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Revisão

Spine radiosurgery and dose tolerance to the spinal cord

Radiocirurgia espinhal e tolerancia da medula espinhal à dose aplicada

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ABSTRACT

Radiosurgery is the utmost form of targeted radiation treatment that can eradicate the gross tumors, and it is a non-invasive procedure. It requires a high degree of accuracy and precision in targeting the deep-seated tumors which are usually surrounded by the functionally important normal structures. Recent advances of immobilization method and computerized radiation delivery method with intensity modulation made it possible to perform radiosurgery to the spine. Spine radiosurgery achieved a rapid and durable pain control in majority of patients with spine metastasis. Radiosurgical decompression of the epidural spinal cord compression improved neurological function and ambulation. The most critical constraint of spine radiosurgery is the potential damage to the spinal cord. Nevertheless, the procedure is proven safe and complication has been minimal. Spine radiosurgery can be used for both malignant and benign tumors of the spinal column.

Key-words: *spine radiosurgery, spinal cord tolerance, spine metastasis*

SUMÁRIO

A radiocirurgia é a forma mais avançada de tratamento utilizando radiação direcionada ao alvo, podendo erradicar tumores de uma forma não invasiva. Para sua utilização, a radiocirurgia requer um alto grau de acurácia e precisão no tratamento de tumores profundos que usualmente estão relacionados à estruturas funcionalmente importantes. Avanços recentes nos métodos de imobilização e nas formas de aplicação computadorizada da radiação, utilizando intensidade modulada, tornaram possível a realização de radiocirurgia para a coluna vertebral. Esta técnica atingiu um rápido e duradouro controle da dor na maioria dos pacientes com metástases espinais. A descompressão radiocirúrgica da compressão medular epidural melhorou a função neurológica e a deambulação. A limitação mais crítica da radiocirurgia para a coluna vertebral é a possibilidade de causar lesão medular induzida pela radiação. Apesar disto, este procedimento é considerado seguro e suas complicações tem sido mínimas. O método pode ser utilizado tanto para tumores malignos como benignos da coluna vertebral.

Palavras-Chave: *Radiocirurgia Coluna Vertebral, Tolerância medular, Metástases Coluna Vertebral*

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JBNC Brazilian Journal of Neurosurgery
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Introduction

Conventional therapy for spine metastasis has been mainly with external beam radiation therapy (EBRT) with occasional decompressive surgery. Surgery is usually offered to patients with rapidly evolving neurological deficits, spinal instability, and in patients without an established cancer diagnosis. The efficacy of EBRT has been reported with varying degrees of pain relief being reported in about half to two thirds of patients by three months after radiation[14]. Conventional radiotherapy utilizes generous margins around the involved spine, typically one or two vertebral body segments including healthy spinal cord and functioning bone marrow within the treatment volume. Radiosurgery can deliver a highly conformal large radiation dose to the involved spine only.

The key components of radiosurgery consist of selectivity with rapid dose fall off, conformality with adequate tumor coverage and minimal radiation to the critical normal structures, and proper radiation beam planning and delivery under image guidance. A better understanding of radiosurgery can be obtained through examination of its physical and biological properties.

PHYSICAL ASPECT OF RADIOSURGERY

The physical hallmark of radiosurgery is rapid radiation dose fall-off outside the target. It is usually represented by the distance between the point of high radiation dose to another point of low radiation dose, 90% to 50% isodose line for example. There is usually only a few millimeters between these two isodose lines. This unique physical property allows radiosurgery to deliver a high radiation dose which is not used in conventional radiotherapy. On the other hand to safely deliver this dose, radiosurgery requires accurate targeting and a highly conformal radiation dose distribution encompassing the target volume. These properties of radiosurgery of providing necessary therapeutic radiation to the tumor and rapid dose fall off are optimal for management of small volume targets near critical normal tissues. Small intracranial targets have historically been the prime example of the use of radiosurgery.

The main difficulties in applying radiosurgery to extracranial sites are organ motion and a lack of immobilization methods. A suitable natural model due to the lack of breathing-related organ movement is the spine. Imaging studies were available for improved visualization of the spine and target tumors in relation to the spinal cord, which is the critical structure. The spine is also well visualized using x-ray image-guidance, and thus the spine itself can be used as a fiducial volume for targeting. This concept enables one to overcome the obstacle of immobilization and patient positioning. The advent of intensity modulated radiation delivery, micro-multileaf collimators, and the use of dynamic arcs increased the dosimetric precision to the tumor and the adjacent spinal cord. Progress of all these elements made the application of radiosurgery to targets in the spine feasible[29]. Radiosurgery of the spine has become a prime example of extra-cranial radiosurgery. Radiosurgery of body sites is now called Stereotactic Body Radiation Therapy (SBRT) by the American Society of Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR).

