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Palliative Radiotherapy Column (Review Article)

# Stereotactic radiosurgery/stereotactic body radiation therapy—reflection on the last decade's achievements and future directions

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**Abstract:** Stereotactic radiosurgery (SRS) and its extracranial first cousin, stereotactic body radiation therapy (SBRT) have become increasingly important in the palliative treatment of cancer patients over the past decade. Appropriately designed and adequately powered clinical trials have in many clinical scenarios amply justified the time, effort, and expense associated with the development and delivery of these highly conformal and complex radiation treatment plans. Ongoing trials are anticipated to provide further confirmatory documentation of the benefits that have been readily observed by caregivers, patients, and their families. It may be predicted that future directions for palliative radiosurgery will include simplification, through greater automation, of the detailed steps that are still required for safe treatment, and thereby increase the chances for patients to receive these advanced palliative interventions at local institutions, from local caregivers.

**Keywords:** Cancer; pain management palliative care stereotactic radiosurgery; stereotactic body radiotherapy

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## Introduction

Palliative irradiation is often dismissed as relatively unimportant. It is regarded as something as common as dirt and as old as dirt. However, just like dirt, palliative irradiation is underappreciated. The oldest equipment in the radiotherapy department is often used for palliative cases. Justifications for not attempting to integrate the best palliative irradiation possible into the care of patients should be periodically scrutinized, as the matrix in which care is being provided is continually in flux, and what were reasonable justifications in the past may no longer be adequate.

Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) are some of the most sophisticated and technically demanding radiation oncology procedures being performed. This is because SRS and SBRT require millimeter (or less) level accuracy, and the targets for treatment are often within or adjacent to critical normal tissues that will not tolerate the extremely high doses typically delivered in 1–5 fractions.

The entire process of planning and delivering these treatments requires a higher level of precision than is needed for conventionally delivered radiation therapy. Some form of a customized immobilization device that assures reproducibility of positioning between planning and treatment delivery is mandatory, and highly detailed diagnostic imaging studies are needed to accurately resolve the geometric relationships between targets and normal tissues.

In addition, software and hardware required for SRS and SBRT planning and delivery are more exacting than for conventional radiation therapy. Fortunately, periodic upgrades and purchases of new radiotherapy equipment for image guidance and intensity modulation in conventional radiation therapy often permit SRS and SBRT to be delivered without the purchase of dedicated platforms.

As younger radiation oncologists enter the field that are familiar with stereotaxis and the multifarious requirements for performing these exacting treatments, SRS and SBRT are becoming more ubiquitous. Radiation oncologists are increasingly adopting stereotactic techniques for not only curative cases, but also palliative cases, and it is likely that the greatest numbers of patients are being treated in the palliative setting. SRS and SBRT are able to provide palliative benefits that conventional radiotherapy cannot for many patients who cannot be cured of their underlying malignancies. Thus, the use of these sophisticated treatments should be more frequently integrated into the care regimens of these patients.

Of course, SRS and SBRT have roots extending beyond the past decade, though not as far back as palliative radiotherapy (1). SRS was first utilized in the 1950s as a less invasive and less risky procedure than an open craniotomy performed to ablate a pathological target (2).

Shortly after the first patients were treated with SRS in the late 1950s, ablative SRS procedures for pain, including mesencephalotomy, thalamotomy, and pituitary ablation, were essayed (3-5). Perceived advantages included the minimally invasive nature of a stereotactic headframe placement relative to a craniotomy, and the rapid response that was observed. Targeting of intracranial metastatic disease was not really feasible until after the development of contrast-enhanced CT and MR imaging in the mid-1970s, and software and hardware then needed to be developed to permit the fuller exploitation of the three-dimensional imaging data that these revolutionary technologies could provide.

The first intracranial radiosurgical treatments of brain metastases were remarkably effective, and spurred a series of international clinical trials to clarify its role as an adjunct to, and later as an alternative, to whole brain radiation therapy (WBRT) (6-8). The data clearly indicate that SRS without WBRT is the best initial treatment for patients with 1–4 brain metastases (assuming SRS is suitable based upon metastasis size, good patient performance status, and a controlled/controllable extracranial disease status), because WBRT does not improve survival and degrades cognitive performance (9). Indeed, a meta-analysis of smaller, antecedent trials evaluating SRS with or without WBRT for 1–4 brain metastases documented a worsened survival for patients under the age of 50 who were randomized to receive WBRT (10). This result requires validation, but has shaken the dogma surrounding equipoise with respect to the question of survival and treatment with SRS alone or WBRT plus SRS.

