Review Article :

Role of Cyberknife for spinal metastases

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Abstract

Stereotactic body radiosurgery (SBRS) provide an option to deliver high dose per fraction radiation and a high biologic equivalent dose (BED), typically in one to five fractions with aim to improve clinical response, improve tumor control and reduce retreatment rate.

These aims were applied to patients by using Cyberknife as a single modality or combined modality in unirradiated or reirradiated painful spinal metastases patients with safe and effective response.

Introduction :

Radiosurgery was well established for the intracranial treatment. Cyberknife is a frameless robotic system for radiosurgery which was introduced by Adler JR jr since 1994 (1), first used for intracranial lesions. To date stereotactic body radiotherapy (SBRT) is an increasingly used method for definitive treatment of lung, liver, pancreas, kidney, prostate and spinal lesions (2-4) and also has a role in limited cancer metastases (5) located in variety of organ including spine. Most common lesions in spine include metastatic disease, neurofibroma, schwannomas, meningiomas, lymphoma, myeloma, astrocytomas and vascular malformation (6). Approximately 5-10% of all cancer patients will develop spine metastases. The use of radiation therapy for treatment of spine metastases has been well established and has a role as a primary treatment or salvage therapy. The goals of local radiation therapy in the treatment of spinal tumors have been palliation of pain, prevention of local disease progression and subsequent pathologic fractures, and halting progression of or reversing neurologic compromise.(7)

This article will review the role of Cyberknife in spinal metastases in term of clinical indications and outcome.

Overview of Cyberknife :

Cyberknife (Accuray, Inc., Sunnyvale, CA) (Fig 1) is one of a system capable for SBRT, automatic LINAC positional adjustments to compensate for any detected changes in target positioning. It was approved in 2001 by the United States Food and Drug Administration for use throughout the body.

Cyberknife is a frameless image-guided stereotactic radiosurgical system that uses X-ray radiographic imaging to locate and track the treatment site while controlling the alignment of radiation beams via a robot-mounted linear accelerator. Compact 6-MV linear accelerator that smaller and lighter in weight than conventional

linear accelerator, is used. The smaller size permits the robotic arm to manipulate wider range of beam orientation than conventional radiotherapy device.

Fiducial markers are gold seeds or stainless steel screws that are implanted in and/or around a soft tissue tumor, or within the bony spine, to act as a radiologic landmark, to define the target lesion's position with millimeter precision. The Cyberknife radiosurgerey system has a clinically relevant accuracy of 1.1 + 0.3 mm when CT slice thickness of 1.25 mm is used. (8) For spinal lesions, XsightTM (Accuray, Inc) is used for accurate tracking of the spinal skeletal anatomy and for accurate treatment delivery, thus allowing fiducial-free tracking of spinal lesions. Couch adjustments are still required for translations beyond 10mm, or rotational offsets of 1 degree for pitch and roll and 3 degree for yaw.

Figure 1 : Cyberknife

Role of radiotherapy for spinal metastases :

For patients with spinal metastases who present with spinal instability, i.e., pathologic fracture, significant kyphosis or deformity, surgery remained the recommended management. The adjuvant radiotherapy post operative or radiotherapy alone is optional for palliation of spinal metastases.

The current role of radiotherapy without surgery is recommended for painful spinal metastases without epidural spinal compression, epidural spinal cord compression caused by radiosensitive tumors (such as germ cell tumor, lymphoma) or medically inoperable patients.

External beam radiotherapy can provide significant palliation painful bone metastases in 50-80% of patients. Up to one-third of patients achieving complete pain relief at treated site. (9)

There are vast majority of dose-fractionation schedule used for palliative bone metastases from single fraction to conventional fractions. The most commonly used schedule fractionation schedule was 3Gy X 10. Maranzano et al found that the fractionation schedule was not a significant predictor of pain-related outcomes.(10) As no guideline exist, treatment regimen will probably remain a geographical choice although higher appear to offer some advantages related to longer local recurrence free interval. (9)

The spinal cord consists of bundles of motor and sensory, surrounded by the thecal sac, which encased by the spinal canal. The commonly accepted spinal cord dose to give is 50Gy to less than 5 cm of cord, which yield a 5% or less risk of radiation myelopathy at 5 years. Though rare, RT-induced spinal cord injury can be severe, resulting in pain, paresthesias, sensory deficits, paralysis, Brown-Sequard syndrome and bowel/bladder incontinence.(11) The severe complications are often delayed complication such as radiation myelopathy, which rarely occur less than 6 months after completion of radiotherapy and most cases appear within 3 years. Other toxicities caused by RT are mainly related to the level of the spine. SBRS provide an option to deliver high dose per fraction radiation and a high BED, typically in one to five fractions. The goals of SBRS in spinal metastases are to improve clinical response, improve tumor control and reduce retreatment rate. (12, 13)

These goals were applied to patients by using Cyberknife as a single modality or combined modality in unirradiated or reirradiated patients. (Table 1, 2)

The current indications for the use of radiosurgery as a treatment modality for metastatic spine disease can be summarized into

1. Pain (palliative benefit)
2. Radiographic tumor progression
3. As a primary treatment modality
4. Progressive neurologic deficit
5. Postoperative.

