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Artigo Original

The use of the cyberknife stereotactic radiosurgery system for the treatment of intracranial and extracranial residual or recurrent chordoma

O uso do sistema cyberknife de radiocirurgia estereotáxica para o tratamento de cordomas recorrentes ou residuai intra e extracranianos

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ABSTRACT

Objectives: *Chordomas are relatively rare primary malignant bone tumors that arise from remnants of the notochord along the craniospinal axis. They tend to be locally invasive around the clival or sacro-coccygeal regions and critical neurological structures are often involved. Complete surgical excision is rarely possible and post-resection radiation enhances local control of the disease. The CyberKnife is a frameless image-guided LINAC radiosurgical system that allows treatment of both intracranial and extracranial lesion. We review here the methodology of the system and present our experience of treating skull base and spinal chordomas.* ***Methods:*** *Between 1994 and 2008, 22 patients with a histological diagnosis of a chordoma underwent stereotactic radiosurgery (SRS) at Stanford University Hospitals. 17 patients underwent frameless SRS at the Stanford CyberKnife Center. A retrospective and prospective review of these patients was undertaken by obtaining clinical and radiological information from an institutional review board-approved prospective database.* ***Results:*** *There were 11 males and 6 females with an average age of 42 years (range 10-73). 12 lesions were in the clivus, 3 in the cervical spine below C2, 1 lumbar and 1 sacral region. All but one patient had prior surgery. 9 had undergone one resection, 5 had two and 2 had three resections. Three patients had prior radiation or proton beam therapy. The average tumor volume treated was 10.9 cm^3 (range 1.9-31.6 cm^3), with a mean radiation dose of 29.3 Gy (range 18-50 Gy), and a mean maximum intratumoral dose of 41.0 Gy (range 24.1-67.6 Gy). Patients were followed up for an average of 4 years. Tumor control was achieved in 12 out of the 17 cases (70.6%). 5 of the 12 patients showed tumor size reduction. However, 5 out of the 17 cases showed progression with one developing a new lesion at a lower cervical vertebra despite good local control. None of the patients with tumor control developed new neurological deficits, but 4 of the 5 cases with tumor progression showed worsening neurological deficits. There was no radiation associated complications.* ***Conclusions:*** *Good tumor control rates can be achieved with no significant morbidity with CyberKnife based stereotactic radiosurgery. Cases with poor control tended to have complex multiple surgical resections. Longer follow-up in larger series is required to adequately compare this technique with other forms of radiation therapy.*

Key-words: *Chordoma, Radiosurgery, Cyberknife, Stereotaxis, skull base, spine, sacrum*

SUMÁRIO

Objetivos: *Cordomas são tumores primarios ósseos malignos relativamente raros que se originam de remanescentes da notocorda ao longo do eixo cranioespinal. Eles tendem a ser localmente invasivos em torno do clivus ou região sacrococcigea e estruturas neurológicas criticas são frequentemente envolvidas. A ressecção cirúrgica completa é raramente possível e a radioterapia pós-ressecção melhora o controle local da doença. A Cyberknife é um sistema de radiocirurgia com LINAC guiado por imagem e que não necessita o uso de frame estereotáxico que permite o tratamento de lesões intra e extracranianas. O presente estudo revisa a metodologia do sistema e apresenta a experiência dos autores no tratamento de cordomas da base tratmento de cordomas espinais e da base do crânio.*

