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An Image-guided Radiosurgery for the Treatment of Metastatic Bone Tumors using the CyberKnife Robotic System

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ABSTRACT

Bone is a common site for metastatic spread from many kinds of malignancies. The morbidity associated with this metastatic spread can be significant, including severe pain. When it comes to spinal metastasis, occupying nearly 40% of skeletal metastases, the risks of complications, such as vertebral body collapse, nerve root impingement, or spinal cord compression, are also significant. Because of the necessity of preserving the integrity of the spinal column and the proximity of critical structures, surgical treatment has limitations when durable local control is desired. Radiotherapy, therefore, is often used as an adjunct treatment or as a sole treatment. A considerable limitation of standard radiotherapy is the reported recurrence rate or ineffective palliation of pain, either clinically or symptomatically. This may be due to limited radiation doses to tumor itself because of the proximity of critical structures.

CyberKnife is an image-guided robotic radiosurgical system. The image guidance system includes a kilovoltage X-ray imaging source and amorphous silica detectors. The radiation delivery device is a mobile X-band linear accelerator (6 MV) mounted on a robotic arm. Highly conformal fields and hypofractionated radiotherapy schedules are increasingly being used as a means to achieve biologic dose escalation for body tumors. Therefore, we can give much higher doses to the targeted tumor volume with minimizing doses to the surrounding critical structures, resulting in more effective local control and less severe side effects, compared to conventional fractionated radiotherapy. A description of this technology and a review of clinical applications to bone metastases are detailed herein.

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INTRODUCTION

The CyberKnife is an integrated image-guided, frameless radiosurgery system. This system emerged as a tool to counter the limitations of traditional radiosurgery systems whose accuracy rely on rigid fixation, such as Gammaknife. The CyberKnife is capable of delivering highly precise crossfired radiation beams that yield conformal radiation dose distributions with rapid fall-off of dose at the perimeter of the target lesion[1]. We can give higher radiation dose to tumor itself without significant complications than conventional methods.

Patients with bone metastases comprise the largest group of patients receiving palliative radiation therapy. Traditionally, local-field radiation therapy has been used for patients with symptomatic bone metastases[2]. There is a wide variation in the pain relief rates reported both in clinical reports and in randomized clinical trials. Of the randomized clinical trials comparing single fraction of 8 Gy to multiple fraction regimens, there was no statistically significant difference in the pain relief rate or the duration of relief[3-6]. However, the reirradiation rate is consistently higher in the single fraction groups. In addition, for most patients who achieve pain relief after irradiation, the relief lasts for less than two-thirds of their remaining life. In most series, 10% to 30% of patients never obtain relief[7-10]. McQuay reported the pooled results of 12 randomized published trials and found that only 41% of patients treated with local-field external beam radiation therapy received at least 50% pain relief at 1 month[11]. The goal of freedom from symptoms until death is reported in about 10% of long-term survivors[12]. Therefore, it is necessary to seek for another new radiation tool for increasing the rates of pain relief.

The biologic effectiveness of radiation therapy depends on the total dose and dose per fraction. Recently, stereotactic body radiation therapy (SBRT) was developed in response to a clearly identified need in oncology to improve local control of deep-seated tumor. Although often associated with clinical implementation of high-end technology, SBRT is best characterized by its unique radiobiology, leading to both dramatic tumor and normal tissue effects. The CyberKnife system is a very specialized and sophisticated form of SBRT and shares many technical characteristics with SBRT, such as secure immobilization avoiding patient movement for the typical long treatment sessions, accurate repositioning from simulation to treatment, minimization of normal tissue exposure, rigorous accounting of organ motion, stereotactic registration of tumor targets via fiducial markers, and ablative dose fractionation delivered to the patient with subcentimeter accuracy[13]. Unlike traditional radiosurgery, however, the CyberKnife uses near real-time imaging to achieve accurate target localization and high-speed robotics to achieve accurate dose delivery.

The CyberKnife system was installed first at Stanford University Hospital in 1994. In 2001, the Stanford clinical experience confirmed the accuracy of CyberKnife and helped to gain the United States FDA approval of the device for treatment of tumors anywhere in the body where radiation treatment is indicated. Since then, the CyberKnife technology has been adopted by university hospitals, private hospitals, and free-standing radiation facilities across the USA, Asia, and Europe to treat tumors and lesions of the brain, spine, thorax, abdomen, and pelvis[14]. In Korea, this system was introduced first to Korea Cancer Center Hospital in 2002. Since then, about 1,600 patients have been treated with promising clinical results. Among them, about 200 patients were those with metastatic bone diseases, including spines. Here I would like to review the clinical results of CyberKnife for treatment of metastatic bone tumors.

