Clinical Report of 46 Intracranial Tumors with LINAC Based Stereotactic Radiosurgery

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Between July 1988 and December 1992, we treated 45 patients who had deep seated inoperable or residual and/or recurrent intracranial tumors using LINAC based stereotactic radiosurgery at the Department of Therapeutic Radiology, Kangnam St. Mary's Hospital, Catholic University Medical College.

Treated intracranial tumors included pituitary tumors (n=15), acoustic neurinomas (n=8), meningiomas (n=7), gliomas (n=6), craniopharyngiomas (n=4), pinealomas (n=3), hemangioblastomas (n=2), and solitary metastatic tumor from lung cancer (n=1). The dimension of treatment field varied from 0.23 to 42.88 cm^3 (mean; 7.26 cm^3). The maximum tumor doses ranging from 5 to 35.5 Gy (mean; 29.9 Gy) were given, and depended on patients' age, target volume, location of lesion and previous history of irradiation. There were 22 male and 23 female patients. The age was varied from 5 to 74 years of age (a median age; 43 years). The mean duration of follow-up was 35 months (2~55 months).

To date, 18 (39.1%) of 46 intracranial tumors treated with SRS showed absent or decrease of the tumor by serial follow-up CT and/or MRI and 16 (34.8%) were stationary, e.g. growth arrest. From the view point of the clinical aspects, 34 (73.9%) of 46 tumors were considered improved status, that is, alive with no evidence of active tumor and 8 (17.4%) of them were stable, alive with disease but no deterioration as compared with before SRS. Although there showed slight increase of the tumor in size according to follow-up imagings of 4 cases (pituitary tumor 1, acoustic neurinomas 2, pinealoma 1), they still represented clinically stable status. Clinically, two (4.4%) patients who were anaplastic astrocytoma (n=1) and metastatic brain tumor (n=1) were worsened following SRS treatment. So far, no serious complications were found after treatment. The minor degree headache which could be relieved by steroid or analgesics and transient focal hair loss were observed in a few cases. There should be meticulous long term follow-up in all cases.

Key Words: Stereotactic radiosurgery, Linac based, Pituitary tumor, Acoustic neurinoma, Meningioma, Glioma, Craniopharyngioma, Pinealoma, Hemangioblastoma, Metastatic brain tumor.

INTRODUCTION

Stereotactic radiosurgery (SRS) is an elegant non-invasive technique that delivers a single large fraction of ionizing radiation to a well defined, small intracranial target with very sharp peripheral dose fall off resulting in minimal exposure of normal surrounding brain[1~10]. So far, various techniques for SRS have been developed using multiple cobalt beams, linear accelerators and charged particle beams.

Although the technique was originally applied to the treatment of benign tumors and arteriovenous malformations, it has increasingly been applied to the treatment of recurrent or inoperable intracranial tumors with promising early clinical results[2].

MRI and CT imaging combined with microsurgical techniques have facilitated the resection of circumscribed tumors from even deep or functional brain regions. However, the length of hospitalization required and potential morbidity of surgical resection warrant continued concern. The spherical

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Table 1. Patients Characteristics and Lists of the Intracranial Tumors

	M: F	Age (year)	Field Size (cm)	Maximum Dose (Gy)	Follow-up Duration (Mo)
Pituitary tumor (n=15)	9:6	22~55 (40)	0.5~2.5 (1.5)	15~25 (20.2)	3~55 (24.6)
Acoustic tumor (n=7+1*)	3:4	21~58 (48)	1~2 (1.4)	15~35.5 (27.7)	2~51 (24.4)
Meningioma (n=7)	3:3	29~74 (44)	1~3 (2)	16~29.6 (20)	14~50 (36)
Glioma (n=6)	3:3	5~30 (50)	1.5~3 (2)	16.5~25 (18.4)	6~43 (25)
Craniopharyngioma (n=4)	1:3	5~30 (9)	0.5~2 (1.3)	15~30 (21.9)	22~53 (41)
Pinealoma (n=3)	2:1	16~54 (33)	1~2 (1.6)	13.2~27.4 (21.7)	33~52 (41)
Hemangioblastoma (n=2)	0:2	28~37 (33)	2~3.5 (2)	5~30 (17.5)	34~45 (40)
Metastasis (n=1)	1:0	49	1	17	30
Total (n=45+1*)	22:23	5~74 (43)	0.5~3.5 (1.94)	5~3.5 (20.9)	2~35.5 (35)