While the general categories as defined by Sahgal et al (14) into 4 general categories.

1. Unirradiated patients: spinal metastases in a previously unirradiated volume treated with SBRS

2. Reirradiated patients: spinal metastases in a previously irradiated volume now containing new, recurrent, or progressive metastatic disese treated with SBRS
3. Postoperative SBRS patients: spinal metatases treated with SBRS after open surgical intervention, with or without spinal stabilization
4. Mixed patients: mixed populations involving patients in the previous 3 categories in which outcomes are not separately reported.

Exclusion criteria for spine SBRS was summarized by Sahgal et al (12) into

1. Pacemaker such that MRI cannot be performed or the treatment cannot be delivered safely
2. Scleroderma or connective tissue disease as a contraindication to radiotherapy
3. Unable to lie flat
4. Treated with 89Sr or systemic chemotherapy within 30 days before SBRT
5. External beam radiotherapy to the same area within 3 months before SBRT
6. Significant or progressive neurologic deficit
7. >25% spinal canal compromise
8. Malignant epidural spinal cord compression or cauda equina syndrome
9. Spine instability or neurologic deficit resulting from compression of neural structures

Three common primary malignancies are breasts, renal and pulmonary cancer. The prescribed dose of radiation to the tumor is determined based on the histology of the tumor, spinal cord or cauda equina tolerance and previous radiation dose to normal tissue, especially spinal cord.

Table 1. Summary of unirradiated patients

Reference	Total no. tumor/ patients	Primary	Indication for CK	Target volume	Total dose/ number of fx of CK	BED at Cord	Follow-up months	Outcome
Sahgal, 09 (14)	23/14	Radioseneitive: 34.78% Radioresistant (Sarcoma, renal call, Drop metas from glioma, melanoma): 65.21%	Pain 56.52% Post op 21.74%	8.3 (2.1-106)	24 (7-40) Gy/ 3(1-5)	56 (30-114) Gy2	8 (1-26)	1& 2 year progres-sion-free probability of 85% and 69% No radiation induced myelopathy or radiculopathy

Table 2. Summary of reirradiated patients

Reference	Total no. tumor/ patients	Primary	Indication for CK	Target volume	Previous BED/ α/β of cord	Previous EQD_2	Total dose/number of fx of CK	EQD2/α/β of cord (Total)	Follow-up months	Outcome
Gerszten, 04 (15)	125/115	Breast 19.2% Renal 16% Lung 8.8% Colon 4.8% Prostate 4% MM 4% Hemangioblastoma 3.2% Laryngeal CA 3.2% Melanoma 2.4% Lymphoma2.4% Sarcoma 2.4% others 16% Benign Tumor 13.6%	Pain 63.2% Progressive deficit 14.4% Primary 11.2% Post op 7.2% Boost 4%	Mean 27.8 cm^3 (0.3-232)	NA	NA	mean 14Gy (12-20Gy/1fraction)	NA	18 (9-30)	Safety feasibility and effectiveness 18 cases with myelopathic due to cord compression
Gerszten, 07 (16)	500/336	Renal 18.6% Breast 17.2% Lung 16% Melanoma 7.6% Colon 6. 4% Sarcoma 5.2% Prostate 4.8% MM 3.6% Unknown 2.8% Sq cell (larynx) 2.4% Thyroid 2.2% Other 13.8%	Pain 67.2% Progressive deficit 14.4% Primary 11.2% Post op 7.2% Boost 4%	Median 29cm^3 (0.2-264)	62Gy_3 (60-64Gy_3)	37Gy (36-38.5 Gy)	12.5-25 Gy/ 1 fraction	NA	21 (3-53)	Image control 88% Pain improvement 86%
Gibbs, 07(17)	102/74	Renal 19.6% Breast 17.64% Lung 11.76% Melanoma 11.76% GI 8.82% Sarcoma 6.86% H&N 6.86% Prostate 2.94% Unknown 2.94% other 10.78%	Pain & neurologic dysfunction 81% Asymptomatic 19% **Exclude** - Patients with paralysis - Spinal instability - Spinal lesions extending beyond 2 consecutive vertebral segments - Receiving previous radiation within 3 months	12.2 cm^3 (0.025-685.3)	50/74 patients had previous radio-therapy 66.67 (21.67-124) Gy_3	66.67 (21.67-103.33)Gy	16-25Gy/ 1-5 fractions	Maximal BED3 of spinal cord/ cauda equina 4.5-182 Gy	9 (0-33)	Medain time to death 11 months 1 year actuarial survival 46.3%
Gagnon, 07 (18)	NA/18	Breast 100%	-Failed prior external beam radiation -Primary treatment	NA	NA	NA	21-28Gy/3-5	NA	1-24	Similar ambulation, performance status and pain worsened between cyberknife and conventional external beam radiotehrapy groups
Saghal 09, (14)	37/25	Radiosensitive 91.89% Radioresistant (Sarcoma, renal call, Drop metas from glioma, melanoma) 8.1%	Imaging confirmed of progression 100%	21 cm^3 (0.4-177)	66.85Gy_3 47Gy_{10}	40.1Gy	24 (8-30)Gy/ 3(1-5) fractions	36 (20-98) Gy_2	7 (1-48)	1 & 2 year progression-free probability of 85% and 69% No radiation induced myelopathy or radiculopathy
Gagnon, 09 (19)	NA/151	Breast 23.84% NSCLC 15.89% Renal 11.92%	- Pain	NA	NA	NA	Mean 26.4Gy/3	NA	12 (1-51)	Significant decrease pain score from 40.1 to 28.6 No significant improvement in quality of life
Choi, 2010 (20)	51/42	Breast 31%, Other 26%, NSCLC 21% Salivary gland 7% Colorectal 5% Thyroid 5% Lymphoma 5%	Recurrent lesion that locate close to spinal cord	10.3cm^3 (0.2-128.6)	67Gy_3 (40-82 Gy_3)	40Gy (24.2-50.4Gy)	20Gy (10-30Gy)/1-5 fractions	76Gy_3 (32-122Gy3)	7 (2-47)	6/12months local control = 87%/73% 6/12months overall survival = 81%/68%