COMPONENTS OF CYBERKNIFE

The physical components include a compact 6 MV X-band linear accelerator mounted to the mobile arm of a robotic manipulator and a real-time imaging system connected to a remote image registration console (Fig. 1). The position of the treatment volume is defined with respect to radiographic features such as skeletal anatomy or implanted fiducial rather than a stereotactic frame. The complete process of image acquisition, processing, registration, and retargeting is automatic and fast enough to be performed repeatedly during treatment. Shifting the beam rather than relying on rigid target fixation compensates changes in patient position. In addition to the standard component, the Synchrony system allows for treatment of thoracic, abdominal, and pelvic lesions with respiratory tracking. Unlike respiratory gating, the Synchrony system delivers radiation throughout the respiratory cycle during normal active breathing. Coupling the image-guidance of internal fiducials with chest wall respiratory excursion ensures the accuracy of radiation dose delivery[15].

TREATMENT SET-UP, PLANNING, AND DELIVERY

A custom non-rigid immobilization device consisting of an Aquaplast face mask or a vacuum foam body cradle is used. Digital reconstruction radiographs (DRR) are generated from a thin section (1.25~3 mm slice thickness) CT dataset. The target lesion and critical structures are contoured on axial CT slices to obtain 3-dimmensional reconstruc-

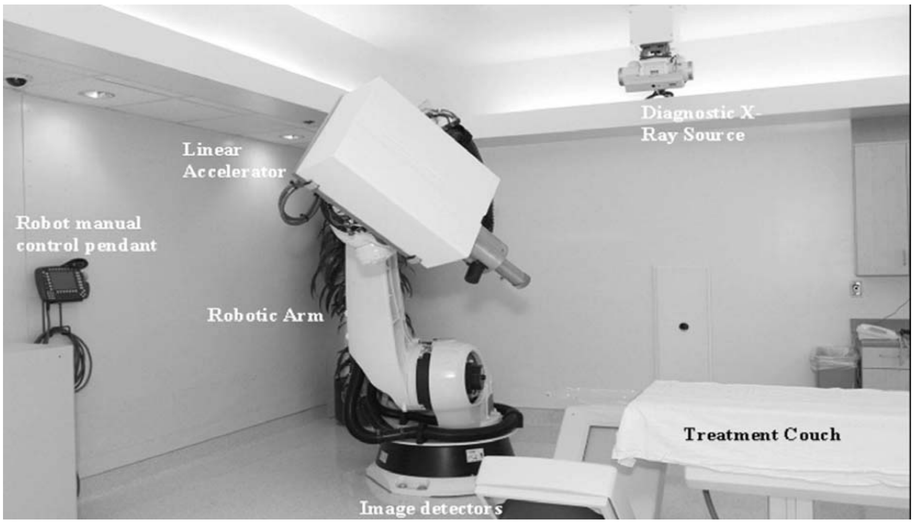

Fig. 1. Whole view of CyberKnife system

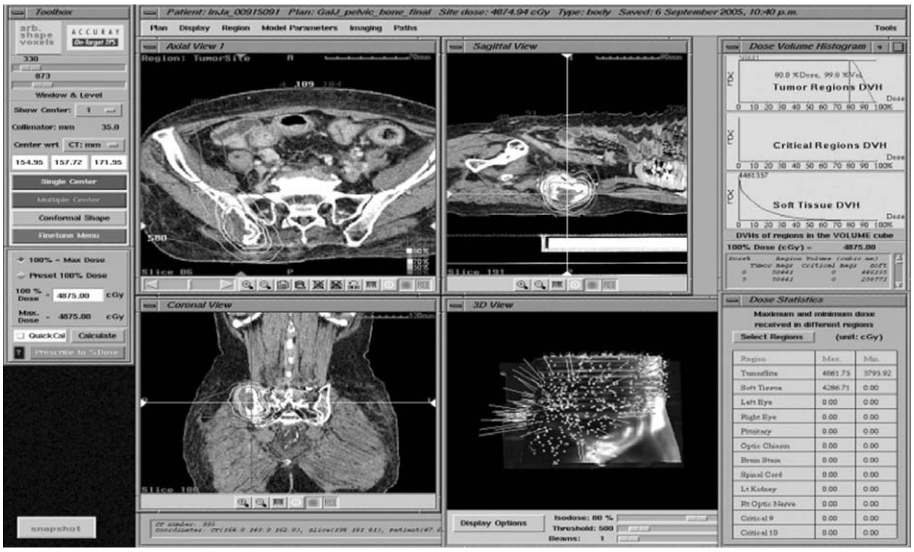

Fig. 2. Single metastasis to the right iliac bone from uterine cervix cancer. This patient received 39 Gy in 3 fractions, corresponding to 74 Gy in conventional fractionation. Severe pain subsided promptly after CK treatment. She is alive now.

tion using the CyberKnife treatment planning software (Accuray, Inc.). A margin of up to 2~3 mm is used to account for uncertainties in target contouring as well as total system error.

Treatment plans are generated with the CyberKnife inverse treatment planning software. A dose of 16~36 Gy in 1~3 fractions is described, depending upon the pathologic types of metastases or the presence of surrounding critical organs. When metastatic tumor is located adjacent to the spinal cord, the maximum permissible dose to the spinal cord should not exceed the usual tolerable dose, i.e., 10 Gy in a single fraction or 45~50.4 Gy in conventional fractionation schedule with 1.8~2.0 Gy/day. Dose-volume histograms are generated for the target lesion and critical structures. The quality of the treatment plans in terms of dose homogeneity, target coverage, and dose conformity is evaluated based upon modifications of the Radiation Therapy Oncology Group (RTOG) guidelines[16]. A typical treatment plan is shown in Fig. 2. Usually, radiosurgery is performed as an outpatient procedure. Using the process described above, approximately 100~150 non-isocentric beams are delivered sequentially. Treatment times typically last 30~90 minutes.