*: bilateral lesion, Gy: Gray, Mo: Month
( ): median

dose distribution produced by SRS is well suited to treat spherical intracranial targets using single or multiple isocenter techniques. SRS appears to be an effective treatment alternative for patients with circumscribed primary brain tumors[1~4].

The present study was performed to evaluate the potential effect of SRS using the linear accelerator to treat small primary brain tumors or recurrent tumors after surgical resection and/or conventional irradiation. We tried to analyze a retrospective review of treated 45 patients' outcomes.

MATERIALS AND METHODS

From July 1988 through Dec. 1992, 45 patients with intracranial tumor were treated with linear accelerator based SRS at the Department of Therapeutic Radiology, Kangnam St. Mary's Hospital, Catholic University Medical College.

We used a 6 MV photon beam from the linear accelerator (NELAC-1006X, NEC). Table 1 lists the intracranial tumors treated by stereotactic radiosurgery. A single isocenter was used in all patients. There were 22 male and 23 female patients. The ages of the patients treated varied from 5 to 74 years with a median age of 43 years. The duration of median follow-up was 35 months (range; 2 to 55 months).

Composition of multiple noncoplanar arc irradiation from different angular approaches results in a spherical isodose pattern with a steep isodose fall off. It becomes approximately a 10% decrease at every millimeter of increasing radial distance from the isocenter within the isodose interval from 90% to 30%[4~5]. The treatment field dimension varied from 0.13~42.88 cm^3 (mean; 7.26 cm^3). The maximum tumor doses ranging from 5 to 35.5 Gy (mean; 20.9 Gy) was given depending on patients' age, target volume, its location and previous irradiation. Other physical parameters, quality control and dosimetry of this technique have been described in another reports[6~8].

Patients were selected for SRS in case of following situations; 1) the patients had an intracranial tumor considered unresectable by conventional neurosurgical techniques, 2) the patients was elderly or had a significnt associated medical condition posing excessive surgical risks, 3) despite prior surgery, residual or recurrent tumor remained, and 4) direct surgical removal was recommended but was refused by the patient, who requested SRS instead.

RESULTS

The treated intracranial tumors with SRS were

Table 2. Imaging Response Using CT and/or MRI and Clinical Results following Stereotactic Radiosurgery

Response / Tumors	Tumor size					Clinical status				Total (%)
	absent	decreased	stable	increased	not checked	improved	stable	worsen	not checked	
Pituitary tumor	2	2	6	1	4	13	1		1	15 (32.6)
Acoustic tumor		3	1	2*	2	6	2*			7+1*(17.4)
Meningioma		4	2		1	5	1		1	7 (15.2)
Glioma		1	4		1	2	3	1		6 (13)
Craniopharyngioma		4				4				4 (8.7)
Pinealoma		1	1	1		2	1			3 (6.5)
Hemangioblastoma		1	1			2				2 (4.3)
Metastasis			1					1		1 (2.2)
	2(4.3)	16(34.8)	16(34.8)	4(8.7)	8(17.4)	34(73.9)	8(17.4)	2(4.3)	2(4.3)	46(100)

