1. Introduction

Metastasis to the spinal column is an emergent problem in cancer patients which is not rare and occurs in almost 40%. (1) The aim in management of metastasis to the spinal column is to decrease the sequelae including pain, instability, and neurological deficit to avoid progressive myelopathy resulting in the loss of motor, sensory, and autonomic functions. Although the treatment is palliative, the durability of the progression free period without any sequel is essential. As the treatment options increase in number, comprehensible multidisciplinary approach needs to be in charge to effectively implement the proper treatment. Surgery is inevitable in case of cord compression, however if there is no vertebral instability in immediate requirement of reconstruction and stabilization of the spinal column, radiotherapy has developed into a noninvasive and effective modality by Stereotactic body radiotherapy (SBRT) option. Conventional radiotherapy of 30 Gy in 10 fractions or 45 Gy in 25 fractions can be effective in acute palliation of pain and neurological symptoms of spinal metastases; however the outcome might not be robust in many consequences without the conventional reirradiation possibility. Spinal SBRT has the advantage of minimizing dose to the spinal cord while delivering higher doses to the spinal tumor; and is a potential treatment option for preferably low volume vertebral metastases as a primary choice, whereas it can also be offered in postoperative setting or in salvage setting subsequent to previous irradiation or recurrence after surgery.

Stereotactic body radiotherapy (SBRT)

SBRT is a non invasive image-guided process of radiotherapy intervention which uses a three-dimensional coordinate system to locate small targets inside the body in order to deliver high precision and an increased load of radiation for highest local control possible. “Stereotactic” (or “stereotaxic”) means “solid ordering” in Greek. The American Society of Therapeutic Radiology and Oncology (ASTRO) defines SBRT as an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions with high targeting accuracy and rapid dose falloff gradients encompassing tumors. (2,3) Theoretically, any location inside the body can be subjected to SBRT with required reliable set up and imaging. Single-fraction SBRT with simulation, planning, and treatment on the same day is called as Stereotactic body radiosurgery (SBRS), while SBRT covers all fractionated treatment sessions using larger daily doses of radiation than conventional fractionated doses of 1.8-3 Gy/fraction/day.

Single fraction SBRT has been reported by many centers with various dose ranges, (4-6) as growing literature for multiple fraction SBRT exist. (7-10) The reasoning of single or multiple fractionations in spinal SBRT depends on clinical judgment; small volume tumors with enough safety margins from spinal cord might be preferred to be treated with single fraction SBRT, while tumors with paraspinal extension, or having multiple level or prevertebral involvement, or being close to bowel could be elected to be treated with 3 to 5 multiple fractions SBRT. General conservative consideration is the capability of more than one fraction to balance possible positional set up inaccuracies in comparison to single fraction SBRT. Therefore, the safety band of fractionated SBRT with adequate confidence could be the first option in conditions with
high setup or normal tissue toxicity risk despite its disadvantage of inconvenience. Examples of Intensity modulated SBRT are given in Figures 1-5 as our current clinical approach of delivery in three fractions. Single fraction SBRT is mainly built on strict one-time immobilization for same day simulation, planning and delivery of treatment while increasing real time imaging capabilities such as cone beam CT mounted on the linear accelerators for exact setup provides flexibility in the timing of simulation and treatment on different days.

Experience on spinal stereotactic radiosurgery was set off with the early series of Hamilton et al at University of Arizona that used an invasive rigid fixation device for immobilization of the spine in nine patients with recurrent spinal tumors and prescribed median 8 Gy. (11) One of the initial important studies demonstrating targeting accuracy within 1.5 mm for actual patient treatment was reported by Ryu et al. (12) These were establishing clinical feasibility of the accuracy and precision of SBRT to treat tumors adjacent to the spinal cord. Chang et al detailed near-simultaneous computed tomographic image-guided SBRT at M. D. Anderson Cancer Center for 15 patients with metastatic spinal disease using a comparatively conservative regimen of 30 Gy in 5 fractions with a maximum dose constraint for spinal cord of 10 Gy with no neurologic toxicity in median 9 months. (13) Bilsky et al reported on their preliminary Memorial Sloan Kettering Cancer Center clinical experience in treating 16 paraspinal tumors with stereotactic IMRT where used 20 Gy tumor dose in 4 or 5 fractions with a maximum dose constraint for spinal cord of 6 Gy. (14)