BIOLOGICAL ASPECT OF RADIOSURGERY

The radiobiological effect of radiosurgery is not well understood. Most radiobiological studies have been performed with conventional radiation therapy (ie, 1.8-2 Gy per fraction)[12]. Mammalian cells die through different molecular and cellular mechanisms following exposure to ionizing radiation. Depending on the cell type, irradiated cells primarily undergo reproductive cell death, otherwise known as mitotic death. This is the predominant mode of cell death in the majority of human tumors following irradiation. Another mechanism of cell death is apoptosis, which is an interphase cell death. It can occur in normal tissues and in some tumors particularly during the acute phase of radiation response. Some stem cells of self-renewal normal tissues such as hematopoietic and the intestinal crypt cells undergo apoptosis following a moderate dose of radiation. The late tissue response to radiation is a result of terminal growth inhibition of either self-renewing or differentiating and metabolically active cells.

While radiosurgery uses high doses of radiation in a single fraction or in a few fractions in contrast to conventional fractionated radiotherapy, it is not well understood whether a single high dose of radiosurgery has a different mechanism of cell killing mechanism compared to the conventional fractionated radiotherapy. Recent radiobiological evidence suggests that tumor response to radiation regulated by intestinal endothelial cell apoptosis is seen at a single dose of less than 10 Gy, while higher doses of 18 to 20 Gy causes death of tumor cells independent of endothelial apoptosis[3]. This supports an alternative pathway of molecular events within the cell following a high single dose of radiosurgery. Preliminary radiobiological experiments suggest initial molecular events may include rapid upregulation of gene transcription of inflammatory cytokines, angiogenic factors, and transcription activators, and various gene products involving the repair of DNA damage. Taken together, there appears to be a rather well orchestrated cascade of cell death following radiosurgical treatment. A better radiobiological understanding will help selection of radiosurgical dose, fractionation pattern, and potential combination of radiosurgery with other treatment modalities.

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Application to the spine

The first step toward the development of spine radiosurgery was to determine target accuracy. Many phantom studies have demonstrated clinical feasibility. The first phase I clinical study with image-guided intensity-modulated radiosurgery for spine patients showed the accuracy of targeting and reproducibility of patient positioning to be within 1.5mm[25]. The dose fall off from the 90% to 50% isodose line was less than 5mm towards the spinal cord. A similar level of accuracy has been reported with several different radiosurgery technologies[15]. The overall procedure of spine radiosurgery includes patient positioning and immobilization, image acquisition, tumor and normal tissue delineation, radiation treatment planning, repositioning and treatment delivery. With the proven accuracy of targeting and immobilization coupled with image guidance, the use of radiosurgery for spine metastases is growing in many institutions.

PATIENT POSITIONING AND IMMOBILIZATION

Virtually there is no or minimal, if any, breathing-related organ motion of the spine. Albeit there can be motion associated with pulsation, cough, or any other voluntary or involuntary motions. Although the concept of spine radiosurgery goes back even 50 years before the start of cranial radiosurgery, clinical application was limited mainly because of the difficulty with immobilization. Initially an attempt was made by anchoring hardware to the cervical spine and skull. A method of immobilizing the lumbar spine by Hamilton et al was an invasive procedure that required anchoring of the stereotactic frame to the spinous process under general anesthesia[13]. Other less invasive immobilization devices include a body frame with contour mold fixation was developed by Lax[17]. More recently, Ryu and Yin et al started using a frameless and non-invasive positioning method for spine radiosurgery[25,28]. Most institutions now use the newer type of positioning devices for spine radiosurgery. These are closely linked with radiosurgery equipment and chosen by the preference of each institution. A description and comparison of different radiosurgery units are beyond the scope of this discussion. It is important to remember to use a method that the patient feels comfortable with in the treatment position.

