ASCO15 Study:

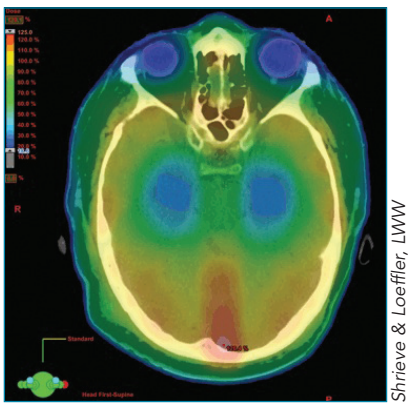
Balancing the Pros and Cons of Whole Brain Radiotherapy

BY ROBERT H. CARLSON

"Whole brain radiotherapy does what we want it to do—it reduces the risk of recurrent metastases, but why it does not improve survival is not known."

CHICAGO—Which is worse, the disease or the treatment? Patients undergoing stereotactic radiosurgery for brain metastases have a high rate of recurrence, and additional treatment with whole brain radiation can reduce recurrence and de novo tumors.

But the treatment has negative consequences. It is particularly detrimental to cognitive function and increases the need for salvage therapy. A randomized Phase III trial presented here at the American Society of Clinical Oncology Annual Meeting may help answer that conundrum (***Abstract LBA4***).



Shrieve & Loeffler, LWW

The NCCTG N0574 (Alliance) trial with 213 patients showed that adding adjuvant whole brain radiotherapy to stereotactic radiosurgery does not increase overall survival in patients with newly diagnosed brain metastases, despite improved local control. Moreover, the addition of whole brain radiotherapy increased the incidence of decline in cognitive function at three months compared with use of stereotactic radiosurgery alone (92% vs. 64%), primarily in immediate and delayed recall, and verbal fluency.

The report concluded with a recommendation of initial treatment with stereotactic radiosurgery and close monitoring to better preserve cognitive function.

"We expect that practice will shift to reserve the use of whole brain radiation therapy for salvage treatment and end-stage palliative care," said the study's senior author, Jan C. Buckner, MD, Professor of Oncology at the Mayo Clinic, speaking at an ASCO news conference at the meeting.

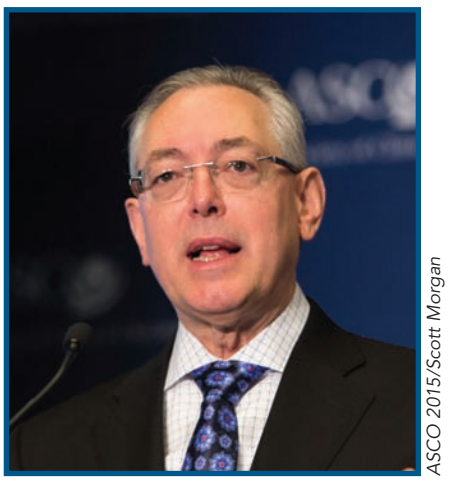
The lead author, Paul D. Brown, MD, Professor of Radiation Oncology at the University of Texas MD Anderson Cancer Center, presented the data in the plenary session. In his presentation, Brown said that adjuvant whole brain radiotherapy added to stereotactic radiosurgery improves local intracranial control from 70 to 90 percent.

"Therefore, a clear understanding of the risks of whole brain radiotherapy—specifically to cognitive function, becomes paramount in treatment decisions," he said.

Whether tumor recurrence or whole brain radiotherapy has a worse cognitive impact is not clear, as Phase III trials show mixed results. He cited a study by Eric L. Chang and colleagues (***Lancet Oncology 2009;11:1037-1044***) that found that adding whole brain radiotherapy to stereotactic radiosurgery resulted in worse cognitive function compared with stereotactic radiosurgery alone.

But Hidefumi Aoyama and colleagues (***Int J Rad Oncol Biol Physics. 2007;5:1388-1395***) found that tumor control is the most important factor, and that tumor recurrence with stereotactic radiosurgery alone resulted in relatively worse cognitive function. And Jing Li et al (***JCO 2007;10:1260-1266***), in a study of whole brain radiotherapy for palliation, confirmed that tumor control is the most important factor.

