INTERVIEW

For reprint orders, please contact: reprints@futuremedicine.com

Current state of brain and spine radiosurgery and future applications

Arjun Sahgal*: Arjun Sahgal works in the field of high-precision stereotactic radiation to the brain and spine. After training at the University of Toronto (ON, Canada) in radiation oncology, he completed a fellowship at the University of California, San Francisco (CA, USA) in brain and spine radiosurgery with Professor David Larson. Since then, he has been recognized as a national and international clinical expert and research leader in radiosurgery. His main focus is on developing spine stereotactic body radiotherapy (SBRT), also known as spine radiosurgery, as an effective therapy for patients with spinal tumors. Research

achievements include publishing spinal cord tolerance guidelines for spine SBRT as part of an international multi-institutional effort. This work elucidated safe dose limits for the spinal cord specific to spine SBRT, and was the first of its kind. He has developed the spine SBRT program for the University of Toronto and is conducting the first Phase II clinical study on spine SBRT for metastases in Canada. He has also recently written national guidelines on behalf of the Canadian Association of Radiation Oncology (CARO) for the practice of spine, lung and liver SBRT, and continues to lead national and international multi-institutional groups dedicated to spine and brain radiosurgery research.

Q What led to your initial interest in radiotherapy for nervous system neoplasms?

It was the patients in neuro-oncology who were so sick and needed so much help that made me realize early on that they were the population I wanted to dedicate my career to. Unlike a lot of other cancers, patients with brain tumors and CNS metastases tend to receive less attention and funding. This means there is a lot of work that needs to be done to try and improve patient outcomes, and requires extreme dedication to take on the challenge of advancing this disease to the next level, and so it became the focus for my career. With respect to radiotherapy, there is no doubt that it is a powerful cancer treatment that can often provide immediate symptomatic relief and has the power to extend patients' survival;

these factors led to my decision to train in radiation oncology. Moreover, as I found radiotherapy to be delivered rather crudely at the time, I realized that there were major opportunities to advance the field and deliver radiation in a better way to maximize the treatment's potential while minimizing harm.

Q What has been your biggest achievement in the field?

The biggest achievements so far have been in the area of radiosurgery of the brain and spine. In terms of the brain, we have been able to pool published data from the major randomized studies studying whole-brain radiotherapy (WBRT) alone, radiosurgery alone and WBRT plus radiosurgery boost, and publish a meta-analysis [1]. This paper was recognized by the

News & Views

News

Journal Watch

Ask the Experts

Interview

Conference Scenes

*Department of Radiation Oncology, Princess Margaret Hospital & the Sunnybrook Health Sciences Centre, University of Toronto, 5th Floor, 610 University Avenue, Toronto, ON, M5G2M9, Canada; Tel.: +1 416 946 6513; Fax: +1 416 946 2227

“...as I found radiotherapy to be delivered rather crudely ... I realized that there were major opportunities to advance the field and deliver radiation in a better way to maximize the treatment's potential while minimizing harm.”

European Association of Neuro-Oncology (EANO) as one of the best papers of 2011. Essentially, we were able to clarify that although there are gains in distant brain control and local control with WBRT when added to radiosurgery, they did not result in a survival difference. Therefore, to spare the patient from the neurocognitive adverse effects of WBRT, radiosurgery as a first-line therapy and deferral of WBRT as a salvage therapy, may be best for selected patients. We are now trying to take this meta-analysis to the next level by analyzing the individual patient data, as provided by each of the lead authors of the randomized trials. We are hoping for some results within the next year.

With respect to spinal research, I have dedicated a lot of my training and efforts to spine radiosurgery for spinal metastases. The field of spine radiosurgery is where brain radiosurgery was some 20 years ago. It has the potential to be a standard of care for selected patients and requires major research to drive it forward. It represents the transition from treating the patient with spinal metastases with a locally palliative intent to a locally curative intent. This technique pushes modern radiotherapy technology to the limit as it demands extreme precision in treatment delivery. Again, this parallels the transition from treating all patients with brain metastases with WBRT, to the current standard of using focal radiosurgery alone. I have led several multi-institutional reviews on the subject to promote uniformity in practice and safety [2–4].

