

Clinical application of CyberKnife for high-risk central nervous system tumors: A clinical trial report of 60 cases

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Abstract. The objective of the present study was to evaluate the application potential of CyberKnife for high-risk tumors of the central nervous system and to analyze the effectiveness of CyberKnife in relation to dose recovery and gain division (times). A total of Eighty-one targeted areas from 139 central nervous tumor lesions in 60 patients were treated with I-VI ranged CyberKnife for 1 week. Following CyberKnife treatment, imaging tests revealed a decrease in tumor volume, reduction of central nervous system symptoms and an increase in the life quality of patients. The advantages of CyberKnife include non-invasiveness, individualized treatment, flexibility, high accuracy and rapid treatment. CyberKnife produces slight damage and a favorable therapeutic effect and expands our concepts concerning precise radiotherapy for tumors. It is an indispensable method for personalized tumor treatment.

Introduction

Patients with high-risk central nervous system tumors commonly refuse surgery or receive partial resection due to the difficulty and risk of surgery, and the rapid recurrence of tumors (1-3). Palliative treatment is often applied because of the inability to perform surgery, regular radiation or chemotherapy due to the invasion of central organs with important functions by tumor infiltration and multiple metastases (4-6). Direct involvement or activation of local nociceptors as well as adjacent nerves, vessels, central nervous tissue as suppressed by tumors may lead to paralysis or paraplegia accompanied by pain and tumor compression complex (7-9). Using CyberKnife to control or reduce local lesions, we attempted to improve the

internal environment, to reduce adverse reactions, to control tumor progression and to alleviate clinical symptoms.

Materials and methods

Subjects. A total of 139 central nervous system tumor lesions in 60 patients who received palliative treatment at the Center for Non-Traumatic Treatment and Diagnosis of Tumor, Binzhou Medical College Affiliated with the PLA 107th Hospital, from October 2010 to May 2011, were selected for the study according to the following standards. i) Diagnosis of tumors was confirmed by pathology or imaging tests, such as CT and MRI, and were ranked as stages III-IV according to the WHO clinical staging system. ii) Patients had an ECOG Performance status 2-4. iii) Patients exhibited crudescence following surgery, invasion of central organs with vital functions, infiltration of lymph and neurons or multiple metastases and had no indications for surgery or were unable to undergo standard chemical or radiotherapy. iv) Patients provided informed consent. The exclusion criteria included i) associated Tb, undetermined diagnosis, early stage disease with surgical indications; ii) intractable increased intracranial pressure; iii) recent repeated radiotherapy or suspected radiotherapy complications.

A total of 38 males and 22 females, 6-63 years of age, with an average age of 50 years, were enrolled. There were 81 targeted areas from 139 lesions including 9 gliomas, 23 brain metastases, 8 meningiomas, 11 pituitary tumors, 8 intramedullary spinal cord tumors and 1 spinal meningioma. Between 1 and 24 lesions were noted in each patient, 1-6 lesions were planned to be targeted, and 31 cases suffered from brain swelling.

Methods. CT slices (1.25-mm) were performed after hospitalization. IMR, PET-CT or DSA image fusion was conducted when necessary to determine the target areas. Centrum or skull 6D tracking outlined target CTV. Treatment plans and treatment doses were determined according to the number of tumor lesions and tumor size. Treatment was carried out 1-6 times, and complete treatment spanned 1 week.

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Key words: central nervous system, high-risk tumor, CyberKnife, radiotherapy, dose response

Evaluation. Stereotactic radiowave surgery platform specifications: CyberKnife System (Accuray Group Co., Ltd., USA). The