Succeeding clinical studies with spinal SBRT demonstrated the efficacy for rapid pain relief and improvement of neurological function. (14,15,19) In general palliation of pain is the most invested and reported main cause of irradiation of spinal column metastases with complete pain relief after SBRT was reported in various series at 33% to 86%. (5,12,20,21) Other cancer related symptoms besides pain also need to be investigated. Quality of life is also improved secondary to pain relief. (19) SBRT could help in reduction of symptom burden in terms of other cancer related symptoms such as fatigue, pain, sleep disturbance, drowsiness, and distress with better local control and activity of daily living, ability to work, and mood. (13)

Ryu et al. at Henry Ford Hospital reported on 49 patients treated with single doses of 10–16 Gy with a complete pain relief of 46% at 8 weeks and both complete and partial pain relief of 83%, while pain relapsed in 7% and tumor progressed in 5%. (4) Gerszten et al published SBRT of 12.5–25 Gy with long-term pain improvement in 86%. (5) Yamada et al. noted that patients without local failure after single fraction SBRT doses of 18–24 Gy had long term symptom palliation. (6) Gibbs et al. used 16–25 Gy in one to five fractions and disclosed 84% improvement of initial symptoms. (7,8) Nelson et al reported 39% and 51% complete and partial pain relief at one month respectively with three fractions of SBRT (range, one to four fractions). (9) Gerszten et al at the University of Pittsburgh treated 500 cases of spinal metastases with 12.5 to 25 Gy Cyberknife based single-fraction SBRT. (5) Long-term pain improvement occurred in 86% while tumor control was achieved in 90% of treated lesions. Ryu and colleagues defined that median duration of pain control with spine SBRT was 13.3 months. (16) The currently ongoing RTOG 0631 trial will assess pain relief as its primary endpoint where patients with spinal metastases are randomized to receive either 8 Gy x 1 fraction of conventional radiation therapy or 16 Gy x 1 fraction of SBRT. (20)

Conventional palliative radiotherapy has recognized role on pain control for bone metastases for an intermediate period of time, while robust tumor control on spinal metastases likely require higher doses. Spinal SBRT might be a promising solution to decrease pain and neurological complications including metastatic epidural spinal cord compression (MESCC) due to inadequately conventionally treated spinal metastases. (23,24) Higher doses than conventional fractionation of 30 Gy in 10 fractions might have a better chance of preventing bony destruction of the spinal column leading to spinal instability. The major limiting factor avoiding higher dose prescription to spinal column is the low threshold of spinal cord radiation tolerance.

SBRT is a competent technique with ability of image-guidance to precisely deliver higher doses to secure a safe dose gradient at the spinal cord and tumor interface. This noninvasive modality achieves more than 80% of objective radiological tumor control at the treated spine. (5,10,15) Thus, a new era of therapeutic window with low risk of spinal cord injury is in charge with SBRT. Spinal SBRT could become a smart
alternative to surgery in selected cases with avoidance of possible operative risks, besides a proper way of reirradiation of spinal column metastases which are generally not irradiated by conventional means.

2. Indications

Rationale of the large dose per fraction in SBRT is to ablate tumor cells and/or overcome radioresistance resulting in greater log cell kill. There are four major indications:

- spinal metastases without instability
- postoperative adjuvant approach for high risk local recurrence
- postoperative salvage approach for clinical progression
- salvage approach for local disease progression or recurrence after conventional radiotherapy to the spine

Conditions of Patient Eligibility

- Localized (solitary or not more than two contiguous spine levels) spinal column metastasis.
- Distance to spinal cord is important for eligibility and SBRT is considered if ≥ 3 mm gap is present between the spinal cord and the edge of the epidural lesion. Surgery is preferable if closer than 3 mm to cord. SBRT might be opted if surgery is not an option despite underdosage of epidural component.
- Paraspinal mass component ≤ 5 cm in the greatest dimension contiguous with spine metastasis
- Well-controlled systemic disease
- Karnofsky Performance Status ≥ 40
- Previous irradiation not more than 45 Gy (1.8-2 Gy/fraction) or 30 Gy (3Gy/fraction)
- Radioresistant tumors metastatic to spinal column such as renal cell carcinoma, melanoma, and sarcomas are considered to benefit more in comparison to other cancers.