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Métodos: *Entre 1994 e 2008, 22 pacientes com diagnóstico histológico de cordoma foram submetidos a radiocirurgia estereotáxica (SRS) nos Hospitais da Universidade de Stanford. SRS sem halo estereotáxico (frameless) foi realizada em 17 pacientes no Centro de Cyberknife da Universidade de Stanford. Uma revisão retrospectiva e prospectiva destes pacientes foi realizada através da obtenção de informações clinicas e radiológicas através de um banco de dados prospective aprovado pelo comite de ética em pesquisa da instituição.* ***Resultados:*** *Foram incluidos neste estudo 11 homens e 6 mulheres com uma idade média de 42 anos (variação 10-73 anos). Em relação a localização anatômica, 12 lesões estavam no clivus, 03 na coluna cervical abaixo de C2, 01 na coluna lombar e 01 na sacral. Apenas um paciente não foi previamente submetido a tratamento cirúrgico. Uma ressecção prévia foi realizada em 9 pacientes, duas em 5 e três em 02 pacientes. Três pacientes foram previamente submetidos a radioterapia ou terapia com "próton Beam". A media do volume tumoral tratado foi de 10.9 cm^3 (variação: 1.9-31.6 cm^3), com uma dose media de 29.3 Gy (variação: 18-50 Gy), e uma média da dose intratumoral máxima de 41.0 Gy (variação: 24.1-67.6 Gy). Os pacientes foram seguidos por um período médio de 4 anos. O controle tumoral foi obtido em 12 dos 17 casos (70.6%). Redução do volume tumoral foi observada em 5 dos 12 casos. Entretanto, 5 dos 17 casos evoluiram com progressão da doença, sendo que um paciente desenvolveu uma nova lesão em uma vértebra cervical inferior apesar do bom controle local. Nenhum dos pacientes com controle tumoral desenvolveu novo déficit neurológico, mas 4 dos 5 casos com progressão tumoral demonstraram piora do déficit neurológico. Não houve complicação associada a radiação.* ***Conclusões:*** *Uma boa taxa de controle tumoral pode ser obtida sem significativa morbidade com a utilização de radiocirurgia com Cyberknife. Casos com pobre controle tumoral apresentavam múltiplas resecções cirúrgicas complexas prévias. Um seguimento mais prolongado em séries maiores é necessário para comparar adequadamete esta técnica com outras formas de radioterapia.*

Palavras-chave: *Cordomas, Cyber Knife, Radiocirurgia, Radioterapia estereotáxica fracionada.*

Introduction

Chordomas are rare tumors that arise from remnants of the primitive notochord and histologically appear relatively benign[12,18]. However, aside from myeloma, they are the commonest primary malignant bone tumors and have an incidence of approximately 1 in 1.25 million per year[17]. Chordomas can occur anywhere along the axial skeleton and rarely metastasize. They tend to occur either at the cranial base around the clivus, or in the sacro-coccygeal region.

Skull base cases account for less than 0.2% of all intracranial tumors[10]. Even though they are slow growing, chordomas are locally aggressive and their location around the clival region make these lesions particularly challenging to treat[1,20,23]. Optimal results can be achieved with surgery and radiotherapy, but chemotherapy has a limited role currently. Best results are usually obtained by radical surgery to reduce tumor mass while avoiding further neurological deficit. Unfortunately, even with gross or near total resection, local recurrence is common. Furthermore, because of the high-risk anatomy, residual tumor is common[1,10,20,23].

Post-operative radiotherapy is important and has been shown to improve progression free survival. However, like surgery, radiation therapy is also challenging since these tumors respond only to high-dose radiation and the tolerance dose of normal structures that abut the tumor is much less[7]. Improvements in treatment planning and delivery techniques in the form of fractionated proton beam radiotherapy and stereotactic radiosurgery have been encouraging with improvements in progression-free survival and low treatment morbidity[13,15,24].

Stereotactic radiosurgery uses multiple cross-fired beams from a highly collimated high-energy radiation source in conjunction with stereotactic localization to deliver a large radiation dose to a target accurately. We describe here the use of the CyberKnife, a frameless image-guided LINAC stereotactic radiosurgical system, to treat patients with intracranial and extracranial chordoma. An account of the planning and treatment protocol applied to this group of patients is given and the results of our experience with the treatment of chordomas discussed.

Clinical material and methods

PATIENT POPULATION

Between 1994 and 2008, 22 patients with a histological diagnosis of chordoma underwent stereotactic radiosurgery (SRS) at Stanford. 17 patients underwent frameless SRS at the Stanford CyberKnife Center. A retrospective and prospective review of these patients was undertaken by obtaining clinical and radiological information from an institutional review board-approved prospective database.