* Bilateral acoustic tumor

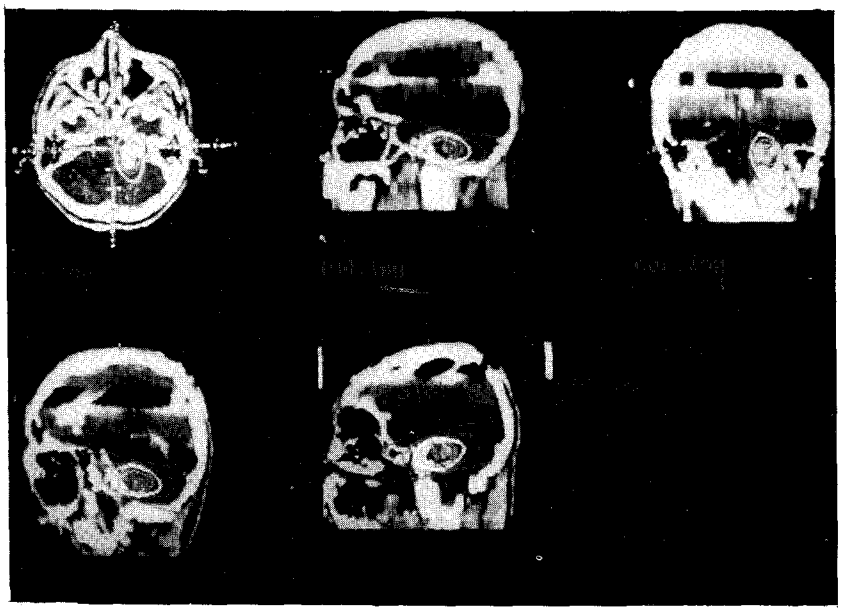

Fig. 1. CT images showing head contour, arc paths, and acoustic tumor. Isodose distributions (80, 40, 20, 10% curves) were shown, and 80% isodose curve sufficiently covered the acoustic tumor in all directions of arc, sparing doses of eyes and surrounding normal structures[20].

pituitary tumors (n=15), acoustic neurinomas (n=8), meningiomas (n=7), gliomas (n=6), craniopharyngiomas (n=4), pinealomas (n=3), hemangioblastomas (n=2) and solitary metastatic tumor from lung cancer (n=1) (Table 1&2). Clinical status of patients and the tumor responses following SRS which were evaluated by imaging studies (CT and/or MRI) were summarized in table 2. All the tumors were enclosed within 50~90% isodose shells of SRS treatment plan (Fig. 1)[20].

1. Pituitary Tumors

Fifteen pituitary macroadenomas consisting of 9 prolactinomas, 2 mixed prolactin-growth hormone secreting tumors and 4 nonsecreting ones had been treated. Postoperative irradiation were performed for all but one Cushing disease. The maximum doses ranged from 15 Gy to 25 Gy (median; 20.2 Gy). Among the 15 pituitary tumors, there noted absence of tumor in 2, decrease of tumor in

2, stable in 6, and increase of the tumor size in 1 through follow up imagings but remaining 4 were not examined. However, in view of the clinical status during 3 to 55 months of follow-up days, 13 were considered improved status, and one was stable and remaining one was not examined.

2. Acoustic Neurinomas

One of seven acoustic neurinoma patients had bilateral lesions of which one side did not proved pathologically. Therefore, we counted eight tumors, totally. Postoperative irradiation was done in all cases except the opposite side of bilateral invador. The maximum tumor doses ranged from 15 Gy to 35.5 Gy (median; 27.7 Gy). Serial post-SRS imagings showed decrease of tumor in 3, growth arrest in 1, increase of tumor with central low density in 2, and two were not followed up yet. According to the clinical status of patients, there noted 6 improved disease in terms of much better hearing acuity as well as no nerve palsy and two were stable diseases during 2 to 51 months of follow-up days (median; 24.4 months).

3. Meningiomas

Five patients who had undergone previous operations and two medically inoperable patients were treated. Treated maximum doses ranged from 16 Gy to 29.6 Gy (median; 20 Gy). No patients had shown subsequent tumor growth within the observation period for 14 to 50 months (median; 36 months).