Brown said the current study was undertaken to clarify the issue.



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Patients, Treatments, Outcomes

The trial took 11 years (2002 to 2013) to enroll the 213 patients, with 111 patients randomly selected to receive stereotactic radiosurgery alone and 102 to stereotactic radiosurgery plus whole brain radiotherapy. The patients' median age was 60 and all had one to three brain metastases of less than 3 cm as shown by contrast MRI.

The primary tumor was in the lung in 68 percent of patients. In the stereotactic radiosurgery-alone arm, patients with lesions of less than 2 cm received 24 Gy and those with lesions 2 to 2.9 cm received 20 Gy. In the combination arm, lesions of less than 2 cm received 22 Gy stereotactic radiosurgery, and lesions 2 to 2.9 cm received 18 Gy, plus whole brain radiotherapy of 30 Gy in 12 fractions.

The primary endpoint of the trial was the cognitive decline at three months following treatment.

With a median of 7.2 months of follow-up (range of zero to 63 months), the decline in cognitive function at three months was 91.7 percent with the combination versus 63.5 percent with stereotactic radiosurgery alone.

With combination radiotherapy there was more deterioration in immediate recall (31% with the combination

HUSSAIN

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GETUG-AFU 15 Phase III trial with 385 patients compared androgen-deprivation therapy plus docetaxel with androgen deprivation alone for patients with hormone-naive metastatic prostate cancer. That trial showed a nonsignificant longer median overall survival for patients receiving chemo-hormonal therapy—60.9 months versus 46.5 months for hormonal therapy alone.

The results of GEFUG-AFU 15 were not inconsistent with those of CHAARTED, she said, but there were important differences between the two—namely the size of the trial (514 for CHAARTED vs. 183 for GEFUG-AFU 15), and volume of disease.

"Fewer than half of the patients in GEFUG-AFU 15 had high-volume disease compared with two-thirds of patients in CHAARTED," she said. The overall lower volume of disease was also reflected in the median PSA of CHAARTED—approximately 20 ng/mL, compared with more than 50 ng/mL in CHAARTED.

'Smart Cancer'

"Metastatic prostate cancer is a complex, 'smart cancer' with marked inter- and intra-patient heterogeneity," Hussain said. "Androgen receptor signaling is important, but it's not the whole story."

The limitation of androgen deprivation, coupled with the established biologic heterogeneity of prostate cancer and its adaptation capability, provide the rationale for a preemptive multi-targeted strategy aimed at a cytotoxic impact.

"We stand at a crossroads," Hussain concluded. "Do we alter the standards of care, or do we bury our heads in the sand?"

WBRT

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vs. 8% for stereotactic radiosurgery alone), delayed recall (51% vs. 20%), and verbal fluency (19% vs. 2%). Brown reported that the decline in cognitive function persisted at six months—98% with the combination vs. 78% for stereotactic radiosurgery alone.

On the other hand, intracranial tumor control at six and 12 months was 66 and 50 percent with stereotactic radiosurgery alone, versus 88 and 85 percent with the combination.

But median overall survival was 10.4 months for stereotactic radiosurgery alone versus 7.4 months for the combination, a not statistically significantly difference, with no difference between treatment arms when stratified by age, systemic disease, or number of brain metastases.

In addition to the findings of cognitive tests, patients also reported significantly worse quality-of-life measurement scores with the addition of whole brain radiation, but those data are still being evaluated, Brown said.

He speculated that the lack of survival advantage for combination therapy might be due to more patients randomized to radiosurgery alone who later received salvage therapy.

Patients in this trial did not have resected brain metastases, but whole brain radiotherapy continues to be an option for patients with resected brain metastases, Buckner said, noting that an ongoing NCCTG/Alliance trial is testing the whole brain radiotherapy versus stereotactic radiosurgery to the surgical cavity, and it is hoped that this will determine which treatment approach is better.