Within the research sphere of spine radiosurgery, a major area of development for safe practice is in the area of normal tissue tolerance. In particular, we needed to work out spinal cord tolerance when using high-dose-per-fraction radiation. The consequence of overdosing the spinal cord is radiation myelopathy, which can leave a patient paralyzed, and this is an unacceptable complication. Through a major international collaboration, we have been able to gain the data for cases of spine radiosurgery-induced spinal cord myelopathy and compare the doses with those obtained from controls. As a result, we were able to publish guidelines for spinal

cord tolerance specific to spine radiosurgery, and for both patients with and without prior radiation exposure [5–7]. Prior to this, there were almost no data on this topic; now these proposed dose limits have been incorporated into clinical practice at many centers worldwide.

Q What are the main differences between stereotactic radiotherapy for spinal metastases compared with when it is used for metastases of the brain? What are the main limitations of using radiosurgery for the spine?

Radiosurgery was first applied in the brain as it was an ideal area to start given that the targets are not mobile (unlike, for example, lung tumors), the tumors tend to have well-defined borders, are small and round, and a rigid stereotactic head frame could be applied to keep the head position fixed to provide the 3D coordinates for stereotaxy [8]. Therefore, high ablative doses of radiation could be delivered focally within the brain, and this is, by definition, stereotactic radiosurgery. As the technique developed and the technology became more widely available, the use of stereotactic radiosurgery has become a front-line therapy for brain metastases, various benign brain tumors and even neurologic conditions.

Similar treatments for spine targets were not achievable as the technology for body stereotaxy lagged behind the brain. It is only with recent developments in radiotherapy technology (which includes image-guidance systems incorporated onto the treatment delivery apparatus, sophisticated body immobilization devices allowing near-rigid body fixation, intensity-modulated radiotherapy and robotic positioning devices) that spine radiosurgery was born. Essentially, we are able to achieve millimeter precision in delivery for a spine target, akin to what we demand for brain radiosurgery. The University of Toronto (ON, Canada) technique has been published and evaluated, and confirms the ability to treat a spinal target with extreme precision [9,10]. In 2012, as the chair of the Canadian Association of Radiation Oncology Task Force on Stereotactic Body Radiotherapy, my colleagues and I were

able to publish guidelines that detail the technical requirements and scope of practice for radiation oncologists with respect to spine, liver and lung tumors [11]. This is an excellent resource for any department to refer to when deciding to start a stereotactic body radiosurgery program.

There are several challenges unique to spine radiosurgery compared with brain radiosurgery. First, target delineation is much more complex. It requires a margin of normal tissue within the spinal segment to be included in the high-dose target volume to reduce the risk of failure. We have learned that in certain clinical situations, for example, if the posterior elements are spared, then the risk of failure is higher within that anatomy. It is only recently that international consensus guidelines have been published that detail the anatomic considerations for target volume delineation [12]. Second, the complexity of the shape and the inherent task to spare the spinal cord from the high dose intended for the adjacent tumor challenges the treatment planning system and requires multiple iterations before a treatment plan can be achieved. Moreover, in all directions there are several different normal tissues to be considered that ultimately compete with the goal of covering the target adequately. Therefore, major decisions must be made as to what dose is allowed to be delivered to these tissues. This is not an easy task given that as yet there is very little information on how much the various body tissues can tolerate when treating with high-dose-per-fraction radiation. Although the most significant risk lies in overdosing the spinal cord, we are also learning about new major toxicities associated with the bone tissue manifesting as vertebral compression fractures and major complications from overdosing the esophagus.

Q Do you envisage that the spinal cord dose limits your group has produced will be reviewed again & updated?