There were 11 males and 6 females with an average age of 42 years (range 10-73). Among the patients with intracranial chordoma, the most frequent symptom was visual disturbance, with 8 out of 12 presenting with diplopia. The other 4 patients presented with facial palsy, headache, slurred speech and progressive torticollis respectively. Patients with extracranial spi-

nal lesions presented most frequently with neck or back pain and radiculopathy. One patient presented with upper arm weakness and sensory loss.

TREATMENT PRIOR TO RADIOSURGERY

Twelve tumors were located in the clivus, 3 in the cervical spine below C2, one in the lumbar spine and one in the sacral region. All but one patient had prior surgery. Nine had undergone one resection, 5 had two resections and 2 had three procedures specifically for tumor resection. Three patients had prior radiation or proton beam therapy.

IMAGE-GUIDED RADIOSURGERY TREATMENT

Image-guided radiosurgery in the form of the CyberKnife (Accuray Inc., Sunnyvale, CA) was used throughout this study (Figure 1). The system consists of a 130kg, 6MV x-ray linear accelerator (linac) mounted on a commercially available robotic arm. With its six degrees of freedom, the linac can be positioned to any point in space and achieve an average treatment precision of 0.3mm^3.

Figure 1. Cyberknife image-guided linear accelerator radiosurgery system (Accuray Inc., Sunnyvale, CA).

To minimize rotational changes in the patient's position, all patients underwent construction of a noninvasive head restraint, such as the molded Aquaplast mask (WFR/Aquaplast Corp., Wyckoff, NJ) during cranial treatments without requiring a metal stereotactic head frame. A custom alpha cradle mold (Smithers Medical Products, Inc., Akron, OH) was used for spinal treatments for the same reason.

Thin-slice contrast-enhanced CT (1.25mm) and MR (2.0mm) scans were obtained, loaded onto the treatment planning computer and fused. The geometry of the lesion was outlined on CT or MR images, and the amount of radiation each structure can tolerate specified. The system then created a three-dimensional map of the lesion based on the contour data and organized beams that allow equal coverage of the tumor (Figure 2). To determine the location of the target within the robotic coordinate system, alignment radiographs were taken prior to treatment using an x-ray imaging device (amorphous silicon detectors) placed in the floor of the treatment room on both sides of the patient. These real-time digital radiographs are registered to digitally reconstructed radiographs (DRRs) from the treatment planning CT study, enabling the skull or spine (and thus treatment) position to be translated to the coordinate frame of the linac (Figure 3). The robotic arm receives information about the target position and compensates for any patient movement by aligning the linac with the treatment site.

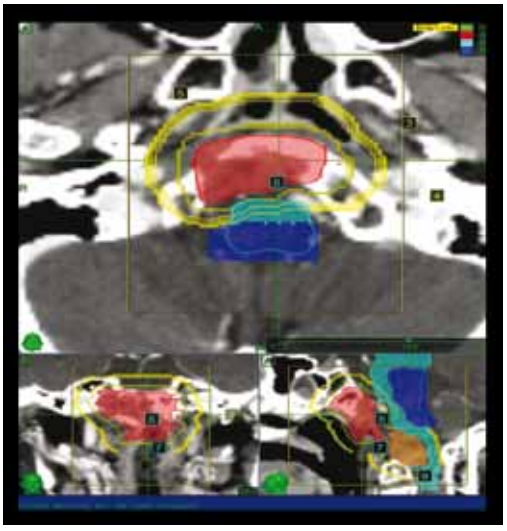

Figure 2. Cyberknife planning system showing conformal radiation coverage of a skull base chordoma based on a three-dimensional map on the contour data of the lesion.

For spinal treatments, tracking of spinal bony landmarks were suboptimal prior to 2005. Patients therefore underwent implantation of either straight gold fiducials or stainless steel screws. The implantation was performed in the operating room in an outpatient setting. Typically, 4 to 5 fiducials are placed, allowing tracking of the spinal lesion using image guidance as described above. Following implantation, the patient returned to the outpatient department for a treatment planning CT. More recently, the development of the Xsight spine tracking system (Accuray Inc., Sunnyvale, CA) has eliminated the use of fiducial implantation. Instead, the system localizes spinal targets by direct reference to the adjacent vertebral structures.

