

Taking new aim at an old target

Dr. Christopher Duma's "Leading Edge®" Gamma Knife radiosurgery technique stops glioblastoma multiforme in its tracks

In 2004, the RT 93-05 protocol¹ ostensibly removed all doubt about the role of stereotactic radiosurgery for patients with glioblastoma multiforme (GBM), a tumor that carries with it a dismal prognosis with standard therapies. The 203-patient study showed that stereotactic radiosurgery did not improve outcomes in patients with GBM, nor could it change the patient's quality of life or cognitive functioning. Veteran Leksell Gamma Knife® user and neurosurgeon Christopher Duma, MD, however, maintains his clinical findings demonstrate that the radiosurgery target in RT 93-05 and many other studies has been wrong all along.

"They were targeting the part of the tumor that is enhancing in MRI scans," asserts Dr. Duma, a neurosurgeon with Brain and Spine Surgeons of Orange County (Newport Beach, California). "The real target should be the leading edge, the area of the lesion that has already wended itself away from the tumor's epicenter. Where the GBM begins is not an issue with this tumor. You could irradiate or extirpate the enhancing area *ad infinitum* and still lose the patient to the leading edge."

And doctors have been losing patients by the thousands to GBM. WHO-classified grade IV astrocytomas, GBMs are highly malignant and aggressive and, at about five percent, have among the worst three-year survival rates for human cancers. A GBM grows energetically in brain tissue, sending out tendrils of cancer cells from its central mass to other parts of the brain. Conventional treatment (the so-called Stupp protocol²), which cures less than five percent of patients, includes gross total resection, concomitant radio-chemo-therapy with 60 Gy and Temozolomide, followed by six cycles of Temozolomide. The median survival time is about 15 months if this

standard protocol is followed.

"Everything we do with respect to GBMs is based on that benchmark," he says. "If you do any better than that then you're doing OK."

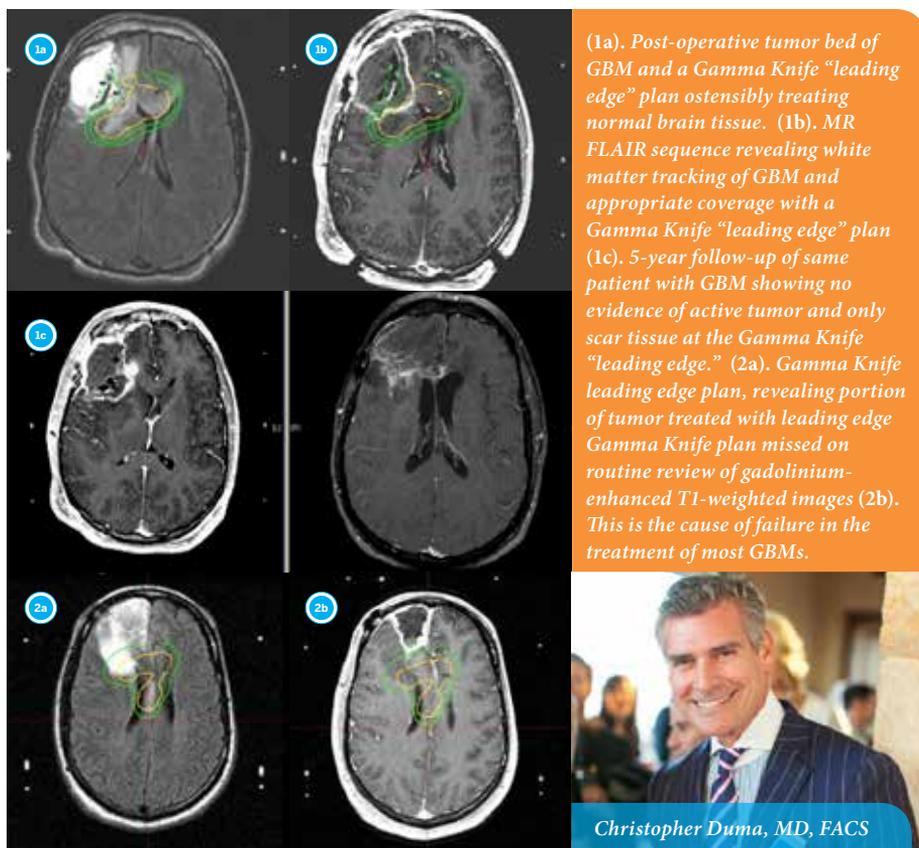
With his Leading Edge Gamma Knife radiosurgery technique, Dr. Duma has been doing more than "OK." His cumulative results in the treatment of 109 patients since 1998 show major increases in two- and five-year overall survival rates; 43 percent and 12 percent respectively.

"These numbers are astounding," he says. "Compared to EORTC and looking at RPA class, median survival with radiotherapy alone is 13 months, and Temozolomide plus radiation is 16 months, whereas the median survival for our patients was 23 months. Our two-year survival of 43 percent is significantly higher than that of the best standard therapy – radiation and Temozolomide – at 28 percent. For the first time, we're finally making an impact on GBMs."

GBM behavior

In the early 1990s, Dr. Duma conceived of his idea of Leading Edge Gamma Knife radiosurgery for GBMs by contemplating the lesion's behavior. GBMs are unique among tumors in the way they grow and in their motility. They don't add mass uniformly from the first few cells, like a snowball rolling downhill picking up snow. In fact, it's the opposite.