PATIENT SELECTION

The primary goal of spine radiosurgery is to maximize local tumor control of the involved spine while preserving neurologic function. Radiosurgery has been most frequently used to treat solitary spine metastasis as shown in (Figure 1a). Any soft tissue extension of the tumor causing epidural compression or a paraspinal mass is included in the target volume. Two contiguous spine levels can also be treated with radiosurgery (Figure 1b). Radiosurgery may be used to treat separate isolated spine metastases that are not adjacent to one another (Figure 1c). When there is diffuse spine involvement with one or two levels of more severe pain or epidural compression, radiosurgery can used as a boost to these sites concurrent with conventional radiotherapy (Figure 1d). In cases of more wide-spread metastatic involvement, conventional radiotherapy is indicated instead of radiosurgery (Figure 1e). We now have found that patients with diffuse spine metastasis can also be treated with single fraction radiosurgery if the symptomatic site is identifiable radiographically and clinically.

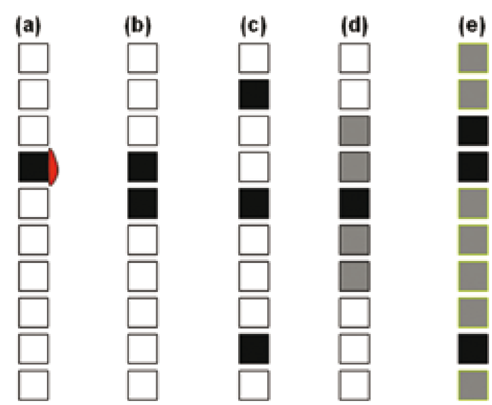

Figure 1. Treatment algorithm of radiosurgery for spine metastasis. (a) Solitary spine metastasis with or without spinal cord compression (red). (b) Two contiguous pine involvement. (c) Detached metastasis. (d) Diffuse spine metastasis with more for significant involvement. (e) Wide-spread spine metastasis with focal severe symptoms. (adopted from Ryu and Gerszten ed. Spine Radiousrgery. P74, Thieme 2008).

TARGET DELINEATION

Our method of target delineation is illustrated in Figure 2. This philosophy encompasses the clinical target volume concept as opposed to just contouring the lesion only. There can be many different scenarios of spine involvement.

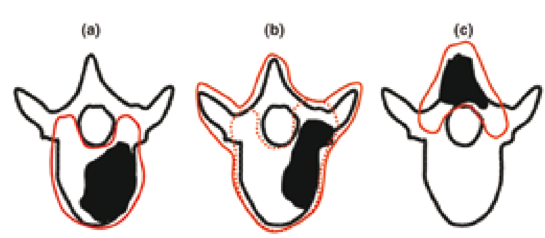

Figure 2. Method of target delineation for radiosurgery of spine metastasis and ty-

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pical example of radiosurgery dose distribution. (a) Involvement of vertebral body. (b) Extensive vertebral body and pedicle involvement. (c) Involvement of dorsal elements. (Adopted from Ryu et al. Cancer 109:628-636, 2007.

In general, vertebral body involvement can be categorized to three different scenarios: the spine metastasis involves most of the vertebral body (figure 2a), involvement of the vertebral body with extension to the pedicles (figure 2b), or involvement of the dorsal elements such as spinous process and lamina (figure 2c). Lesions involving more extensively vertebral body and pedicles are treated with generous margin or both anterior and posterior elements are treated together (Figure 2b).

DELINEATION OF SPINAL CORD

The most critical normal structure for spine radiosurgery is the spinal cord. Planning simulation CT images using 1-3mm slice thickness are used for delineation of the spinal cord with MR image fusion, T1 weighted contrast enhanced and/or T2 weighted MR images are useful. At Henry Ford Hospital, the spinal cord volume has been consistently defined as the volume extending from 6mm from above the target volume to 6mm below the radiosurgery target[21]. This method of spinal cord volume delineation is diagrammatically shown in Figure 3. Using this spinal cord tolerance constraint, there was no acute or long-term spinal cord complications except for one case of probable radiation-induced myelopathy (described in IV.2 Neuro complications below). Additional clinical trial of radiosurgery for myeloma spinal cord compression using the same spinal cord dose did not show any spinal cord complications[16]. Therefore, an average spinal cord dose of 10 Gy to the 10% partial volume of the spinal cord defined from 6mm above to 6 mm below the radiosurgery target volume appears to be safe for the practice of spine radiosurgery.

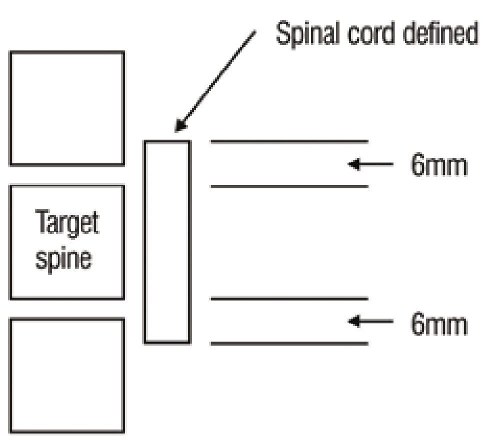

Figure 3. Diagrammatic representation of spinal cord volume definition.