We need to constantly review the guidelines and we will only learn more about the generalizability of these dose limits as more institutions publish their results. Initially, many cases of spinal cord myelopathy

came from the direct consequence of too high a dose being allowed to the spinal cord, and it was no surprise that patients were being hurt. However, we have been observing cases that are somewhat unexpected according to the dosimetric data, which shows that we have much to learn as to why this technique is resulting in spinal cord myelopathy. Although our work has concluded that the dose within small volumes of spinal cord is a major factor in the development of spinal cord toxicity, it is only with further analysis and greater experience that the relationship between other dosimetric factors will become clear. This will allow the treatment to mature, develop and maximize its potential.

Q How far do you think the field is from confidently predicting complications of stereotactic radiation therapy?

We are certainly at a point where we have practiced stereotactic body radiotherapy long enough that we are gaining the necessary data to develop dose limits for safe practice and are able to consent patients appropriately. For the most part, we are no longer basing practice, or patient discussions, on experience alone. There are reasonable thresholds for many organs including the lung, esophagus and spinal cord; however, these are not yet broad enough to be applicable to all the various fractionation schemes currently in use. There are also several organs at risk that we still need dosimetric data to formulate normal tissue complication probability estimates for, both in the radiation-naïve patient and the patient with prior radiation exposure.

One other major area that we are looking at is vertebral compression fracture. What we are learning is that high doses of radiation may be quite toxic to the bone. Therefore, although we are doing a good job of local control, patients are suffering from fractures. There has been variability in the literature, and the Memorial Sloan Kettering Cancer Center (NY, USA) reported almost 40% of their patients fracturing [13], while the MD Anderson Cancer Center (TX, USA) reported 20% of their cohort experiencing a fracture [14]. From the University of Toronto, we recently published our risk at approximately 11% [15].

“Radiosurgery alone not only gives patients a chance to preserve their memory, but also results in fewer delays in initiating systemic therapy and allows more cycles of systemic therapy to be given.”

We showed that high-dose single-fraction radiosurgery increases the risk of fracture, as compared with delivering the dose in a few fractions. Although some advocate single-fraction radiosurgery as biologically advantageous in treating the tumor, we showed that this may come at the expense of damaging normal tissues. This is a major concern in the metastatic patient. Ultimately, what we do is not helping survival but local control, and if we jeopardize systemic therapy by negatively impacting the patient's condition, performance status or causing delays to fix iatrogenic complications, then this may have serious implications on their life expectancy. We are currently working on a multi-institutional analysis, specific to fracture, to identify more robust anatomic- and dose-related predictors of this adverse event that will hopefully guide safe practice.

Q You recently published an updated Cochrane review & a meta-analysis into WBRT for brain metastases that suggested no overall survival benefit of this treatment method compared with radiosurgery alone. How do you see WBRT being used in the clinic going forward?

Based on both the Cochrane review (led by my colleague May Tsao) [16], and the meta-analysis I led and published in *Cancer* [1], we concluded no survival benefit with the use of WBRT in conjunction with stereotactic radiosurgery. Therefore, with the randomized controlled trial published by Chang *et al.* in *Lancet Oncology* [17] that concluded a negative impact on the use of WBRT on memory, radiosurgery alone for selected patients is a favorable therapeutic option. We must keep in mind that as systemic therapies are getting better and people are living longer, oncologists should consider the long-term adverse neurocognitive side effects of WBRT when making treatment recommendations. Radiosurgery alone not only gives patients a chance to preserve their memory, but also results in fewer delays in initiating systemic therapy and allows more cycles of systemic therapy to be given. These factors are important in patient survival. My position is that radiosurgery alone should be the standard of care for patients who present with a limited

number of brain metastases, who do not need surgical intervention, and WBRT should be reserved as a last resort salvage therapy. The studies are quite clear that approximately half of patients treated with radiosurgery alone will be spared WBRT. Furthermore, if new metastases occur then further radiosurgery is still possible, which again gives the patient the chance to avoid WBRT during their lifetime.

