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Commentary

Arguably, the most significant advances in radiation oncology in the last 10 years have been the ability to escalate (increase) radiation dose to the tumor and minimize (reduce) radiation dose to the uninvolved surrounding “normal” tissues. The desired goal, of course, is to improve tumor control with a concomitant reduction in side effects. Four methods of achieving this goal have been developed:

1. Three-dimensional conformal radiation therapy (3DCRT)
2. Intensity-modulated radiation therapy (IMRT)
3. Charged-particle radiation therapy (protons or neutrons)
4. Radiosurgery

In this issue of *BUMC Proceedings*, Drs. Giller and Berger have provided an excellent review of radiosurgery using two commercially available products: the Gamma Knife for intracranial tumors and the CyberKnife for both intra- and extracranial tumors. They are to be commended for their comprehensive effort.

In general, the term *radiosurgery* is somewhat misleading to most physicians and patients. There is no argument, however, that the term is immensely marketable. As discussed clearly in the article by Drs. Giller and Berger, no surgery is involved. The reference to surgery can imply that the target tumor is completely ablated and that the treatment is close to or equal to surgical resection. At best, this is a highly optimistic goal and certainly not applicable to all targeted tumors. The authors substantiate this fact when, in many instances, “local control” is defined as “lack of growth.” Thus, radiosurgery is just one of the techniques from the above list that allows a higher dose of radiation to be administered to a limited volume, providing a myriad of tumor responses ranging from ablation to growth restraint to size reduction. Because it has been a part of the medical literature for decades, the term will remain unchanged despite its limitations and ambiguities.

As discussed in the article, the Gamma Knife can be used to treat many intracranial tumors, both benign and malignant, including metastases, malignant primary brain tumors, benign primary brain tumors, vascular malformations, and, in certain cases, functional disorders. A reasonable amount of clinical data has been published for the use of the Gamma Knife or other forms of radiosurgery in the above clinical settings. The most common use of the Gamma Knife has been for treating brain metastases, and in the vast majority of cases radiotherapy has been combined in some fashion with whole brain radiation therapy.

In the September 1, 2005, edition of the *International Journal of Radiation Oncology • Radiobiology • Physics* (the official journal of the American Society for Therapeutic Radiology and Oncology, or ASTRO, the largest professional organization of radiation oncologists in the world), a consortium panel published an evidence-based review of the use of radiosurgery in patients with

brain metastases (1). They believe there is level I–III evidence of improved survival for the addition of radiosurgery boost with whole brain radiation therapy in patients with a single brain metastasis. The issue of treating patients with four or more brain metastases is more controversial, as there is a limited amount of data to support the use of radiosurgery in these patients. The panel’s recommendation is to reserve the use of radiosurgery as a boost for patients with up to three brain metastases (and possibly four, based on one randomized trial) in conjunction with whole brain radiotherapy. In addition, the panel could not make recommendations as to the clinical benefit or risk of radiosurgery treatment in the clinical setting of recurrent or progressive brain metastases. Although the patients in case example 1 and case example 3 of the article appear to have done well, the data supporting their respective treatments are lacking. These are examples of patients we feel are best treated on protocols or studies so that data on outcomes, side effects, and other parameters can be accrued and followed.

If the amount of data for the use of radiosurgery in intracranial tumors can be described as reasonable, then the literature supporting the extracranial use of radiosurgery can best be described as minuscule. To the best of our knowledge, there are no multi-institutional, prospective, randomized trials supporting the use of the CyberKnife (or any other form of extracranial radiosurgery) as superior to surgery, chemotherapy, radiation therapy, or any combination of the three conventional forms of cancer treatment. We applaud Drs. Giller and Berger for their disclosure of this and their even-handed portrayal of the role of the CyberKnife in extracranial radiosurgery. However, given current marketing initiatives and the multitude of questions from patients as well as other physicians, we felt a brief discussion of the literature was well within the scope of this editorial. Some particular tumor sites that have been proposed as being ideal for extracranial radiosurgery include the lung, liver, and pancreas.