CLINICAL EFFECTIVENESS

PAIN CONTROL

The usual presenting symptom of spine metastases is back pain with or without muscle weakness and numbness. Therefore, the purpose of spine radiosurgery has been primarily for pain control, and for local control of epidural or paraspinal extension of tumor causing neurological symptoms. Pain control of spine metastasis by radiosurgery has been reported in the range of approximately 90% using different radiosurgery equipment[8].The optimum dose of radiosurgery necessary to achieve pain control is not well defined at this time. In the analysis of a phase II trial at Henry Ford Hospital with dose escalation, there was a strong trend towards increased pain control with a radiation dose of higher than 14 Gy. The one year actuarial pain control rate was 84% with doses higher than 14 Gy delivered in a single fraction[20]. Experiences at the University of Pittsburgh and other investigators also showed consistently higher pain control with doses higher than 16 Gy in breast and renal cell carcinoma spine metastases[7,9].

A dose-response relationship for pain control appears to exist following radiosurgery for spine metastases. A recent meta-analysis of 10 randomized studies, 10 randomized clinical trials containing single fraction radiotherapy for painful bone metastases showed single fraction radiation (8 to 10 Gy) achieved a complete pain response in 33% and overall response in 62%[27]. The experience of spine radiosurgery at Henry Ford Hospital and University of Pittsburgh showed consistently higher rate of pain control with the use of higher radiosurgery dose in the range of 16 to 20 Gy. These are compiled in table 1. Majority of the spine metastases quite consistently responded to higher doses of radiosurgery regardless of the histology. Although there is no clear consistency and a caveat of comparing different trials, the results generally suggest a trend towards improved pain control with higher radiosurgery doses.

Table 1. Dose response of pain to single fraction radiosurgery

Single dose	Overall pain Response(%)	Complete response(%)	Time to pain relief	Duration of pain control	Reference
8 Gy	85		4 week	4 mos	Dutch study (17, 18)
8 Gy	78	57			Royal Marsden (19)
8 Gy	65	15			RTOG 9714 (12)
10 Gy	83	39		2.9 mos	Gaze (20)
≥ 12 Gy	60	39			Henry Ford Phase II
≥ 14 Gy	82	50	2 week	13.3 mos	Henry Ford Phase II (13)
≥ 16 Gy	>80	59			Henry Ford Phase II
≥ 18 Gy	>90				Henry Ford Phase II

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19 Gy* (15-22.5)	96				Univ Pittsburgh (14)
20 Gy* (15-25)	89				Univ Pittsburgh (21)
20 Gy* (17.5-25)	89				Univ Pittsburgh (15)
22 Gy*	92				Univ Pittsburgh (22)

* Mean dose with range in parenthesis.

Durability of pain control after radiosurgery is another important parameter. In patients with solitary spine metastasis treated with radiosurgery, the actuarial median duration of pain control was 13 months[20]. The data is more limited than radiation dose response. Accurate assessment of durability of pain control is even more difficult, since these patients further develop systemic tumor spread as well as new spine metastases. Overall one year survival rate of patients with solitary spine metastases was 49%[21]. This survival time was significantly different according to the histology of primary tumors, outlining the importance of durable pain control.

CONTROL OF EPIDURAL OR SPINAL CORD COMPRESSION

Another potential use of radiosurgery in spine metastases is for treatment of epidural and spinal cord compression. At Henry Ford Hospital, a phase II trial was conducted examining the use of radiosurgery as a single modality for spinal cord compression. The target volume encompassed the involved spine and epidural or paraspinal soft tumor component. The radiation dose ranged from 16-20 Gy in a single fraction. Patients with a neurological deficit prior to radiosurgery became clinically stable or improved in 75% of the cases. Patients who were neurologically intact prior to radiosurgery remained intact in 85% of the cases after radiosurgery[22]. There was an approximately 70% reduction of volume in epidural tumors. The results suggest that radiosurgery can reduce the epidural tumor volume, and thus achieved epidural decompression. Surgical decompression is effective because it removes the tumor immediately, whereas the effect of radiosurgery is not as immediate. Thus, an argument could be made that patients with minimal neurological signs (ie, ambulatory patients) can be treated with radiosurgery, and surgery reserved for those who progress. Great caution is required for the use of radiosurgery for spinal cord compression as careful patient selection is required and the spinal cord is intimately located with the epidural tumor. Further studies are needed to better select the patients who may benefit from radiosurgery for spinal cord compression.

