomized clinical trials (RCT) of SRS and WBRT conducted to date.

Of those 364 patients, 51% were treated with SRS alone and 49% received both SRS and WBRT.

Nineteen percent of patients (n = 68) were aged \leq 50 years.

Patients aged \leq 50 years who received SRS alone had a median survival of 13.6 months after treatment compared with 8.2 months for patients aged \leq 50 who were treated with SRS plus WBRT.

Patients aged $>$ 50 years had a median survival of 10.1 months when treated with SRS alone, and those who received SRS plus WBRT had a median survival of 8.6 months.

Age was a significant effect modifier ($P = .04$) on survival, favoring SRS alone in patients aged \leq 50 years, and no significant differences were observed in older patients, Dr Sahgal and his coinvestigators report.

Hazard ratios for patients aged 35, 40, 45, and 50 years were 0.46 (95% confidence interval [CI], 0.24 - 0.90), 0.52 (95% CI, 0.29 - 0.92), 0.58 (95% CI, 0.35 - 0.95), and 0.64 (95% CI, 0.42 - 0.99), respectively.

Dr Sahgal has financial relationships with Medtronic and Elekta AB. The editorialists have disclosed no relevant financial relationships.

Lancet Oncol. 2015;16:249-250.

Int J Radiat Oncol Biol Phys. 2015;91:710-717 and 718-720.

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Cite this article: 'Sun Is Setting' on Whole-Brain Radiation for Mets. *Medscape*. Mar 03, 2015.