3. Contraindications

- Radiosensitive metastases such as plasmacytoma, lymphoma, and germ cell primary: Conventional fractionation radiation therapy with 1.8 - 3 Gy/fraction/day to a total dose of 45-30 Gy is the standard first choice of treatment in these histology due to tumor control curve lying to the left of the normal tissue complication curve.
- Tumors enclosing the spinal cord, compressing the cord or thecal sac, involving the epidural space require surgical decompression which subsequently requires SBRT after resection of the proximal disease to the spinal cord.
- Cord or cauda equina compression with neurologic deterioration: Emergent surgery is encouraged
- Unstable spine (e.g. compression fracture; > 50% loss of vertebral body height): Emergent surgery is encouraged
- Non-ambulatory patients
- Previous radiotherapy dose greater than 45 Gy (1.8-2 Gy/fraction) or 30 Gy (3Gy/fraction)

4. Procedures

Spinal SBRT requires extensively improved immobilization, imaging and delivery precision to limit target movement during planning and delivery. Delivery can be via planar or non-coplanar multiple static beams or rotational fields of varying degrees with or without beam intensity modulation. Stereotactic localization of the lesion is essential by appropriate imaging modality, such as bony landmarks, fiducials, or computed tomography (CT) to ensure accurate beam placement. Quality assurance (QA) must be followed strictly for SBRT accuracy. The quality of a SBRT treatment depends on the coordinated team effort along an accurate treatment planning and delivery process with reliable verification.

The responsible radiation oncologist (RO) carefully evaluates the planned treatment impact through benefits and potential risks, educated design and conduct of treatment, and cautious follow-up after SBRT. RO needs to determine patient-specific and reproducible positioning, and stability of setup appropriately; and to supervise simulation process with spatial accuracy and precision of the imaging modality. After defining the target, RO prescribes dose, sets limits according to normal tissue dose constraints, approves the final treatment plan prepared by the medical physicist, and closely directs the actual treatment process.
SBRT targeting and treatment ensures adequate dose coverage of the target with rapid falloff to normal tissues by numerous coplanar or non-coplanar beams or large arcs of radiation with apertures, as well as by intensity-modulated radiation delivery. Intensity-modulated radiation therapy (IMRT) is a sophisticated form of three-dimensional conformal radiation therapy granting necessary and appropriate coverage of tumor with falling doses to the spinal cord in constraints. Computer-controlled multileaf collimation of the modern linear accelerators provides precision and conformity to irradiate any shape of tumors such as surrounding the spinal cord. The use of a newly developed fusion and matching capacities of real time on board imaging as KV portal films and cone beam CT accurately identifies planned target for treatment.

4.a. Immobilization

As SBRT is designed to deliver high ablative doses to the spinal column tumor in one to couple of fractions; limiting the volume and maximum dose of the spinal cord that is irradiated is crucial to avoid potentially catastrophic toxicities. Tumor motion in general is a very complicated challenge for SBRT in other body SBRT approaches due to respiratory movement of organs. Fortunately, spinal column is a comparatively less mobile axis with respiration. If a reproducible minimization of target motion via immobilization is ensured, physiologic tumor motion is not an issue to be accounted via tracking or gating which is an obligation such as for lung or liver tumors. Precise imaging and positioning are mandatory to accompany and unify immobilization. Despite conventionally fractionated approach, irradiating a large volume of normal tissue to account for setup uncertainty is unacceptable in SBRT dose range. Therefore, the basics of spine SBRT are patient positioning, targeting, and delivery with minimal dosimetric margins.