During the actual treatment, the CyberKnife treatment algorithm places the LINAC at a determined position, using real-time imaging to locate the target and adjust for movements. The radiation beam is then delivered and the process repeated

at various preset points, called nodes, surrounding the patient. Therefore, the target position is continually updated using x-ray image-to-image correlation, obviating the need for skeletal fixation to localize the target. The precision of localization is 0.3mm, comparable with that which can be achieved by frame-based techniques.

Figure 3. Target determination using real time digitally reconstructed radiographs (DRRs), enabling the skull or spine position to be translated to the coordinate frame of the linear accelerator.

TREATMENT CHARACTERISTICS

Three patients with clival chordomas underwent two separate radiosurgery treatments for recurrence or progression of the disease at a previously untreated site. All other patients had one treatment. Among the clival chordomas, 7 lesions received 5 fractions, 7 received 3 fractions, one received 2 fractions and 2 received a single fraction.

The average tumor volume treated was 10.9cm^3 (range 1.9cm^3-31.6cm^3). The treatment dose ranged between 18-50 Gy, with a mean of 29.3 Gy, prescribed to the 74-95% isodose contour at the edge of the tumor. The maximum intratumoral dose ranged between 24.1-67.6 Gy with a mean of 41.0 Gy. The diameter of the circular secondary collimators ranged from 5-20mm (Table 1).

Table 1 - Treatment characteristics of 17 consecutive patients with chordomas undergoing CyberKnife radiosurgery.

Case no.	Tumor Location	Treatment dose (Gy)	Fractions	Tumor coverage within margin prescription dose
1	Clivus	18	2	94%
2	Clivus	20	3	95%
3	Clivus	18	1	91%
4	Cervical spine	18	3	91%
5	Cervical spine	19	3	95%
6	Clivus	30	5	85%
7	Clivus	20	1	78%
8	Lumbar spine	30	3	79%
9	Cervical spine	30	3	82%
10	Sacral spine	42	5	75%
11	Clivus	28	3	82%
12	Clivus	43	3	85%
13	Clivus	40	5	80%
14	Clivus	50	5	74%
15	Clivus	25	5	80%
16	Clivus	30	5	75%
17	Clivus	37	5	80%

FOLLOW-UP

Patients underwent clinical follow-up at 3 and 6 months post-treatment, and then every 6 months for the first 2 years. They were also evaluated with MR images at 6 month intervals for the first two years and then yearly thereafter. Images with a minimum of 3.5mm slice thickness were obtained and tumor size calculated by measuring along the three axes. The images were compared to pre-treatment dimensions. Any net decrease in the dimension along one or more of the axes by 3mm was recorded as tumor reduction. Likewise, a net increase of 3mm in any of the dimensions was considered to indicate tumor growth. Follow-up images were also assessed for evidence of radiation necrosis. Clinical and radiological information of patients who were unable to return to our institution for follow-up was forwarded to us from referring physicians.

RESULTS

Clinical and radiological follow-up were available for all patients. Follow-up ranged from 6 months to 10 years, with a mean of 4 years. Based on the multidimensional measuring criteria described above, 5 (29.4%) lesions decreased in size, 7 (41.2%) were unchanged and 5 (29.4%) showed tumor progression. One patient with no change in size of a clival chordoma at one year subsequently developed a C5 lesion. This was treated with radiosurgery and no change in size in the second lesion could be seen at 6 months. Three of the 5 patients who demonstrated progression of the disease underwent further radiosurgery and all demonstrated further progression of the tumor between 6 months to 1 year.

Patients with extracranial lesions had improved symptoms subsequent to their primary surgery. However, one patient who underwent radiosurgery for primary treatment of a L3 lesion had significant improvement of back pain. Radiosurgery did not improve existing neurological deficits. Four of the 17 (23.5%) patients with tumor progression demonstrated new symptoms, one with increased neck pain and radiculopathy, and 3 with worsening neurological deficit. However, there were no new neurological deficits after radiosurgery treatment in any of the

patients. Similarly, there were no clinical or neurological evidence of radiation necrosis or other radiation-induced complications.

ILLUSTRATIVE CASE - INTRACRANIAL CHORDOMA

A 7-year-old male presented to an external hospital with a one month history of progressive torticollis. MR imaging of the brain and spine revealed a mass extending from the clivus to C2 with severe mass effect on the upper cervical cord (Figure 4).