I do contend that there is a role for WBRT in the modern management of patients with brain metastases, given that the majority of patients still present with multiple lesions disseminated throughout the brain. Although technologic innovations allow for multiple lesions to be treated with radiosurgery alone (i.e., more than the traditional limit of four lesions), the standard of care in these patients is still WBRT. As the technology is evolving for radiosurgery, it is also being applied to modernize WBRT. Strategies to minimize adverse neurocognitive effects are currently based on sparing the hippocampus. There is a large trial currently evaluating hippocampus sparing WBRT with neurocognitive primary end points. The other major strategy lies in improving local control rates, given that current whole-brain doses are low and suboptimal. This is achieved by exploiting modern radiation techniques to simultaneously integrate a boost to the gross disease while still radiating the entire brain tissue. Both have promise and eventually will be combined and tested against radiosurgery alone.

Q Aside from the research conducted by your group, what other recent research on nervous system tumors has been of particular interest to you?

We have a lot of interest in the neurocognitive impacts of various cancer treatments in the brain. For example, the effects of chemotherapy and new targeted systemic therapies that can penetrate into the brain are of major importance. Furthermore, new alternatives to radiation as focal noninvasive treatments are emerging and include MRI-guided focused ultrasound. I think novel imaging techniques that can advance our understanding of radiation response are of critical importance; this

“...the whole area of how to determine response for spine radiosurgery is a brand new focus of research, and there is a major need for consensus.”

includes perfusion imaging, PET imaging with novel radioactive labeled tracers, and apoptosis quantification MRI. With respect to imaging and glioma, the use of MRI spectroscopy to detect gliomas with *IDH1* mutations is exciting and innovative. For the spine, some groups are trying to determine the impact of various fractionation schemes within the radiosurgery sphere. We need to know if a single fraction versus delivering the dose in a few fractions is actually any different. Novel MRI- and computed tomography-based imaging techniques that determine responders to spine radiosurgery are evolving, and this is critical as we are learning that traditional MRI may not be the best way to determine response. In fact, the whole area of how to determine response for spine radiosurgery is a brand new focus of research, and there is a major need for consensus.

Q What are your individual goals for the next 5 years in terms of your work in the neuro-oncology field?

The main areas I would like to contribute to include evolving the role of radiosurgery for multiple metastases and determining the neurocognitive effects of radiosurgery as the sole modality for patients with ten, 20 or even 30 metastases. Eventually, brain metastases will be more or less a chronic condition requiring maintenance therapy with focal ablative techniques and most patients will be spared WBRT. Another major area that I am very keen to explore includes the use of hypofractionated stereotactic radiotherapy for patients with large brain metastases, which would otherwise not be treated with single-fraction radiosurgery or underdosed to avoid normal tissue toxicities. I think that few-fraction stereotactic radiotherapy using frameless techniques is the future, and a randomized controlled trial is needed to determine the optimal strategy. Similarly, for post-surgical brain metastases patients, the use of WBRT has been the mainstay but cavity radiosurgery has evolved into accepted practice. Currently, surgical cavity radiosurgery is being evaluated in a randomized trial to WBRT with the primary end point being neurocognitive function. However, my bias is to treat surgical cavities with

hypofractionated stereotactic radiosurgery, as the volumes tend to be large and irregular, and I postulate that the long-term control rates may be better. Therefore, the use of few-fraction surgical cavity stereotactic radiosurgery needs evaluation in comparison with single-fraction radiosurgery, and is a trial I would like to initiate.