PRIMARY SPINE TUMORS

Primary vertebral body and spinal cord tumors, both benign and malignant, can be treated with stereotactic radiosurgery. It is important to evaluate the role of radiosurgery for these tumors since the mainstay treatments are surgery, radiation therapy, and chemotherapy depending on the histology and location. Radiosurgery can be used as a part of combined modality treatment in the initial or recurrent setting. While many primary cord tumors are relatively radioresponsive, most of the primary spine tumors tend to be radioresistant, such as chondrosarcomas, chordomas, and osteogenic or soft tissue sarcomas. Pain at the involved spine and/or radiculopathy is invariably present in all. Neurological deficits can cause varying degrees of disability with signs of sensory changes, motor weakness, or urinary incontinence.

In Henry Ford Hospital, radiosurgery was delivered with a dose range of 12-20 Gy depending on tumor type and previous therapy. Overall symptoms and neurological status were improved in 56% of the patients, and stable in 28%. The symptoms progressed after radiosurgery in 2 patients, one with chordoma and the other with hemangiopericytoma. Follow up radiographic imaging studies showed local tumor control in 94%, tumor control being defined as the lack of progression. Of these, complete response was seen in 26%, partial response in 26% and stable in 42%[23].

The role of stereotactic radiosurgery in the treatment of benign and malignant primary spinal tumors is not established. The results shown above indicate a potential role of radiosurgery for these tumors. The results are consistent with other experiences. Gertszen et al have reported on the use of radiosurgery for benign spinal lesions[11]. They also used 12 to 18 Gy with similar symptom response. The Stanford experience also showed a similar experience with intramedullary tumors[2]. In all of the series, pain relief was significant and there no acute radiation induced toxicity although long-term follow up is needed.

Treatment failure and complications

In order to maximize a successful clinical response of spine radiosurgery while minimizing the toxicity profile, it is helpful to carefully analyze the patterns of treatment failure and the complications of the treatment. Because of the steep dose gradient and often small target volumes, the treatment failure must be carefully correlated to the dosimetric profile of each case.

PATTERNS OF FAILURE AFTER RADIOSURGERY

The treatment failures after spine radiosurgery can be divided into three different categories. In-field failure refers to tumor regrowth inside the target volume. Marginal failure is a failure within the region of rapid dose fall-off immediately outside of the target volume. Causes of marginal failure could be geographical miss or patient set up error, or underestimation of target volume. Then there is distant failure, due to progressive metastatic spread involving other untreated vertebra in the spinal column.

Results of failure after radiosurgery at Henry Ford Hospital show an in-field failure rate of 6%. More importantly, there was only a 5% incidence of failure at the immediately adjacent spine (marginal failure)[24]. The low incidence of infield or marginal failure justifies the use of radiosurgery for localized spine metastasis and has been corroborated by other institutions[8]. Though the persistent or progressive pain seems to be solely due to tumor progression at the treated spine, there can be other causes of pain recurrence at the treated spine. One typical example could be spine instability and/or compression fracture. Therefore, any effort should be given to minimize the symptoms secondary to structural problems of the spinal column.

NEURO COMPLICATIONS

The potential consequence of radiation-induced spinal cord injury can be severe. The best way to prevent radiation induced myelopathy is to avoid unnecessary or excessive radiation to the spinal cord. Therefore, it is crucial to achieve good dose conformality to the tumor volume while minimizing the dose to the spinal cord. The tolerance dose of the spinal cord using traditional external beam radiation has been 45 Gy delivered in 25 fractions. This dose is given to the entire diameter of the spinal cord. Therefore, this conventional dose constraint is not applicable for spine radiosurgery because there is a sharp dose fall-off within the spinal cord.

A recent analysis of spinal cord tolerance dose in a total of 230 procedures at Henry Ford Hospital showed that 10 Gy to the 10% partial volume of the spinal cord defined as 6mm above and below the radiosurgery target was safe[21]. Clinical use of the spinal cord dose constraint should be exercised with caution. It is prudent to review the radiation dose distribution in every slice of imaging studies obtained during tumor localization. A diagram of spinal cord dose distribution is shown in Figure 4. There was one incidence of spinal cord damage clinically and radiographically 13 months after 16 Gy radiosurgery for C1 and C2 breast cancer epidural compression. The patient improved with the steroid treatment. Since spinal cord complications can occur after a long latency period, long term follow up is certainly needed.