4. Gliomas

Four of 6 gliomas consisting of 2 oligodendrogliomas and two astrocytomas were diagnosed by stereotactic biopsy. Remaining two were only diagnosed through imaging studies because of patients' poor performance status, senility and location of the lesion. The maximum tumor dose ranged from 16.5 Gy to 25 Gy (median; 18.4 Gy). All patients were considered stable or improved status after SRS for 25 months of median follow-up days (range; 6~43 months), but one eldest 74 years old gentleman survived for 6 months without benefits.

5. Other Neoplasms

Four patients with craniopharyngioma had undergone prior surgery and treated by SRS with a median maximum dose of 29.9 Gy (range; 15~30 Gy). They showed shrinkage of the residual tumor mass by follow-up imagings accompanying with fair clinical status for 22 to 53 months of follow-up days.

Three patients with pinealoma where SRS provided a boost to conventional external beam radiation therapy (whole brain; 20 Gy/2 wks) showed mild to moderate hydrocephalus and Parinaud's syndrome. Two of 3 patients had taken venticuloperitoneal shunt operation and one of them proved to a pineocytoma. Even though they are clinically well being in 2 and one in stable after SRS, there showed variable sized asymptomatic small residual lesions at the treated pineal area by imagings for 41 months of median follow-up (range; 33~52 months). The maximum doses ranged from 13.2 Gy to 27.4 Gy (median; 21.7 Gy). A 16 years old high school boy received SRS two times with doses of 17 Gy and 10.4 Gy by one year apart because of reappearance of pineal mass following initial complete remission should be followed conventional whole brian irradiation (20 Gy/2 weeks). Neither of them revealed positive tumor marker since the base line studies for SRS.

Two patients with hemangioblastoma were treated with 5 Gy and 30 Gy, respectively. One patient previously irradiated with conventional method (50 Gy/5 weeks) at 5 years ago received 5 Gy of SRS on the regrowing mass. The other was also treated two times of SRS with the doses of 20 Gy and 10 Gy, respectively, by one year apart because of progression of the treated tumor. However, no one was worsened clinically yet with a median follow-up for 40 months (range; 34~45 months).

One solitary metastatic tumor from known adenocarcinoma of lungs was treated 17 Gy with devoid of conventional whole brian irradiation and followed up for 30 months. Afterward, he had suffered from multiple bone metastases. Of course, his survival is related to the progression of disease outside the treated tumor volume.

No treatment related critical complications were observed except the immediate minor degree headache which could be relieved by steroid or analgesic drugs and transient focal hair loss were shown in a few cases.

DISCUSSION

The aim of stereotactic radiation therapy is to control radioresistant cerebral neoplasms by focusing a high radiation dose inside the target volume. Moreover, because of the steep dose gradient, critical brain structures such as optic

nerves, motor pathway and the brain stem can be accurately spared[9]. Our experience seems to suggest that a large single dose concentrated within tumor volume can be safe and adequate. Therefore, SRS is an effective, and cost saving alternative to conventional neurosurgical removal by craniotomy in selected patients who have intracranial arteriovenous malformations or brain tumors.

To date, 18 (39.1%) of 46 treated intracranial tumors with SRS showed absence or decrease of the tumor size by serial follow-up CT and/or MRI and 16 (34.8%) of 46 were stationary, e.g. growth arrest. By the clinical aspects, 34 (73.9%) of 46 tumors were considered improved status, that is, alive with no evidence of active tumor and 8 (17.4%) were stable, alive with disease but no deterioration as compared with before SRS. The increase of tumor size with slight to mild degree was revealed in 4 (8.7%) according to the follow-up imagings, however, clinically representing stable status. These requiring close observation were one pituitary tumor, 2 acoustic neurinomas and one pinealoma. Clinically, 2 (4.4%) of 45 patients were exacerbated after SRS. They were one anaplastic astrocytoma and one solitary metastatic brain disease. The former, 74 years old man, diagnosed as anaplastic astrocytoma by stereotactic biopsy at the another hospital was survived for 6 months after SRS without clinical improvement. The latter, 49 years old man, sustained of endobronchial adenocarcinoma of lungs revealed not only lateral ventricular mass resembling choroid plexus papilloma but also multiple disseminated bone metastases. Initially, he was planned to be treated using SRS followed by conventional whole brain irradiation, however, his general condition was improved a little after SRS then he refused the further cranial irradiation.