A reproducible immobilization method is required which facilitates the real-time imaging and positioning at the SBRT linear accelerator. The immobilization is to decrease the set-up uncertainty in multiple fractions while verification of isocenter is required at each fraction by cone beam and/or KV image guidance. Immobilization should be in a stable supine and comfortable position to prevent patient movement. Stereotactic whole body cradle vacuum bag or alpha cradle with or without shrink-wrapping is used in general for customized immobilization to surround the patient on three sides to conform patient’s external contours with reference to the treatment delivery coordinate system. There is couple of commercial systems used to ease the reproducible immobilization such as Body Pro-Lok™ or BodyFIX® Stereotactic Systems. A rigid head and neck immobilization device such as thermoplastic mask should be used for metastasis to cervical spine or cervicothoracic junction.

4.b. Target and Critical Structures delineation

The gross tumor/target volume (GTV) is contoured with relevant imaging studies; GTV is expanded to the clinical target volume (CTV) due to the pattern of microscopic spread, and coordinate the proper planning target volume (PTV) beyond the CTV with information of the mechanical and setup uncertainty. Gross tumor volume (GTV): Contour gross lesion
Clinic tumor volume (CTV): GTV=CTV
Planning tumor volume (PTV): CTV + 1-2mm
Lower-dose CTV (CTV lower-dose): Contour remaining entire vertebral body and posterior elements and ensure more generous margin posterior to diseased vertebrae
The spinal cord volume is contoured 5-6 mm superior to 5-6 mm inferior to the GTV.
Critical structures are contoured starting at 10 cm above the target volume to 10 cm below the target.

4.c. Physics and Dosimetry of SBRT

SBRT is performed with high conformity of the prescribed potent dose to the tumor volume, with steep dose fall off to decrease normal tissue toxicity. This delivery requires multiple, non-opposing, non-coplanar beams or arcs. While minimizing the entrance dose to prevent severe acute skin toxicities, beam angles, beam number and beam weighting to isocenter are arranged to reduce the volume of tissue at intersection of beams to maintain an acceptable maximum dose in target and circumferential dose falloff. SBRT physics seek to provide 95% planning target volume coverage with an appropriate prescription isodose line (Figures 1-5).
Figure 1a:
Intensity modulated SBRT was delivered for thyroid carcinoma metastasis to T11 vertebral body to 27 Gy in 3 fractions at 9 Gy per fraction using 6 MV photons with multiple coplanar beams. Dose distribution in axial, sagittal and coronal view. Prescription is to 95% of CTV.

Figure 1b:
8 coplanar beams are assigned to this prescription: 180, 205, 225, 245, 095, 115, 135, 155.

Figure 2a:
Intensity modulated SBRT was delivered for breast carcinoma metastasis to T8 vertebral body to 27 Gy in 3 fractions at 9 Gy per fraction using 6 MV photons with multiple coplanar beams. Dose distribution in axial, sagittal and coronal view. Prescription is to 92% of GTV.
Figure 2b:
Dose volume histogram demonstrating the doses to regions of interest.

Figure 3:
Intensity modulated SBRT was delivered for metastatic colorectal cancer to C6-C7 vertebral bodies, neural foramina and posterior elements to a total dose of 27 Gy in 3 fractions at 9 Gy per fraction using 6 MV photons with semi-coplanar beams.
The medical physicist is responsible for the technical aspects of SBRT. This requires acceptance testing and commissioning of the SBRT system for its geometric and dosimetric precision and accuracy; monitor and assure proper functioning of the linear accelerator and CT simulator of SBRT system, the image guidance system, the image-based 3D and/or intensity-modulated treatment planning system, determine and check the appropriate beam-delivery parameters, and calculation of the radiation beam parameters consistent with the beam geometry according to the plan approved by the radiation oncologist. (2)

4.d. Quality Assurance (QA)

QA is basically verification process of radiation isocenter, cone beam isocenter, CT-CT matching software. SBRT QA secures the combined testing, proper functioning and communication of image-guidance and treatment delivery systems within acceptable tolerances which guarantees the information from the imaging system matching the planned beams to the exact position within the patient. This is performed with designation of image guidance system to define ≥1 test points of predefined coordinates and then testing treatment planning system to irradiate these same test points. Adequate image guidance is mandatory according to coordinate the stereotactic targeting of tumor between imaging system and delivery system, and body frames based only on frame fiducials are not adequate without proper image guidance. The frame-based SBRT includes a stereotactic body frame with adequate imaging system, and the
frameless SBRT includes one or more of the following, implanted metallic seeds within or close to the tumor; or landmark bone anatomy as a fiducial marker for matching with the planning digital reconstructed radiographs (DRR), or volumetric data obtained from on board CT to match the planning CT.