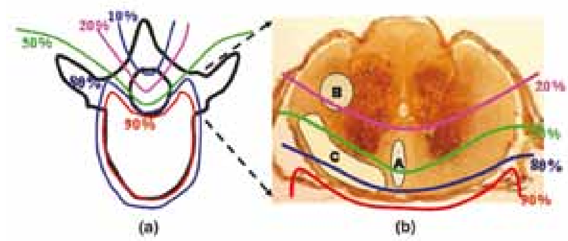

Figure 4. Diagramatic representation of radiosurgy dose distribution within the spinal cord at a cross-sectional level. (a) the radiation dose distribution, (b) the cross-sectional spinal cord anatomy. A: anterior corticospinal tract; B: lateral corticospinal tract; C: most ascending sensory tracts. (Adopted from Ryu et al. Cancer 109:628-636, 2007).

NON-NEURO COMPLICATIONS

Other normal tissues are defined depending on the level of the involved vertebral body. Normal tissues such as the larynx, pharynx, esophagus, bowel, or kidney should be carefully delineated for radiation treatment planning. Vascular structures such as the aorta, carotid arteries, vertebral arteries, or vena cava are not usually delineated unless there is concern for tumor invasion.

Non-neurological complications may include mucositis of the pharynx or esophagus in the cervical or upper thoracic spine treatments. These symptoms manifest with sore throat and swallowing difficulty. Every effort should be given to minimize any radiation dose to the adjacent tissues. Acute side effects associated with mucositis generally resolve within two weeks. Skin reactions are seldom seen after radiosurgery unless the tumor involving the posterior element extending close to skin. Toxicity to the kidney has not been encountered. The tolerance dose of these organs to these organs to radiosurgery is not defined. It is prudent to minimize the unnecessary radiation doses.

There are many factors that may influence radiosurgical complications. These may include proximity and the extension of the tumor to the adjacent normal tissues, concurrent systemic therapy, compounding comorbidities such as acute infection, prior surgery, and host factors such as diabetes, collagen vascular disease, hypertension, or any genetic predisposition to the radiosensitivity. A careful assessment of the patient's clinical condition and dosimetry of radiosurgery is necessary in order to reduce the potential risk of radiation induced complications.

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Combined modality approach

The combined use of radiosurgery with open surgery has been reported. Post operative radiosurgery was tested following open surgical resection in 18 patients with spine metastases[19]. Radiosurgery was performed usually after one to two weeks of open surgery, 92% of the patients remained neurologically stable or improved. The drawback of postoperative radiosurgery is difficulty in delineating the tumor and the spinal cord due to poor image quality secondary to the interference of hardware used for spine stabilization. Despite this, our experience with radiosurgery given post operatively for residual spine tumor and to the surgical bed was well tolerated and associated with little or no significant morbidity[19].

Combined treatment of radiosurgery and vertebroplasty or kyphoplasty is being explored. The experience of the combined procedure at the University of Pittsburgh was well tolerated with excellent results of pain control. Radiosurgery was usually given within one to two weeks after vertebroplasty[29]. At Henry Ford Hospital, vertebroplasty or kyphoplasty is considered when there is concern of spine instability or compression fracture that might be causing pain.

Combined treatment with chemotherapy or medical therapy is not well explored. Since radiosurgery was usually given in a single fraction to the involved spine, the chemotherapy schedule was not usually altered, but chemotherapy was not usually given on the same day. There is no supporting data whether chemotherapy can be combined with radiosurgery at this time. A special caution should be applied for a potential interaction with drug therapy and radiation. A more practical advantage of radiosurgery is that the functioning red marrow can be preserved in patients who need systemic chemotherapy.

Tumors involving the spinal column are complex. They manifest not only with the symptoms of pain or neurological deficits but also with other general oncological problems, even with many socio-economic issues. In addition, any symptoms arising from the weight bearing central skeleton directly affect the function and the quality of life. More complicating issues include intercurrent degenerative change, osteoporosis and associated bone changes, and spine instablility problems. In order to deal with these issues a multidisciplinary approach is very important. At our own institution, a spine tumor board has been formed to promote interdisciplinary group discussion thereby offering comprehensive care of spine tumor patients.

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