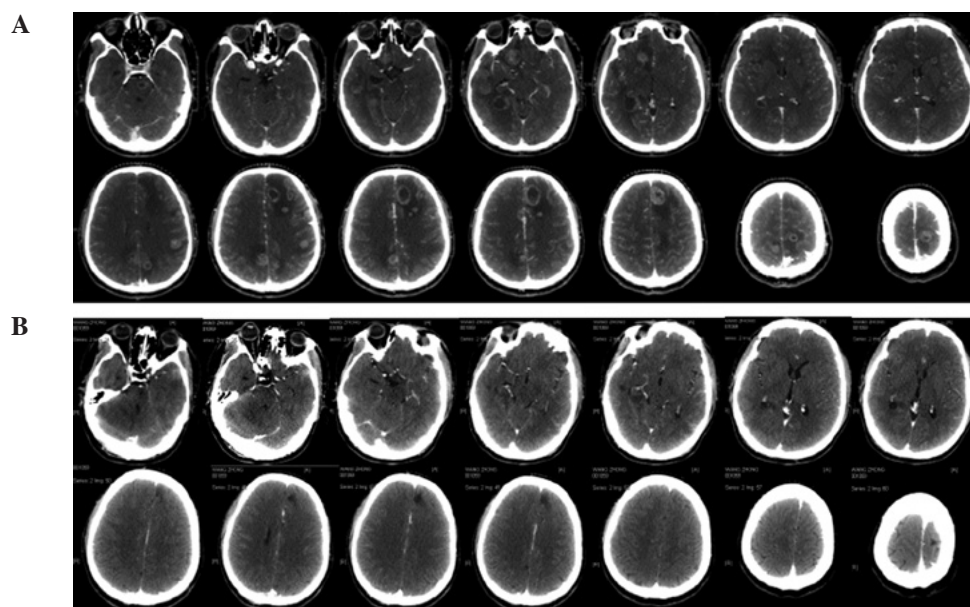


Figure 1. Multiple intracranial metastases (24 lesions). CT revealed that tumors generally disappeared after CyberKnife treatment. (A) CT before CyberKnife therapy (2010-12-04); (B) CT after CyberKnife therapy (2011-02-22).

output dose rate was 400-600 cGy. The US FDA granted market access for systemic treatment as certified in August 2001. Tumor dose coverage was 85-95%. For patients with small and single-tumor lesions, the general dose was 1-3 F; for those with large and multiple tumor lesions the general dose was 4-6 F. The tumor dose DT was 18-60 Gy, with a single dose of 4-18 Gy.

Criteria. Evaluation: i) imaging examination, shrinkage; ii) RIA and endocrine hormone detection, decrease or recover; iii) Zubrod-ECOG-WHO (ZPS) (10) scale 1-4: 0, normal activity; 1, some symptoms but still almost fully ambulatory; 2, <0% of daytime spent in bed; 3, >50% of daytime spent in bed; 4, completely bedridden; 5, deceased.

WHO objective criteria of curative effect (11). CR, complete remission with symptoms and physical signs totally disappeared for 4 weeks; PR, partial remission with tumor volume shrinkage >50% for at least 4 weeks; NC, no significant change observable for at least 4 weeks with a tumor volume increase of $\leq 25\%$ or shrinkage $\geq 50\%$; PD, progressive disease with new lesions appearing or the original lesion increasing >25% in size. The total effective rate was calculated with the following equation: (CR + PR)/total cases $\times 100\%$.

Statistical analysis. All values are expressed as the means \pm standard deviation (SD). Differences were evaluated using Statistical Package for Social Science 13.0 (SPSS13.0). Statistical analysis was performed using the two-sided Student's t-test. Differences were considered statistically significant at the level of $p < 0.05$.

Results

Case statistics. A total of 63 cases were assessed. Three cases were excluded; 2 cases could not follow the study instructions because of age and 1 case experienced financial problems. A total of 60 cases were involved in the final analysis.

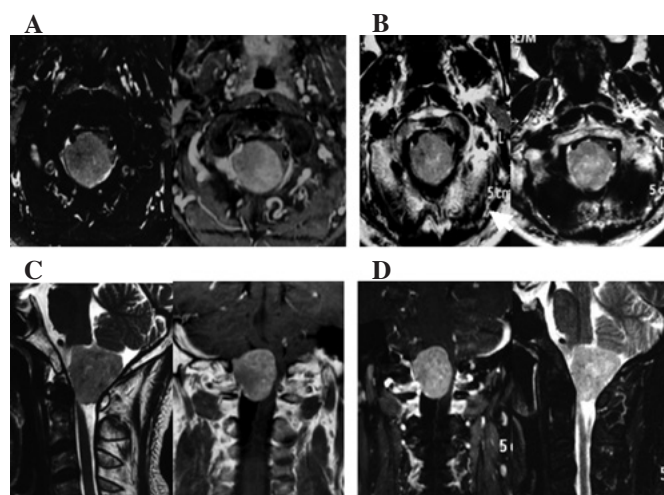


Figure 2. Meningioma (3.4x3x2.7 cm). Although there was no significant change in radiographic imaging, the patient experienced improvement in the quality of life after CyberKnife therapy. (A) MRI before CyberKnife therapy (2011-02-25); (B) MRI after CyberKnife therapy (2011-04-25); (C) MRI before CyberKnife therapy (2011-02-25); (D) MRI after CyberKnife therapy (2011-04-25).

Imaging tests. High-risk patients with at least one of the following conditions (tumor recurrence after surgery, multiple metastases, disease uncontrollable by either radiation or chemotherapy, invalid conservative therapy, or diagnosis at an advanced stage) exhibited significant shrinkage or disappearance of lesions as confirmed by imaging compared to 120 advanced patients who received only conservative therapy by conformal radiation therapy.

RIA monitoring and endocrine hormone condition. Compared to the control group, 5 of 24 patients with increased tumor markers or endocrine hormone became negative, 10 cases were degraded to varying degrees, 6 cases had no obvious changes and 3 cases increased following CyberKnife treatment.