> "With this study the burden of proof is now switched, and the question is: Can we prove that whole brain radiotherapy is beneficial in a subset of patients?"

Discussant: Combination Increases Survival in Appropriate Context

The Discussant for the study, Andrew B. Lassman, MD, Chief of the Division of Neuro-Oncology at Columbia University Medical Center, congratulated the researchers on their "herculean effort," taking 13 years from inception, with detailed neurocognitive evaluations in all patients and conducted in a cooperative group setting.

"The obvious conclusion from this trial, with no improvement in survival and a decline in neurocognition, is: don't use whole brain radiotherapy," he said. "But there are other interpretations if we place this trial in context."

For one, in appropriate patients the combination does lead to an improvement in survival. Also, omitting whole brain radiotherapy leads to more recurrent brain metastases, and that in itself increases neurocognitive deficits. So rather than "don't use it," Lassman suggested: "use in selected cases."

Life-threatening brain metastases could change the picture, for example. In RTOG 9508 (***Andrews et al: Lancet 2004; 363:1665-1672***), adding surgery or stereotactic radiosurgery to whole brain radiotherapy decreased local recurrence and increased survival, if the brain metastases were life-limiting. And patients with controlled systemic disease lived longer with combined therapy.

Lassman cited the 2007 paper by Aoyama that Brown also cited, but he said further analysis released only two weeks before this meeting demonstrated a clear prolongation of survival for patients with lung cancer and favorable prognostic factors, but no difference for other patients.

"Alternative approaches are possible," Lassman said. There are now agents that target ALK or EGFR in lung cancer, BRAF in melanoma, and HER2 in breast cancer, plus emerging immunotherapies.

Pharmacologic alternatives are available, such as using memantine with whole brain radiotherapy, which has shown improved delayed recall at six months (***Brown et al: Neuro Oncol 2013;10:1429-1437***). And RTOG 0933 showed that hippocampal-avoidance whole brain radiotherapy improved delayed recall at four months (***OT 11/25/13 issue***).

Lassman said the NRG CC003 trial is currently testing prophylactic cranial irradiation with and without hippocampal-avoidance whole brain radiotherapy. And NRG CC001 is testing memantine with and without hippocampal-avoidance whole brain radiotherapy.

ANDREW B. LASSMAN, MD: "Although whole brain radiotherapy is a crude tool with significant toxicities and is now over 60 years old, it remains useful in the right context and should not be discarded."

"Whole brain radiotherapy is a crude tool with significant toxicities that is now over 60 years old and is clearly inadequate, with response rates of less than 50 percent," Lassman concluded. "But it remains a useful tool in the right context and should not be discarded. Refinements and new approaches are needed and in development."

New Paradigm

An ASCO designated expert on the topic, Brian M. Alexander, MD, MPH, Disease Center Leader of Radiation Oncology in the Center for Neuro-Oncology at Dana-Farber Cancer Institute, also speaking at the news conference, said that treatment of brain metastases is a complex scenario, and "I take a lot of time talking with my patients about their choices. … Whole brain radiotherapy does what we want it to do: It reduces the risk of recurrent metastases, but why it does not improve survival is not known."

He speculated that progressive disease outside the brain is driving mortality, in which case a population of patients unlikely to die from progression of disease outside the brain may be the only patients who would benefit for whole brain radiotherapy.

"With this study the burden of proof is now switched, and the question is: Can we prove that whole brain radiotherapy is beneficial in a subset of patients?"

Despite tremendous advances, physicians still don't always know when the benefits of aggressive therapy outweigh the possible side effects, commented the moderator of the news conference, Jyoti D. Patel, MD, Associate Professor in Medicine-Hematology/Oncology at Robert H. Lurie Comprehensive Cancer Center.

"What we do up front is so impactful to the ability to live clearly full and contributing lives for years. So this message is the new paradigm." OT

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> —*Brian M. Alexander, MD, MPH*