SBRT is basically an image-based and guided treatment with relevant image fusion, and/or localizing of target volumes. The images are necessary to delineate the gross tumor volume and normal tissue margins besides defining target coordinates of treatment beams. CT is practical and spatially undistorted to be used for SBRT where a virtual patient model for treatment planning can be established for the treatment plan evaluation and dose calculation. MRI is also helpful for exact delineation and MRI with CT images fusion is used to minimize geometrical distortions inherent in MR images. These images input are used in 3D planning process.

It is viable to mention that treatment planning software estimates doses to critical structures which is definitely restricted by the accuracy of irradiation beam data measurements by ion chambers under effect of size or volume of the system, and possible leakage of multileaf collimators besides leaf shape. Therefore, one should be aware of the potential risk on treatment planning of over or under-estimating the actual doses delivered in order to be conservative to limit doses to the spinal cord. It is essential to establish QA of the delivery system to increase the confidence of safety and setup data demonstrating consistent daily patient setups within 1mm of treatment isocenter.

4.e. SBRT Equipment

Currently, many commercially available treatment units capable of refined image guidance can perform spine SBRT. Decreasing the uncertainty with near real-time imaging for positioning and delivery is the major requirement, and patient positional imaging is obtained to align the patient in the treatment position in order to perform shifts at each fraction set up. None of them has a clear superiority to others in spinal SBRT. However, the key is proper training and experience of the team in SBRT.

The treatment devices can be categorized according to their imaging capabilities for positioning and delivery. Integrated gantry mounted cone beam CT and KV & MV on board imaging systems (The Trilogy™ Stereotactic System from Varian Medical Systems, The Elekta Synergy®), CT scanner linked to a linear accelerator via a shared tabletop (The Siemens Primatom), orthogonal X-ray cameras (The CyberKnife, Accuray, Inc., Sunnyvale, CA, USA, the Novalis, Brainlab, Ammerthalstraße, Germany) and megavoltage CT mounted in the system (The Tomotherapy HI-ART, TomoTherapy, Inc., Madison, WI, USA). The SBRT could be delivered as three major ways of application:

(a) Irradiation with a circular approach with a moving source or table, named arc treatment

(b) Irradiation with stationary fields shaped by a multileaf collimator with gantry-based systems

(c) Irradiation with multiple microstationary fields by cylindric collimator with the CyberKnife concept

4.f. Radiotherapy set up and Patient positioning

Acceptable and appropriate image-guidance (IG) for localization includes the accuracy of less than 2 mm from simulation/planning to the end of treatment. There are mainly four ways of IG noted below for image guided radiotherapy (IGRT):

- Cone-beam CT equipment mounted to the linear accelerator performing with the treatment beam or an auxiliary kV x-ray head to acquire multiple images for volume reconstruction to fine tune patient set ups with ultra-precise CT scans;
- Spiral dose delivery equipment using the treatment beam to collect helical CT information for image guidance;
- Any equipment that can produce stereoscopic planar views of the patient in the treatment position using either the treatment beam with a standard electronic portal imaging device (EPID) or a kV x-ray source with opposed imaging panel in order to localize anatomic points in space or implanted fiducial markers to reposition patients quickly and accurately
- A standard CT scanners linked to a linear accelerator via a shared tabletop (e.g., on rails) in the same room with the treatment equipment.

4.g. Fractionation

The prescription dose changes in SBRT with the fraction number from single to five. CTV lower-
dose includes entire vertebral body and posterior elements. Two thirds of prescription dose is planned to be prescribed to entire vertebral body and posterior elements.