Patients sometimes receive anti-emetics, such as Amifostine, given for lower thoracic to sacral lesions.

CLINICAL RESULTS

Until now, there have been no randomized studies for evaluating the effectiveness of CyberKnife for treatment of bone metastases. In addition, a few studies have been reported on the pain management in the bone metastases by using CyberKnife, except for spinal metastases. Generally, the goal of radiation therapy of bone metastases is to prevent or relieve symptoms or dysfunction for the remainder of the patient's life. The ideal patient for the best long-term benefit of radiation therapy is one with limited and uncomplicated metastasis to bone detected by a change in bone scan before symptoms of the metastasis develop and with low systemic disease burden elsewhere. For CyberKnife treatment, patients receiving previous radiation within 3 months prior were generally excluded. In cases of spinal metastases, patients presenting with paralysis, spinal instability, or spinal lesions extending beyond two consecutive vertebral segments were ineligible.

Gibbs and colleagues reported 84% of symptomatic patients experienced improvement or resolution of symptoms after treatment and robotic radiosurgery would be effective and generally safe for spinal metastases even in previously irradiated patients[1]. Gerszten et al. also reported clinical pain improvement in 89~96% of patients with spinal metastases treated by CyberKnife robotic system[17]. As previously mentioned, CyberKnife can deliver higher dose very effectively than common palliative regimens and its treatment is sufficiently efficacious as to preclude the need for any further intervention. In addition, while conventional radiotherapy was an option for some of the patients, an abbreviated course of irradiation is especially attractive in patients with a limited life expectancy.

The need for retreatment or any further intervention is of most concern in patients with good performance status and limited metastatic breast or prostate cancer, in whom the life expectancy may be from 2 to 4 years. The rate of retreatment ranged from 11% to 29% in common palliative regimens. However, CyberKnife treatment could reduce the rate of retreatment up to 2~5%. The rate of local recurrence within previously irradiated sites can be estimated from collected prospective series in which standard fractionation regimens were used. These series showed complete relief of pain in 15~58% of patients[18]. It can be estimated that some 42~85% of patients have less than complete relief of pain and so might benefit from further treatment. Collected series also showed median durations of pain relief of 22~50 weeks[18], so a significant portion of patients surviving over 6 months will suffer recurrence of pain and might need further treatment. Retreatment rates of 2~44% are also reported in selected series, supporting the need for further treatment in a significant proportion of patients[18].

