Ten brain metastases

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Sometimes the questions are complicated and the answers are simple.

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How many brain metastases make a patient ineligible for stereotactic radiosurgery (SRS)? Neurosurgeons have been seeking an answer to this question for quite some time. Current evidence-based guidelines support the use of radiosurgery largely for patients with 1–4 brain metastases. However, such guidelines frequently lag behind contemporary clinical practice and suffer from a paucity of rigorous, prospective clinical trials conducted by neurosurgeons treating patients with brain metastases.

The ongoing multicenter trial JLGK0901 is a step in the right direction in terms of answering how many metastases are too many for radiosurgery. The study evaluates patients with 1–10 brain metastases undergoing Gamma Knife surgery (GKS) alone without whole-brain radiation therapy. Patients are stratified by groups based on the number of metastastic lesions. The study is expected to show noninferiority of overall survival using GKS alone in patients with 5–10 brain metastases as compared to those with 2–4 brain metastases. Preliminary analysis of the study data suggests that this hypothesis will be validated.

In Grandhi and colleagues’ study of radiosurgical patients with 10 or more brain metastases, improved survival was seen in those with fewer than 14 metastases. Additionally, those with a primary cancer other than melanoma, controlled systemic disease, a higher Karnofsky Performance Scale status, and a lower recursive partitioning analysis (RPA) class demonstrated improved survival. Certainly, it is true that the number of brain metastases is often a surrogate for systemic disease, performance status, and RPA class. However, in the typical cohort of patients with brain metastasis (those with 1–20 brain metastases) commonly seen by neurosurgeons, it seems clear that a pivotal number of brain metastases for which a patient is unequivocally eligible or ineligible for radiosurgery does not exist. The decision about whether or not to use radiosurgery requires careful weighing of a group of parameters including number of metastases, tumor locations, tumor characteristics (for example, cystic vs solid), patient age, performance status, intracranial tumor volume, prior treatment, extent and activity of systemic disease, comorbidities (for example, dementia or multiple sclerosis), tumor histology, and even tumor receptor status. Many but not all of these factors are reflected in the diagnosis-specific Graded Prognostic Assessment (GPA).

In Grandhi and colleagues’ study, 62.3% of patients had undergone prior whole-brain radiation therapy (WBRT). For patients with brain metastases who have had prior WBRT, radiosurgery has been shown to afford a reasonable benefit/risk profile for the treatment of new or progressive disease. However, even more noteworthy, 13.1% of patients in the current study had radiosurgery as their sole treatment. There was no survival difference noted between those in whom GKS was used as a primary treatment versus a salvage treatment. Prior WBRT did not portend improved survival.

It is widely known that the current Gamma Knife and other modern radiosurgical devices can be used to efficiently and safely treat patients with more than 10 brain metastases in a single session. In 2002, Yamamoto and colleagues reported on a series of 80 patients with 10 or more brain metastases undergoing GKS (median number of lesions 17, range 10–43). They determined that the cumulative radiation dose to the whole brain was 4.71 Gy (range 2.16–8.51 Gy). This dose was not believed to exceed the threshold level for induction of necrosis in normal brain tissue. Hence, we have the technology to perform radiosurgery in patients with 10 or more brain metastases, and generally it can be done safely.

Is the magic number for radiosurgery 1, 3, 4, 5, 10, or 14 brain metastases? In short, the answer is simple. For the majority of patients with brain metastases, there is not a pivotal number that solely determines whether or not radiosurgery would add value in terms of survival, much less quality of life and neurocognition. Thus, it seems safe to move beyond this question, at least by itself, and focus on other issues. Neurosurgeons must determine the effectiveness of radiosurgery for patients with multiple brain metastases relative to competing treatment options (for example, resection, various types of external beam radiotherapy techniques such as hippocampal-sparing intensity-modulated radiotherapy, and increasingly chemotherapy). Such effectiveness will be judged in terms of life years saved, quality-adjusted life years, cost for radiosurgery delivery, cost for salvage therapies, total cost of care for such patients, and patient satisfaction. Studies that look at these aspects of radiosurgical effectiveness are difficult to conduct and are rarely performed. However, this type of analysis may be an important consideration given the up-
coming health care reforms. In addition, if the number of brain metastases is less of a determinant for radiosurgery eligibility, it is conceivable that many more patients could undergo such an approach. The profession must ensure adequate training and sufficient numbers of neurosurgeons to perform radiosurgery as well as to treat these patients with multiple brain metastases in the preoperative and postoperative periods.6,9

The authors are to be commended for highlighting the efficacy of SRS for patients with more than the traditional number of 4 brain metastases. Their report points toward a dramatic expansion of the neurosurgeon’s role in the management of brain metastases using radiosurgery.