Reported results of radiosurgical treatment of malignancy are variable. Sturm reported a large number of patients with solitary brain metastasis followed at least 3 months[6~10]. Responses are often dramatic and rapid both neurologically and radiologically. Based on his experience, clinical and CT responses are seen in more than 50% of patients; clinical response usually begin within 2 days. He also treated 36 patients with high grade gliomas, delivering 39 Gy on each of 2 successive treatment days; the results are no better than with conventional treatment. Colombo reported 9 low grade astrocytomas treated with a linac based system and followed by CT at 18~43 months[11]. In 7 cases a response was noted; 6 patients were improved clinically. He also reported treatments of several malignant radiation sensitive tumors such as medulloblastoma, germinoma and lymphoma and noted an almost complete shrinkage on CT within 2~4 weeks. Pozza suggested that clinically favorable responses should not be expected before 6 months[9]. Serial contrast enhanced CT scans demonstrated a gradual increase in tumor size up to 6~9 months, with the simultaneous development of a dense central core which evolved into a contrast enhanced ring. The ring increased in diameter up to 6~9 months, at which time it roughly corresponded to the border of the target volume. From this time until 12~24 months progressive shrinkage of the lesion was noted.

Pituitary tumors may be effectively treated with 45 to 55 Gy, using either radiocobalt or linear accelerator as sources of radiation[12]. Kjellberg and Kliman pointed out that radiation effectiveness was delayed, reaching a maximum about three to five years following Bragg peak proton therapy[12]. They reported remission of about 35% one year following therapy with progressive increase to 80% remission at five years. Unfortunately, they have defined remission from acromegaly as below 10 ng/ml of growth hormone of which this value might occur acromegaly. Our clinical response rates showed 14 (93%) responsiveness of 15 pituitary tumors during the follow-up of 4 to 52 months (mean; 24 months). Acoustic neurinomas are usually approached microsurgical, with a goal of preserving facial nerve function and hearing, and cure in defined as total removal of the tumor[6,13,15]. Despite advances in microsurgical techniques, however, total removal is not always possible. In cases where less than total excision has been accomplished, a decision must be made whether to recommend postoperative irradiation or to withhold further therapy unless the tumor progresses. With radiosurgery, cure is defined as lack of further tumor growth[13]. Wallner has demonstrated that radiation therapy is effective following biopsy. According to Leksell[16,17], in 43% of cases tumor size decreased, and growth was arrested in 42%, for a response rate of 85%. Temporary facial weakness was seen in 15% of cases; no patients developed permanent facial weakness of facial paralysis. Preoperative hearing was preserved in 25% of cases. The peripheral tumor dose was 18~25 Gy depending on lesion size and patient age. The maximum tumor dose was 22~50 Gy. Our response rate was 4 (50%) of 8 tumors in terms of

decrease of tumor size in 3 and one growth arrest. For the management of meningiomas, the majority of recurrence are clinically and radiographically manifested between the 2nd and 4th years postoperatively[6,14]. Therefore with the current median follow-up period in our study of 36 months, we can not draw any hard conclusions concerning arrest, remissions or recurrence free survival. We can conclude, however, that in out small series of patients, the meningioma responded to single high irradiation doses at least on a par with what might be expected from conventional fractionated irradiation. It is still too early to drive definitive conclusions regarding optimum dose and target volume. Talking about craniopharyngioma, generally solid and multicystic tumors are best treated by external stereotactic irradiation and the sharp limitation of the radiation field by either gamma knife or linac based SRS are a considerable advantage[15]. In our cases, tumors accompanying cystic component showed less responsive to irradiation than those of solid ones.