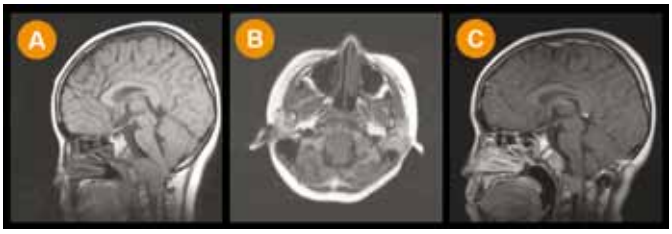

Figure 4. Pre-treatment (A and B) and post-treatment (C) MRI scans of a 7-year-old male submitted to fractionated stereotactic radiotherapy with 25 Gy in 5 fractions to the 80% isodose line. The patient presented with a recurrent tumor after microsurgery and intensity modulated radiation therapy.

He underwent a 2 staged operation, which confirmed the diagnosis of a chordoma. Post-operative MRI showed residual tumor in the clivus and upper cervical spine and he received intensity modulated radiation therapy to a dose of 64.8 Gy. Follow-up MRI at 2 years revealed recurrence of the clival mass and he underwent a third subtotal resection of his tumor. He was then referred to our service and underwent planning for CyberKnife stereotactic radiosurgery to the residual mass as described above (Figure 4). He received 25 Gy in 5 fractions to the 80% isodose line using a combination of 7.5 and 15mm collimator.

ILLUSTRATIVE CASE - EXTRACRANIAL CASE

A 37-year-old male noticed a small swelling that progressively increased in size over his upper sacrum. MRI revealed a sacral-coccygeal mass and he underwent an uncomplicated surgical excision of the tumor, which was confirmed histologically to be a chordoma. Post-operative MR studies revealed residual tumor (Figure 5) and he underwent planning for CyberKnife stereotactic radiosurgery.

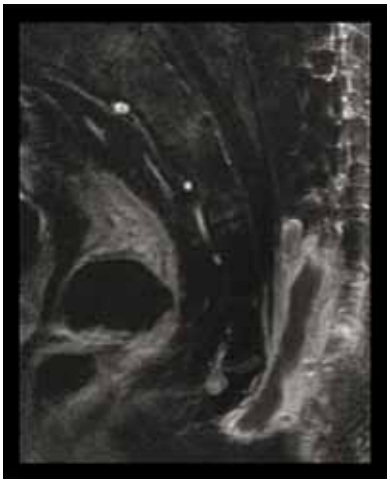

Figure 5. Post-operative MRI of a 37-year-old male Disclosing a residual sacral-coccygeal chordoma.

The patient was placed supine on the treatment table and was fitted with a conformal alpha cradle. In this position, he underwent CT and MR imaging and the images later fused as described above. The target volume and critical structures were contoured and the radiation dose prescribed at 42 Gy delivered to the 75% isodose line using a 20mm collimator. He underwent 5 treatment sessions, lying prone with the custom made cradle fitted each time to ensure consistent stereotactic positioning (Figure 6).

Figure 6. Cyberknife planning software disclosing the dose distribution to the target volume and critical structures of a sacral-coccygeal chordoma. The patient was treated in 5 sessions with 42 Gy delivered to the 75% isodose line using a 20mm collimator.

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Discussion

The importance of surgery has been well established in the treatment of chordomas[4,9,22,23]. Many advocate radical surgery when possible to reduce tumor mass and to prevent neurological deterioration. However, surgery is often limited by the extensive involvement of the skull base or spine, and the surrounding neurological structures, which contributes to the high recurrence and residual rate. The most frequent complications following surgery include CSF leak and transient or permanent cranial or spinal nerve damage[1,9]. Recurrence free survival rates of around 65% over a mean of 5 years can be achieved with surgery[20].