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Disclosure

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References


Response

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We thank Drs. Sheehan and Schlesinger for their thoughtful commentary on our work. The topic is a timely one because there have been challenges to the use of SRS for patients with increasing numbers of brain metastases. For decades, physicians have been concerned with the number of tumors. Perhaps this was attributable to the fact that surgeons would typically want to perform a craniotomy only for a single tumor, and the concept of multiple craniotomies was pursued by very few neurosurgeons. Initial randomized trials focused on patients with solitary brain metastases and the role of surgical removal, again probably because the idea of multiple craniotomies was not commonly pursued.

Stereotactic radiosurgery changed that landscape. Simply from a technical perspective, the ability to target multiple tumors added little more than a few minutes to a radiosurgical procedure. Indeed, for every additional small metastasis treated, another 10 minutes or so of treatment time was added with a newly loaded unit. Initial randomized trials were performed in patients with arbitrarily chosen ranges of 2–4 metastases, which again demonstrated that SRS improved tumor control. Following this, numerous clinical studies that evaluated outcomes of radiosurgery for lung cancer, breast cancer, melanoma, and renal cell carcinoma provided evidence that WBRT provided no additional survival benefit over radiosurgery alone. Prior to SRS, WBRT was the only treatment option and provided patients with an expected median survival of approximately 4 months. The cumulative data provide convincing evidence that WBRT should not be the standard treatment for any patient with one or more brain metastases. Whole-brain radiation therapy can be reserved for patients with miliary disease or carcinomatous meningitis.

The number of tumors should not be a determining issue for initial therapy. The outcomes of brain metastasis management are related to other factors that include the extent of extracranial disease, patient age, and current performance score. The number of tumors is not included in the original RPA but was studied in the recent analysis of the GPA. Those authors categorized number into the groups of 1, 2–3, and >3. For breast or gastrointestinal cancers, the number of tumors did not assist GPA scoring. For lung cancer, melanoma, and renal cell carcinoma, these
groupings did help with the determination of GPA score. However, the category “> 3” is a large and heterogeneous group. As they state, “patients should not be denied treatment because of the number of brain metastases.” In other organs, in general, the number of extracranial metastases is not the most critical factor. It is not necessarily the number of lymph nodes involved in breast cancer or melanoma that is the issue, nor is it the number of pulmonary nodules on a chest radiograph. What is important is the cancer burden. The total number of metastases is a poor estimate of that burden. If radiologists, neurosurgeons, and radiation oncologists had software that easily calculated brain tumor volumes, we would have an actual sense of the tumor burden. In 2012, we do not. For example, a patient in good neurological condition with 10 metastases that are each < 6 mm in diameter has a small tumor burden. In contrast, a patient with 2 tumors, each 2 cm in diameter, has a total tumor volume and intracranial cancer burden that is much greater. So, is it better to have 2 large or 10 small tumors? Many patients in excellent clinical condition present with numerous tumors identified during staging MRI. Such patients may have little surrounding brain edema or mass effect. Radiosurgery is an effective option that preserves cognitive function.

New radiosurgical devices that include robotics have allowed efficient management of increasing numbers of brain metastases and greater efficiency at managing irregularly shaped intracranial target volumes. To simply state that procedures are not warranted in patients because randomized trials have only shown value for up to 4 intracranial metastases reflects a lack of knowledge in the current management of CNS cancer. Interestingly, no existing comparative literature substantiates the value of WBRT as the best treatment for patients with multiple metastases. Reflex use of WBRT dramatically increases the development of leukoencephalopathy in patients who survive more than 1 year. Our goal is efficient and effective management of intracranial cancer. Patients with a lower brain cancer burden have better neurological function and have the potential to live longer than the expected median survivals. The percentage of patients in the survival tail continues to increase. Stereotactic radiosurgery controls CNS metastases in 70%–90% of patients. Oncologists can continue to develop more effective systemic treatments—since systemic failure is now the most common cause of death. We work to ensure that such patients have access to procedures substantiated by the best science and providing the best quality of life. The health care industry and the insurance industry must come to grips with this new reality.

Reference


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