The level 1 evidence in aggregate has been considered by our professional societies; there is increasing support for SRS alone for patients with limited brain metastases. WBRT can be reserved for salvage therapy in the event of relapse. For example, the American Society for Radiation Oncology (ASTRO) Choosing Wisely campaign warned practitioners again routinely treating patients with adjuvant WBRT following SRS owing to the deleterious effects of WBRT with respect to neurocognition and quality of life.

One resounding advantage to SRS for brain metastases, especially for frail and near-terminal patients, is the potential for completion of radiation treatment in a single day. The inconvenience of journeying back-and-forth for treatments is eliminated. This is particularly attractive in a national healthcare system setting where patients frequently travel long distances to get to a tertiary center for their cancer treatments. In addition, the probability of durable lesion control with SRS is far superior to that achieved with WBRT alone, and may be conservatively estimated at ~70–80% after 1 year, with improvements from this baseline for smaller tumors, certain histologies, and the use of systemic therapy (11). Although further treatment may be required in ~50% of patients due to distant brain relapse, the ease of repeating SRS for intracranial recurrence will only serve to ensure that WBRT continues to be a less commonly used palliative intervention reserved for military or leptomeningeal disease.

The use of SRS alone in patients with more than four metastases has been reported in a landmark phase II trial (12). This study enrolled over a thousand patients and determined that there were no differences in survival for patients managed with definitive SRS for 2–4 brain metastases or 5–10 brain metastases. At present, this is the best data available to support the sole use of SRS for between 5 and 10 brain metastases, or indeed for patients with more than 10 brain metastases.

## The utilization of SBRT for extracranial metastases for palliation

SBRT is a spin-off of intracranial SRS that shares key components such as robust immobilization, complex treatment planning, image guidance pre- and intra-treatment, and accurate treatment delivery. However, SBRT must also achieve respiratory motion control or adapt to its presence (13,14). In the past decade, there has been significant improvement of technologies that facilitate the SBRT process. A decade ago, there were a limited number of centers in the US offering SBRT and on-board imaging was not consistently available. Now, nearly every modern cancer treatment center has SBRT capability and there are a few options for each of the key SBRT components mentioned above. There is currently a surge in the use of SBRT for various primary cancers and extracranial metastases (15). While most of these treatments were given with curative intent, there were some studies reporting symptomatic control outcomes, which will constitute the basis of our discussion.

### Spine

SBRT has been most frequently used for metastases located in the spine. The earliest treatments were delivered by investigators who did not have the ability to confirm the accuracy of treatment localization on the linear accelerator immediately before treatment (16). The acceptance of SBRT to treat spine metastases was hastened by the utilization of stereoscopic 2D X-ray imaging to readily detect bony landmarks or implanted fiducial markers for treatment planning (17-19).

Currently, even more sophisticated technologies permit CT imaging to be performed just before SBRT delivery. This CT dataset can be fused with the 3D radiotherapy plan and automated couch position control mechanisms correct misalignments by carrying out six degree-of-freedom translational and roll, pitch, and yaw rotational misalignments. Accuracies of ~1 mm translation and ~1 degree of rotation are achievable with modern technology. The practice of SBRT has increased exponentially across the globe and a large body of experience has been gained on the use of SBRT for spinal metastases in the definitive, postoperative and re-irradiation settings. Local control and pain control are the most commonly reported endpoints. Overall, the reported local or pain control rates are in the 80–85% range (20). Sahgal *et al.* have analyzed risk factors associated with vertebral compression fracture, pain flare, and radiation myelopathy, from which dose tolerance guidelines for the spinal cord in the radiation naïve and re-irradiation settings have been established (21).

Spine SBRT is now part of the armamentarium in the management of spinal metastases and this is exemplified by the fact that this treatment modality has been incorporated in the American College of Radiology (ACR) Appropriateness Criteria documents (22,23).

### Non-spine bone

SBRT for non-spine bone metastasis is also being increasingly offered to patients. In most cases of non-spine bone metastases, critical structures are remote from the treated areas and, therefore, highly conformal techniques delivering high dose or ablative radiotherapy is less frequently necessary. For bone metastases from radioresistant histologies, such as renal cell carcinoma, melanoma and sarcomas, conventionally fractionated radiotherapy is not as effective in relieving pain and obtaining local control of the tumor (24). In such situations, it may be reasonable to consider SBRT aiming to improve the pain and local control, especially in the oligometastatic setting. However, the data on SBRT for painful non-spinal bone metastasis are very limited. Data from Houston Methodist Hospital have demonstrated a radiation dose response in that a biologically effective dose of 85 Gy or higher was associated with faster and more durable pain relief (25). At this point in time, SBRT has not been established as one of the treatment options for non-spine bone metastases. The most current ACR Appropriateness Criteria document does not recommend offering SBRT for painful non-spinal bone metastases routinely (26). Furthermore, its safety in critical areas such as articular surfaces, long bones, and digits is unknown.