abbreviations: NA= not available, CK = Cyberknife, MM = Multiple myeloma, BED = Biological equivalent dose, EQD2 = Total biologically equivalent dose in 2 Gy fractions, fx = fraction

Outcome of the treatment :

The most frequent indication for the treatment is pain. Pain is reported to decrease usually within weeks after treatment, and occasionally within days. Gerszten et al (13) reported a mixed population with an overall pain improvement in 290 of 336 cases (86%), depending on primary histopathology, 96% of cases with melanoma, 94% of cases with renal cell carcinoma, and 93% of lung cancer cases. Gibbs et al reported that 84% of symptomatic patients experienced improvement or resolution of symptoms after treatment.(17, 21) Excellent pain-control and quality of life analysis after spinal radiosurgery has been reported from Georgetown University Hospital. (19) The pain scores were assessed by Visual Analog Scale (VAS). Data reviewed no significant change of 12-item Short Form Health Survey Physical Component scores throughout the follow-up period.

In term of local control and Radiographic Tumor Progression, a series of 500 cases (16) showed 88% of overall longterm radiographic tumor control for progressive spinal disease based of primary pathology: breast (100%), lung (100%), renal cell (87%), and melanoma (75%). Gagnon et al published a matched-pair analysis comparing 18 patients with breast-cancer spine metastases treated with Cyberknife (radiosurgery) to 18 matched patients who received conventional external beam radiotherapy up front. This study concluded that salvage Cyberknife is as efficacious as initial fractionated radiotherapy without added toxicity. (18)

Gerszten et al (16) reported no case of tumor progression within the immediate adjacent vertebral levels based on 500 cases. Chang et al (22) reported their patterns of failure for 74 treated tumors where 23% demonstrated imaging progression. Based on these data, Sahgal et al (14) concluded that it is possible that failure in the epidural space may be due to underdosing of the tumor because of strict spinal cord constraints, uninvolved adjacent posterior elements should be included in the target volume, and encompassing one vertebral body above and below the diseased vertebrae is unnecessary.

Complication associated with radiosurgery are generally self limited and mild. (13) Radiation-induced spinal cord injury is exceedingly rare, and few cases have been reported in the literature. Gerszten et al (16) found no spinal cord toxicity with over 60 months of follow-up. Rye et al (23) specifically addressed the partial volume tolerence of the spinal cord and complication of single-dose radiosurgery which reported a single case of radiation induced cord injury after 13 months of radiosurgery. They concluded that partial volume tolerance of the human spinal cord is at least 10Gy to 10% of the spinal cord volume, defined as 6mm above and below the radiosurgery target.

Conclusion :

Cyberknife is a noninvasive option for patient with painful spinal metastases with safe and effective response and local control, regardless of prior fractionated radiotherapy. The dose fractionations are varies from single fraction to hypofractions. No consensus on dose can be made based on the available evidence. Randomized controlled trials would be helpful to determine the dose prescription and the dose limitation of organs in comparison with conventional radiation delivery.

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