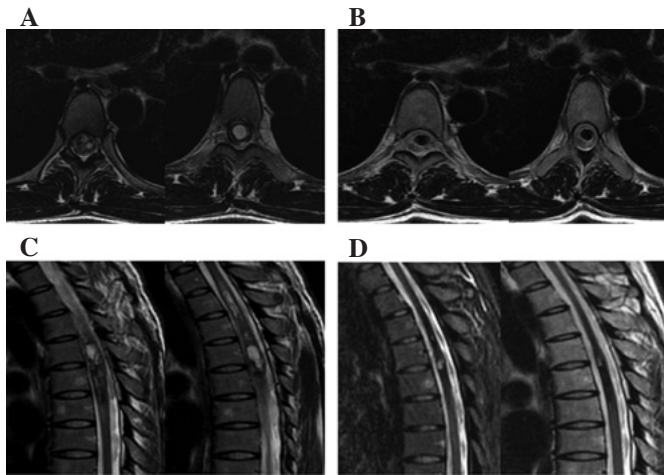


Figure 3. A patient with chest intramedullary hemangioma (14 cm) was able to walk alone after he was treated in four fractions. (A) CT before CyberKnife therapy (2011-01-30); (B) CT after CyberKnife therapy (2011-04-30); (C) MRI before CyberKnife therapy (2011-01-30); (D) MRI after CyberKnife therapy (2011-04-30).

ZPS scores were improved to various degrees in all the patients after treatment, accompanied by alleviation or disappearance of tumor suppression syndrome and pain syndrome.

Objective effect assessment. Patients with advanced cancer who received repeated treatment also showed a high rate of alleviation of symptoms after CyberKnife treatment. The brain stem invaded by intracranial multiple metastases (24 lesions) caused severe central nervous system suppression syndrome, and the treatment plans were divided into six parts with at most one target for six tumor lesions. The patients were able to take care of themselves after completion of treatment in 19 days (Fig. 1). Patients with meningiomas ($3.4 \times 3.0 \times 2.7 \text{ cm}^3$) who refused surgery due to the high risk by severe medulla oblongata placeholder successfully accomplished therapeutic treatment utilizing CyberKnife (Fig. 2). Another case with chest intramedullary hemangiomas (reaching a length of 14 cm) who was paralyzed in bed and could not care of himself recovered after CyberKnife treatment and was able to walk following 4 administrations of CyberKnife treatment (Fig. 3).

Discussion

Palliative treatment is the major treatment for patients suffering from central nervous system tumors, particularly brain glioma, metastatic tumors and spinal cord tumors (12-18). Surgery or conventional radiotherapy is unable to provide a complete cure due to the late diagnosis of these advanced tumors, the rapid growth of the tumors, and compression or infiltration of important organs (13,19-22). CyberKnife is a flexible method having the advantage of high accuracy, timely tracking, shorter treatment times, a high-dose, short treatment course, easy patient access to treatment, improved local cure rate and favorable results (22,23). Statistical results from 60 patients with advanced complex tumors and from 120 patients receiving advanced palliative radiotherapy showed that, after treatment, in some cases CyberKnife even achieved complete remission;

the effective rate was 71.7%, suggesting an effective non-invasive treatment for cancer.

CyberKnife technology facilitates cancer treatment and improves the local control rate, especially in high-risk patients (24-27). Most patients receiving CyberKnife do not require hospitalization (28-31), treatment time is short (32,33), and no toxic side effects occur (34-36). We believe that treatment time, frequency and dose should be based on the number of tumors, size, severity of the disease, repeated during the length of the treatment time. This means that treatment should reflect the individual needs and not blindly pursue a rapid treatment. CyberKnife can be carried out without hospitalization or early discharge. At the end of treatment, normal routine blood examination should be carried out. However, after 1-2 weeks of treatment, if grain dump, brain edema, intracranial pressure and orthostatic hypotension occurs, it is necessary for the patients to be hospitalized for observation, consolidation effect, thus they can be excluded from CyberKnife 'surgery' which may cause potential adverse reactions (37).

CyberKnife also incorporates the merits of the Gamma (X) knife while overcoming its shortcomings, such as the need for tumor shape and oversized target areas (38). It works effectively in the cancer therapy of central nervous system tumors. CyberKnife could interface with a variety of imaging examinations, including CT, MRI, PET-CT and DSA, and obtain three-dimensional image to offer the most direct evidence for gross targeted region delineation (39). CyberKnife requires more strict target delineation than ordinary radiotherapy, but not as traditional as conformal radiation therapy (40). Careful forethought should be given due to the CyberKnife portrait of fewer but larger doses.

In conclusion, using CyberKnife therapy, the quality of life of patients with high-risk central nervous system cancer markedly improves, symptoms are rapidly alleviated and patients need not undergo surgery (41). CyberKnife is a new effective therapeutic method for treating advanced high-risk central nervous system cancers.

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