If radiosurgery is selected as the retreatment modality, we should consider several complicating factors. One major complicating factor is that there are significant dose-limiting surrounding structures, including spinal cord, spinal nerve roots, peripheral nerves, esophagus, bowel, kidneys, bladder, lung and heart. Although several tissues have the capacity for recovery with time, this recovery is not complete and is quite variable among tissue types. While lung and spinal cord have some capacity for occult injury recovery, mesenchymal tissue recovers poorly from prior radiation therapy, and some tissue sites, such as bladder and kidney, have no capacity for long-term recovery[19].

A major difficulty in reirradiation is the determination of the normal tissue tolerance and the avoidance of toxicity. Another significant complicating factor is the potential that the previously irradiated tumor is radioresistant as a consequence of its prior radiation. Weichselbaum et al[20] have shown that cell lines from recurrent squamous cell carcinomas of head and neck tumors were more resistant to radiation than those from tumors not previously irradiated. Therefore, reirradiation carries the double difficulty of reduced tolerance of surrounding structures and a more resistant phenotype. It is our belief that only by employing extreme conformity and precision can large enough doses be delivered to achieve a therapeutic gain in spinal recurrences.

Gagnon et al[21] have reported the results of over 180 patients treated with CyberKnife spinal radiosurgery at Georgetown University Hospital. Among them, 107 patients had prior radiation of the radiosurgically treated spinal region. Central to this review was the determination that the prior radiation dose severely limited the option for reirradiation, either because of prohibitive risks or because of radioresistance associated with conventional irradiation. Prior radiation doses were in the range of 20~59.4 Gy and an average retreatment doses was 20.12 Gy to the 72.3% mean isodose contour, delivered in 1~5 fractions. Pain relief was achieved in 95% of patients in as short a period as one month. There have been no cases of radiation myelitis or neurological deterioration attributable to reirradiation. Treatments were well tolerated, with brief fatigue of 1~2 weeks being the only notable acute effect.

We have treated 226 patients with bone metastases. Among them, 178 patients had spinal metastases. Nearly 85% of patients had subjective pain relief within 3 days after completion of CyberKnife treatment. Especially, complete pain relief was achieved in 100% of patients with metastases from breast cancers and prostate cancers. The rate of response was the lowest in patients having metastases from soft tissue sarcomas. It was very surprising that metastases from liver cancers, renal cell carcinomas, and lung cancers had relatively well responses to CyberKnife treatment with small numbers of fraction(1~3 fractions), even though they didn't do well to conventional fractionated radiation therapy(30.0 Gy/10 fractions). In addition, we could give higher doses to the metastatic tumors to flat bones than those to spines, because there was not spinal cord adjacent to the metastatic tumors. In selected cases, such as metastases from breast cancers and prostate cancers, we could increase the survival. CyberKnife treatment provides an alternative (1) for patients who are unable to have major surgery, (2) as an adjunct to surgery, (3) for patients who have had previous radiation, or (4) for patients who have radioresistant tumors. CyberKnife radiosurgery is a minimally invasive procedure that can be performed on an outpatient basis with few side effects. The goal of CyberKnife radiosurgery is to totally destroy the tissue within the target volume, so it may provide reasonable local control. This technique is not appropriate for patients with radiosensitive tumors who have not had radiation, those with cord compression and neurologic deficit, or those with spinal instability. While any spinal cord compression is considered unacceptable, Gibbs et al[1] showed that this technique was generally safe. In their analysis of dose-volume effects, it is noteworthy that no complication occurred when the volume of spinal cord exposed to a biological effective dose (BED) of less than 58 Gy was less than 0.15 cm^3. Although spinal cord tolerance remains poorly understood, the recent studies suggest that even following previous irradiation, the spinal cord can safely tolerate additional treatment as long as the treated volumes of spinal cord remain relatively small.

CONCLUSION

Stereotactic radiosurgery with the CyberKnife is a highly precise treatment device and is capable of delivering high-dose irradiation to metastatic tumors. This technique, therefore, provides high local control rates, including rate of pain relief, in most patients and increases survival rates in selected patients, such as metastatic tumors from breast and prostate cancers. The advantages of CyberKnife include frameless fixation system with noninvasive method, short treatment period, and large hypofractionation with higher cell-killing effect. In addition, it can provide the treatment for moving tumors with respiratory-gaiting system. Our clinical data shows that CyberKnife radiosurgery is a very safe modality even in patients having previous irradiation and is a very effective alternative for relieving pain in metastatic bone tumors.

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