## Adrenal metastases

Most adrenal metastases are asymptomatic and are detected during the process of imaging staging. However, some patients with bulky adrenal metastases experience visceral or somatic pain for which palliative radiotherapy may be indicated. SBRT has been used to treat adrenal metastasis either as focal therapy for oligometastatic disease or for pain palliation. In the studies from the University of Rochester and the Ohio State University, all patients with baseline pain experienced symptomatic improvement after SBRT (27,28).

## Future directions

Radiosurgery for brain metastases, admittedly nearly always a palliative intervention, has recently been proven to be the best treatment for most patients. Technological advances that permit more ready adoption of focused treatment of intracranial pathology will also hasten the acceptance of this form of treatment, while WBRT becomes more selectively used for patients with leptomeningeal carcinomatosis or other clinical indications where focal treatments are not superior. For example, single isocenter linear accelerator based treatments using multiple non-coplanar arcs and high resolution multileaf collimators are now being used clinically. This advance permits focal radiosurgical treatment to be delivered to multiple lesions in minutes, rather than hours (29,30). This approach is limited by the high potential for geographic miss of small metastases far from the treatment isocenter due to uncertainties in narrow-field dosimetry and misalignments across the mechanical, imaging and radiological isocenters. This is amplified even if a slight difference in patient positioning between planning and delivery occurs. Highly conformal treatments of small targets cannot be easily achieved on linear accelerators with low-definition multileaf collimators, and prescribing different doses to different targets cannot be readily done with this approach as yet. Another problem is the difficulty that current radiosurgery quality assurance procedures have with checking the dosimetric calculations performed *in silico* against those that are delivered to a phantom. This is because irradiating multiple small lesions with many overlapping narrow fields tends to elevate the failure rate of satisfying stringent quality assurance criteria specific to the high-dose radiosurgical beam delivery (31). When these issues can be addressed adequately, this approach is likely to rapidly gain adherents for treating multiple brain metastases.

Similarly, the Gamma Knife Perfexion's most recent model (Elekta AB, Sweden) is also redefining the concept of frameless radiosurgery to an extent that the platform was given a new name: Icon. This latest generation stereotactic radiosurgery system for the brain integrates advanced motion management, adaptive dose delivery and imaging technologies, and significantly increases the versatility of the device. Gamma Knife radiosurgery can now be performed with frameless image-guidance, so that the treatment of multiple metastases can be administered with an easier workflow and more flexible dose fractionation schemes: for example, a patient who has many tumors may be treated in separate target groups and/or with hypofractionation in two or more sessions over a few days time. This will enable patients with even 10 to 20 or more metastases to still be treated conveniently and potentially more effectively over the frame-based single-session treatments. Patient comfort and satisfaction are also likely to improve with the new frameless Gamma Knife radiosurgery as well.

Just as for SRS, SBRT is a particularly attractive treatment modality in a national healthcare system setting where patients frequently travel for long distances to get to a tertiary center for their cancer treatments. There is likely to be an increasing use of this minimally morbid treatment as systemic therapies, including immune system modulators gains better control of systemic cancer and survivals are increasingly protracted.

Although SBRT has been established as one of the standard treatments for spinal metastases, some may argue that it has not been adequately compared with conventional radiotherapy in terms of efficacy and toxicity in a phase 3 randomized trials. Radiation Therapy Oncology Group (RTOG) study 0631 is an ongoing randomized controlled trial comparing conventional radiotherapy (8 Gy in 1 fraction) and SBRT (16 or 18 Gy in 1 fraction) in patients with 1–3 spinal metastases (32). Canadian researchers have opened a randomized phase 2 trial under the aegis of NCI Canada comparing 20 Gy in 5 fractions delivered conventionally to 24 Gy in 2 fractions delivered with SBRT (33). The results of these trials are eagerly awaited.

At many centers around the world additional trials are being conducted of SBRT for various indications such as primary and metastatic liver tumors, primary and recurrent pancreatic cancer, primary and metastatic renal cell carcinoma, as a boost treatment for or salvage treatment for head and neck cancers, and it is expected that as greater experience is gained, there will be clear indications for SBRT in the palliative (or curative) setting to prolong disease-free survivals, to potentiate impactful immunologic therapies, and to improve quality of life and overall survival. It is an exciting time to participate in the transformation currently ongoing in palliative radiotherapy that SRS and SBRT have ushered in.

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