"As a GBM grows, it fades out, theoretically to that very last cell," he says. "In terms of motility, GBM cells change with time – they actually deform and become amoeba-like, enabling them to move in a way that other tumor cells don't. Their invadopodia allow them to contract and move like an inch-worm through the brain, so a GBM can cross over



(1a). Post-operative tumor bed of GBM and a Gamma Knife “leading edge” plan ostensibly treating normal brain tissue. (1b). MR FLAIR sequence revealing white matter tracking of GBM and appropriate coverage with a Gamma Knife “leading edge” plan (1c). 5-year follow-up of same patient with GBM showing no evidence of active tumor and only scar tissue at the Gamma Knife “leading edge.” (2a). Gamma Knife leading edge plan, revealing portion of tumor treated with leading edge Gamma Knife plan missed on routine review of gadolinium-enhanced T1-weighted images (2b). This is the cause of failure in the treatment of most GBMs.

Christopher Duma, MD, FACS

the corpus callosum and go between the temporal and frontal lobes using the white matter pathways.

“Once I learned how a GBM moves through the brain, it made sense why we always knew that – if a patient had a tumor in the frontal lobe on the right side of the brain – in about six months a GBM will appear in the left side of the brain,” he adds. “Yet no one really thought about it in a therapeutic context. They looked at it in a fatalistic way, like: ‘If it crosses the brain, we’re done, it’s over.’”

The therapeutic way to think about a GBM is that it moves because it has to, using up the blood supply in one area and then migrating to a region of higher oxygen tension. The GBM genotype is such that if its cells are inhibited from migrating, it will die.

“We can use this fact to our advantage when treating this tumor,” he says. “The concept is to apply radiosurgery to establish a ‘firebreak,’ a situation in which the tumor cells can’t penetrate anymore; they can’t get

through the white matter tracts. So, it would be a matter of visualizing the cells making up the leading edge of the tumor and treating that area, in effect ‘cutting it off at the pass.’”

He first presented his Leading Edge strategy at the American Association of Neurological Surgeons in 1995, having treated a handful of patients successfully during the preceding two years at Hoag Memorial Hospital Presbyterian, Neurosciences Institute (Newport Beach, California).

“The AANS talk was the first time I exposed Leading Edge Gamma Knife radiosurgery to the world,” Dr. Duma says. “I’ve exposed it a lot to the world since then, but no else has had the fortitude to carry forth with it.”

Targeting for Leading Edge Therapy

Rather than observing T1-weighted gadolinium enhancement zone on MRI images, the way to visualize the GBM leading edge is by noting an abnormality on

FLAIR sequences outside of the enhancing zone. Similarly, Dr. Duma also uses magnetic resonance spectroscopy (MRS) to detect metabolic evidence of tumor activity away from the enhancing zone; the choline-creatinine ratio and NAA levels.

“If the volumetric analysis of the FLAIR abnormality outside of the enhancing area is less than 80 cc in volume, the patient is a good candidate for Leading Edge therapy,” he says.

All of Dr. Duma’s 109 GBM patients from 1998 to 2013 received involved field radiation therapy and Temozolomide (if clinically available). The median age was 59 (range 25-87) and the leading edge median volume was 33.5 cc (range 2.5-220). The median radiosurgical dose was 8 Gy at the 50 percent isodose line (range 6-10 Gy). He has used both Leksell Gamma Knife B and then Leksell Gamma Knife® Perfexion™ systems during that period.

The mechanism by which Leading Edge therapy succeeds in halting the GBM’s spread is unclear.

“It’s purely theoretical, because we don’t know exactly what’s happening,” he explains. “In the center of the 50 percent isodose, these patients are getting 13-14 Gy. That might be enough to kill tumors. Then the other effects from the lower isodose, like at the 50 percent isodose line treating at 6 Gy or 7 Gy, that may just be purely a white matter scarring phenomenon – the white matter tracts no longer accommodate the migration of these cells through them.”

Regardless of the mechanism, Dr. Duma is convinced that in patients who do well with Leading Edge radiosurgery, the therapy has “caught” the leading edge of the GBM, and that this is a function of the extent of tumor growth and the GBM’s location.

“I know how the patient will do based on how far the tumor has spread and where it’s located in the brain,” he says. “If it’s locked in the temporal lobe, it has no other place to go but the temporal lobe and backward down toward the occipital lobe. And, if you block the backward path, you will achieve long survival for that patient.”

Treatment failures are correlated with large tumor volume (with a correspondingly large leading edge), GBM location – a GBM in the thalamus, for example, has perhaps 20 different white matter routes with which to

spread – and the inability to image the leading edge due to insufficient cell populations.

Predicting where a GBM will spread might be improved with the creation of an atlas of tumor cell migration, a project Dr. Duma is eager to initiate. “It would involve examining patterns of failure, and noting where the tumor is at point A in the brain and where it is six months later,” he explains. “So, for example, if the majority of the tumor is in quadrant 31.2, and an atlas indicates the patterns of failure are in quadrants 31, 32 and 34, then that could guide your treatment.”

The future of GBM treatment

The addition of six cycles of Temozolomide in 1999 as a component of the Stupp protocol gave patients just two additional months of median survival, a feeble improvement over pre-Temozolomide therapy. Leading Edge therapy offers the potential for much longer disease-free survival.

“If I were the patient, I’d say don’t bother giving Temozolomide to me – I don’t need the side effects and the extra two months that badly,” Dr. Duma says. “But if you can nearly double my survival time with a single shot of radiosurgery, then I’m all for it. In 10 years I predict Leading Edge radiosurgery will be part of the standard of care. GBM can be stopped if the leading edge is cut off early enough.”

In the meantime, Dr. Duma is attempting to organize a multicenter trial on Leading Edge Gamma Knife radiosurgery.

“If we can get the funding for it, it has to be done, because there is nothing else on the horizon for GBM – zero,” he says. “We believe that we can gain the power of 90 percent with about 215 patients and a trial length of about 25 months.” •

References

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