- 16-24 Gy in single fraction
- 27 Gy in 3 fractions
- 30 Gy in 5 fractions
- Lower total doses with lower dose per fraction (21 Gy in 3 fractions or 25 Gy in 5 fractions) is prescribed owing to the discretion of the responsible RO (e.g., lesion below L2 adjacent to psoas muscle to decrease plexopathy risk, etc)

5. Complications and Avoidance

Spinal cord is the major dose-limiting critical organ at risk in SBRT and radiation-induced myelopathy (RIM) could be a debilitating complication to be avoided. The dose constraints for other organs at risk are detailed in the literature.  

5.a. Spinal Cord Tolerance

An extremely sharp fall-off of radiation dose beyond the tumor is required and this makes it possible to safely treat spinal column metastatic lesions with high total doses in single or fractionated SBRT.

Although radiation-induced myelopathy (RIM) is one of the most critical complications associated with radiation therapy, the factual spinal cord tolerance to SBRT has not been clearly defined due to highly conservative constraints followed in general. The RIM is based on white matter injury with demyelination and necrosis of the spinal cord, as well as on vasculopathies and glial reaction. In spinal SBRT, therapeutic ratio is increased with greater separation between the spinal cord normal tissue complication curve and the spinal tumor control probability curve. The spinal cord is highly sensitive to fraction size as being a late responding tissue where the actual fraction size to the spinal cord needs to be relatively small in comparison to hypofractionated high stereotactic radiation doses. The reported incidence of spinal cord complications is too low in the radiotherapy literature to project threshold of a safe dose of the spinal cord.

Because of different fraction sizes in a mainly palliative setting, it is difficult to conclude spinal cord tolerance to hypofractionation. A cornerstone study from Medical Research Council by Macbeth et al. used various regimens to palliate non-small cell lung cancer patients with 8.5 Gy X 2, 4.5 Gy X 6, 5 Gy X 6, 3 Gy X 10, 3 Gy X 12, and 3 Gy X 13 and estimated RIM as 0.6% (3 patients) with 8.5 Gy X 2 fractions at 8 to 42 months and 1.3% (2 patients) with 3 Gy X 13 fractions at 8 to 10 months.  

As RIM is a very debilitating complication, it is logical to hold spinal cord constraint conservative and schemas limiting the maximum spinal cord dose to less than total 10 Gy in case of prescription dose of 27 Gy in 3 fractions, or 30 Gy in 5 fractions need to be preferred. Single session SBRT series reported safety of limiting the surface dose of the spinal cord to 10 Gy, 12 Gy, and even 14 Gy appears safe, however it sounds rational to keep it to less than total 10 Gy due to the fact that it is currently unclear with limited follow up. Data supporting the single dose constraint of 10 Gy stating no RIM was the report of the Medical Research Council of 114 patients by Macbeth et al that estimated the risk of RIM to be zero by two years,  and single dose constraint of 8 Gy stating no RIM were the reports of the Hamburg University Hospital of 199 patients by Rades et al and The Radiation Therapy and Oncology Group (RTOG) of 455 patients including spinal patients by Hartsell et al. The most recent and solid data is by Ryu et al revealing Henry Ford Hospital experience on a partial volume tolerance of spinal cord after single dose of SBRT in 230 procedures of 177 patients, where the spinal cord volume was defined as 6 mm above and below the SBRT target. They have concluded that partial volume tolerance of the human spinal cord is at least 10 Gy to 10% of the cord volume.  

As the data on reirradiation is also very limited, Rades et al. reported their reirradiation of the spine experience of 62 patients after initial course of 8 Gy in one fraction or 20 Gy in 5 fractions with no incidence of RIM after second course of 8 Gy in one
fraction, 15 Gy in 5 fractions, or 20 Gy in 5 fractions with a median follow-up of 8 months after reirradiation (range 2-42 months). Although retrospective, Rades et al noted that the cumulative BED, ≤120 Gy of spinal reirradiation appeared to be effective and safe. (49)

**Conclusion**

SBRT has becoming to gain a significant and promising role as a non-invasive modality to be used in conjunction with other complementary modalities in the management of spinal metastasis along with the important collaboration of spine surgeons, and radiation oncologists.

6. References