Subtotal resection is often necessary to avoid significant morbidity and optimal treatment usually requires the combination of surgery and radiation therapy. Survival benefits of adjuvant therapy with conventional radiotherapy has been well documented[2,5,6,8,19]. However, chordomas respond well only to high-dose radiation and post-operative radiotherapy to the tumor target can result in an unacceptable radiation dose to the adjacent normal tissue. Heavy particle irradiation has the advantage of a steeper falloff dose and therefore is particularly well suited for treating chordomas. Local control rate of between 46 and 76% at 5 and 3 years respectively have been reported, although these studies were small[13,14]. Others have shown a five-year actuarial survival rate of between 68-79%[3,13]. With improvement in treatment planning and delivery techniques, the morbidity associated with radiotherapy and proton beam radiotherapy have decreased. Radiation related side effects ranged from general symptoms, such as malaise, nausea and headache, to more specific structural injuries, such as visual and hearing impairment, pituitary insufficiency and radiation necrosis[7,21].

Availability of a proton beam facility is limited and the treatment duration, often taking up to 7 weeks, and distance needed to travel to the facility can be difficult for patients, especially children. Stereotactic radiosurgery has been used to treat chordomas relatively more recently but with comparable results to proton beam radiotherapy. The steep dose gradient achievable with radiosurgery can similarly maximize dose radiation to the tumor while minimizing radiation to surrounding critical structures. Five-year tumor control rate ranging between 62-76% and 5-year survival rate of around 80% have been reported[11,16]. These results were limited to treatment of skull base chordomas only since the studies looked at gamma knife radiosurgery, which cannot be used for extracranial lesions.

A major advantage of the CyberKnife system is the ability to treat intracranial and extracranial lesions with complex shapes or locations that are difficult or impossible to treat using frame-based systems. The treatment planning system of the CyberKnife is designed to allow either isocentric or nonisocentric-based treatment planning. As with frame-based radiosurgery, the treatment dose to the tumor margin is based on volume, location, and history of prior radiotherapy.

The average follow up in our study is 4 years, which like many other studies is relatively short for assessing fully the effect of radiosurgery in chordomas. Tumor control was achieved in 70.6% of patients, although the numbers involved were relatively small. Despite this, our experience represents one of the largest single center series for radiosurgery treatment in chordomas. However, the small patient population reported here and in other similar studies demonstrates the difficulty in evaluating the efficacy of radiosurgery for this rare disease with statistical certainty.

Clinical improvement was mostly achieved following surgery, prior to radiosurgery, and despite good tumor control, none showed significant improvement in their existing neurological deficits. Of the 4 patients who developed new symptoms, only 3 showed radiological progression of the disease. Local relapse is thought to be the main reason for treatment failure. It is uncertain whether this may be due to inadequate radiation dosage or coverage since the tumor margin around the skull base or spine may be difficult to define. The complex anatomy and limitations of even modern imaging may not demonstrate reliably the entire extent of the tumor.

Other limitations of radiosurgical treatment of chordomas include tumor volume and the low dose tolerance of the spinal cord and many skull base neurological structures, such as the optic apparatus. Certainly, patients should be evaluated following tumor resection and the suitability of adjuvant radiosurgery determined individually. Large tumor volumes may be difficult to treat without significantly increasing the risk of radiation-related side effects.

Critical structures adjacent to the lesion can be spared based on the contouring of the lesion and surrounding structures. Dose weighting is calculated for different beams to accommodate the dose constraints for each critical structure near the lesion. In addition, the CyberKnife offers flexibility over frame-based systems by allowing multi-session radiosurgical regimens. This further reduces the radiation risk to critical structures. However, such multi-session may reduce the efficacy of radiation to chordomas.

Conclusion

Whenever possible, radical surgery to patients with chordomas should be offered. Patients with residual tumor or recurrences

should be offered radiation treatment. Stereotactic radiosurgery appears to be effective in controlling tumor progression and our study shows efficacy comparable to other forms of radiation treatments including proton beam therapy. Patients in this series tolerated the treatment well, with no radiation-related side effects seen. The CyberKnife system offers the additional advantage of being frameless, allowing the targeting of intracranial and extracranial lesions and the delivery of fractionated radiosurgery regimes if required. This study is limited by the relatively small numbers of patients and short follow-up period. Larger series and longer follow-up periods are required to fully assess the efficacy of this modality in the treatment of chordomas.

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