So far, published experience with SRS suggested that maximum dose as high as 50 Gy to 7 mm, 50 Gy to below 5. 5 cc, 45 GyE He ions to 0. 3 cc and even 160 Gy to 3×5 mm could be administered safely[2]. In our series, there showed still no SRS related critical complications were observed, yet.

Fractionated irradiation techniques have generally been found to be better tolerated by normal tissue and allow for high a cumulative target doses as a result of repair between fractions of sublethal damage to normal tissue[17~19]. This has resulted in increased therapeutic ratios over fractionation schemes using single fraction or a small number of fractions. The use of single doses may be radiobiologically disadvantageous in malignant conditions because of the presence of hypoxic and/or non-cycling tumor cells. In future, we are planning to do SRS with fractionated schemes as well as conformal therapy.

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= 국문초록 =

선형가속기를 이용한 뇌종양 46예의 뇌정위다방향방사선치료 성적

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가톨릭 의과대학 강남성모병원 치료방사선과에서는 1988년 7월부터 1992년 12월 사이에 뇌종양 환자 45명의 뇌내 46개 병소에 대한 뇌정위다방향방사선치료를 실시하였으며, 이들에 대한 영상학적 및 임상적 추적조사 결과를 후향적으로 분석하였다.

뇌종양에 대한 뇌정위다방향방사선치료는 병소가 생명중추에 인접되어 있거나 다른 전신질환과 함께 있어 종양의 수술적 제거가 어려운 경우, 수술후 잔류 병소가 남아 있거나 재발된 경우, 또는 종래 부터 해오던 방사선치료에도 불구하고 잔류병소가 남아있거나 환자가 수술을 거부할 경우 등에서 실시하게 된다. 이는 수술이나 유사한 다른 치료와 비교하여 동일한 치료효과를 얻으면서도 간편하고 비침습적이며 또한 상대적으로 저렴한 치료 경비가 소요됨으로, 최근 방사선치료장비 및 치료계획 프로그램의 개발과 함께 그 치료성적이 관심의 대상이 되고 있다.

환자 분포는 남녀 비가 22 : 33 이며, 연령 분포는 5-74세(중앙값 ; 43세)이었고, 추적조사 기간은 2-55개월(중앙값 ; 35개월)이었다. 6 MV 선형가속기를 사용하여 조사야 용적은 0.13-42.88 cm^3(중앙값 ; 7.26 cm^3)이었으며, 최대치료선량은 5-35.5 Gy(중앙값 ; 20.9 Gy)이었다. 종양 별로는 뇌하수체종양 15예, 청각신경종 8예, 수막종 7예, 뇌교종 6예, 두개인두종 4예, 송과선종 3예, 혈관아세포종 2예, 및 뇌전이암 1예 씩이었다.

총 46예 중 18예(39.1%)에서 추적 영상검사상 종양의 소실 및 위축을 관찰하였으며, 16예(34.8%)에서는 종양크기의 정지상태를 나타냈다. 임상적으로는 34예(73.9%)에서 방사선치료 전보다 양호한 전신상태 및 수행능력을 유지하고 있었으며, 이중 4예(8.7%)에서는 추적검사상 종양 크기가 약간 커졌음에도 불구하고 임상적으로는 안정된 상태이었다. 영상학적으로나 임상적으로 악화된 경우는 2예(4.4%)에서 있었다. 치료에 따르는 부작용으로는 치료 직후, 일시적 두통을 호소하였으나 스테로이드 및 진통제 투여로 개선되었으며 경미한 일시적 탈모를 3예(6.6%)에서 경험하였으며 향후 좀더 정밀 추적검사가 필요할 것으로 생각된다.