In patients with stage I non–small cell lung cancer (NSCLC) who are medically inoperable, data from predominantly single institutions may support the use of extracranial radiosurgery. The patient numbers are small, ranging from 10 to 45 (2–6). Some studies included both medically inoperable stage I NSCLC and lung metastases (4, 6). Another study included lung and liver metastases (7). Most of these papers concluded that radiosurgery was well tolerated and feasible (2, 3, 5, 6). Salazar et al (4) found a high degree of local control and possibly improved survival with the use of radiosurgery; however, a significant percentage of their patients also received conventional external-beam radiation therapy followed by a radiosurgery boost. In addition, this series also included some patients with recurrent lung cancer (4). Based

on a phase I trial by Timmerman et al (5), the Radiation Therapy Oncology Group is planning a phase II trial of radiosurgery in medically inoperable stage I NSCLC patients.

In patients with liver metastases, there is a limited amount of data to support the use of radiosurgery (7, 8). Schefter et al (8) showed that radiosurgery of liver metastases was well tolerated and feasible. A phase II trial is under way. Koong et al (9) performed a phase I dose-escalation study of extracranial radiosurgery in 15 patients with locally advanced pancreatic cancer. Radiosurgery was found to be feasible, and a phase II study is planned. We anxiously await the results of these phase II studies and other studies that may be currently accruing patients. However, we do not believe, at the current time, that extracranial radiosurgery is a substitute for conventional treatments for these tumor sites. We do believe that treatment in these groups of patients with the CyberKnife or other forms of radiosurgery is reasonable if done on protocol or as part of a study where data on outcomes, side effects, and other clinical parameters can be gathered and used to direct future treatments.

Lastly, a contrast must be drawn between 3DCRT, IMRT, and radiosurgery in terms of "fractionation." Nearly 100 years of data support conventionally fractionated radiation therapy, the basis of which is a daily dose fraction given over multiple days that achieves adequate tumor cell kill with an acceptable, low rate of side effects. 3DCRT and IMRT use conventional fractionation and dose escalation to higher doses and can decrease radiation to the normal, uninvolved surrounding tissues to improve outcomes and decrease side effects. Radiosurgery uses larger daily doses given over a smaller number of fractions; this is termed *hypofractionation*. Hypofractionation may be beneficial for a patient treated with the intent of palliation, as for brain metastases, but it is currently unproven and not the standard of care for curative attempts in malignancies such as prostate, breast, gynecologic, gastrointestinal, or head and neck cancers. In addition, with the paucity of long-term data for side effects, especially with extracranial radiosurgery, there is the potential for increased chronic side effects with hypofractionation as opposed to conventionally fractionated radiation therapy using 3DCRT or IMRT.

In conclusion, we congratulate Drs. Giller and Berger for their timely, comprehensive, and excellent article. We believe that the Gamma Knife and the CyberKnife have beneficial roles

to play in the spectrum of cancer therapeutics, and we look forward to their additive and synergistic roles, along with the current conventional treatments of chemotherapy, surgery, and radiation therapy. Finally, we look forward to enrolling patients into protocols and studies using these new technologies, which will hopefully benefit our current and future patients.

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THE AUTHORS REPLY:

We appreciate the thoughtful comments of Dr. Cheek and Dr. Scruggs. We agree that formal protocols will be helpful in the development of extracranial radiosurgery, and we completely agree that radiosurgery is best used as part of a comprehensive treatment plan that can appropriately incorporate surgery, radiotherapy, and chemotherapy.

We disagree, however, with any suggestion that radiosurgical technology is so new or untried that it can be offered only within the confines of a prospective randomized trial. There is ample evidence that radiosurgery can provide local control with acceptable toxicity in many settings; to withhold its use and forego the chance of local control because trials have not fully tested this

new technology seems overly stringent. Furthermore, the complex patterns seen in the oncology clinic do not always fit into the clean categories of formal protocols, so the right decisions are those based more on clinical judgment than perfect science. A surgeon would not hesitate to remove two adjacent tumors simply because the medical literature only addressed solitary lesions, and likewise we feel that the radiosurgeon should be guided by the clinical problems at hand. Finally, when discussing treatment options with a vigorous patient harboring significant disease, we are reminded that it is not inappropriate to offer promising technology on a compassionate basis when the choices are limited and the prognosis is bleak.

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