In the spine, my current aims are to try and answer the question as to whether or not spine radiosurgery is better than conventional radiation. We are still at a point in the field's maturation, and randomized controlled trials are needed before widespread adoption of the technique can be supported. Although there is a randomized trial underway comparing relatively low doses of single-fraction conventional radiation to radiosurgery in patients with no prior radiation exposure, we have a proposal to compare higher doses of fractionated conventional radiation to radiosurgery in a similar patient cohort. Both studies are complementary and desperately needed to answer the question as to whether or not spine radiosurgery yields better pain and local tumor control versus conventional radiation. In addition, the field of post-operative spine radiosurgery is also maturing. Intuitively, after putting a patient through a major spine operation, then it only makes sense to me to deliver an optimal adjuvant therapy in the form of spine radiosurgery. However, the current dogma is to treat the patients with low-dose conventional radiation as they are still regarded as palliative. Hopefully, with the help of co-operative spine surgical and radiation oncology groups, a randomized trial comparing conventional postoperative radiotherapy with spine radiosurgery can be performed.

Financial & competing interests disclosure

A Sahgal has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

"In the spine, my current aims are to try and answer the question as to whether or not spine radiosurgery is better than conventional radiation."

References

- 1 Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer* 118(9), 2486–2493 (2012).
- 2 Sahgal A, Larson DA, Chang EL. Stereotactic body radiosurgery for spinal metastases: a critical review. *Int. J. Radiat. Oncol. Biol. Phys.* 71(3), 652–665 (2008).
- 3 Sahgal A, Bilsky M, Chang EL *et al.* Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient. *J. Neurosurg. Spine* 14(2), 151–166 (2011).
- 4 Masucci GL, Yu E, Ma L *et al.* Stereotactic body radiotherapy is an effective treatment in reirradiating spinal metastases: current status and practical considerations for safe practice. *Expert Rev. Anticancer Ther.* 11(12), 1923–1933 (2011).
- 5 Sahgal A, Ma L, Gibbs I *et al.* Spinal cord tolerance for stereotactic body radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 77(2), 548–553 (2010).
- 6 Sahgal A, Ma L, Weinberg V *et al.* Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 82(1), 107–116 (2012).
- 7 Sahgal A, Weinberg V, Ma L *et al.* Probabilities of radiation myelopathy specific to stereotactic body radiation therapy to guide safe practice. *Int. J. Radiat. Oncol. Biol. Phys.* doi:10.1016/j.ijrobp.2012.05.007 (2012) (Epub ahead of print).
- 8 Sahgal A. Technological advances in brain and spine radiosurgery. *Technol. Cancer Res. Treat.* 11(1), 1–2 (2012).
- 9 Foote M, Letourneau D, Hyde D *et al.* Technique for stereotactic body radiotherapy for spinal metastases. *J. Clin. Neurosci.* 18(2), 276–279 (2011).
- 10 Hyde D, Lochray F, Korol R *et al.* Spine stereotactic body radiotherapy utilizing cone-beam CT image-guidance with a robotic couch: intrafraction motion analysis accounting for all six degrees of freedom. *Int. J. Radiat. Oncol. Biol. Phys.* 82(3), e555–e562 (2012).
- 11 Sahgal A, Roberge D, Schellenberg D *et al.* The Canadian Association of Radiation Oncology scope of practice guidelines for lung, liver and spine stereotactic body radiotherapy. *Clin. Oncol. (R. Coll. Radiol.)* 24(9), 629–639 (2012).
- 12 Cox BW, Spratt DE, Lovelock M *et al.* International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int. J. Radiat. Oncol. Biol. Phys.* 83(5), e597–e605 (2012).
- 13 Rose PS, Laufer I, Boland PJ *et al.* Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. *J. Clin. Oncol.* 27(30), 5075–5079 (2009).
- 14 Boehling NS, Grosshans DR, Allen PK *et al.* Vertebral compression fracture risk after stereotactic body radiotherapy for spinal metastases. *J. Neurosurg. Spine* 16(4), 379–386 (2012).
- 15 Cunha MV, Al-Omair A, Atenafu EG *et al.* Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. *Int. J. Radiat. Oncol. Biol. Phys.* 84(3), e343–e349 (2012).
- 16 Tsao MN, Lloyd N, Wong RK *et al.* Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst. Rev.* 4, CD003869 (2012).
- 17 Chang EL, Wefel JS, Hess KR *et al.* Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* 10(11), 1037–1044 (2009).