Stereotactic Radiosurgery for Intracranial Tumors; Early Experience with Linear Accelerator

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Between August 1988 and December 1991, 24 patients with intracranial tumors were treated with stereotactic radiosurgery (RS) using a 10 MV linear accelerator at Severance Hospital, Yonsei University College of Medicine. There were 5 meningiomas, 3 craniopharyngiomas, 9 glial tumors, 2 solitary metastases, 2 acoustic neurinomas, 2 pineal tumors, and 1 non-Hodgkin's lymphoma. Ten patients were treated as primary treatment after diagnosis with stereotactic biopsy or neuroimaging study. Nine patients underwent RS for post-op. residual tumors and three patients as a salvage treatment for recurrence after external irradiation. Two patients received RS as a boost followed by fractionated conventional radiotherapy. Among sixteen patients who were followed more than 6 months with neuroimage, seven patients (2 meningiomas, 4 benign glial tumors, one non-Hodgkin's lymphoma) showed complete response on neuroimage after RS and nine patients showed decreased tumor size.

There was no acute treatment related side reaction. Late complications include three patients with symptomatic peritumoral brain edema and one craniopharyngioma with optic chiasmal injury. Through this early experience, we conclude that stereotactically directed single high doses of irradiation to the small intracranial tumors is effective for tumor control. However, in order to define the role of radiosurgery in the management of intracranial tumors, we should get the long-term results available to demonstrate the benefits versus potential complications of this therapeutic modality.

Key Words: Stereotactic radiosurgery, Intracranial tumors

INTRODUCTION

After introduction of radiosurgery (RS) for the management of intracranial lesions by Swedish Neurosurgeon Lars Leksell in 1951[1], it has been used for a number of intracranial lesions not amenable to surgical resection and proved to be an effective therapy for some lesions, most notably arteriovenous malformations (AVM). Steiner reported an 85% 2-year complete obliteration rate documented by arteriography for treatment of AVM in over 600 patients using the Leksell gamma unit[2,3]. Because radiosurgery technique was developed to destroy intracranial targets using single high doses of ionizing radiation and has the characteristic sharp dose fall-off outside the target volume, it was useful for well demarcated lesion and application of radiosurgery for intracranial tumors was limited in well defined, small benign tumors. However, role of radiosurgery has extended its role as salvage treatment in recurrent benign or malignant tumors that have previously been irradiated and as a boost treatment in combination with conventional fractionated radiotherapy for malignant primary or metastatic tumors.

In August 1988, we began a stereotactic radiosurgery using modified linear accelerator in patients with AVM and selected brain tumors[4,5]. This report presents the preliminary results of stereotactic radiosurgery in 24 patients with intracranial tumors.

MATERIALS AND METHODS

From August 1988 to December 1991, 24 patients with a variety of intracranial tumors received stereotactic radiosurgery in our Severance Hospital, Yonsei University, Medical College. Patients were

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evaluated by a neuro-oncology team consisting of a neurosurgeon, radiation oncologist, neuroradiologist, and physicist. They were selected for stereotactic radiosurgery by a several criterias, mainly by size, shape, and location of the tumors. Only small, mostly less than 3 cm in diameter, well circumscribed lesions were treated. There was no selection limitation in terms of tumor histology. There were thirteen male and eleven female patients and age range was 13 to 66 years with median age of 39 years. All patients except three had a histopathologic diagnosis before treatment. Two patients were considered as having meningioma by neuroimaging and one patient had a tumor in the trigone of right lateral ventricle which had been considered as choroid plexus papilloma. In nine patients (3 meningiomas, 2 acoustic neuromas, 2 craniopharyngiomas, 2 astrocytomas), radiosurgery was tried for post-op. residual tumors. Ten patients (2 meningiomas, 2 astrocytomas, 1 oligodendroglioma, 2 metastatic tumor, 1 choroid plexus papilloma, 1 mixed glioma, 1 pineal teratoma) were treated as primary treatment after diagnosis with stereotactic biopsy or neuroimaging study. In two patients (1 grade III astrocytoma, 1 primary non-Hodgkins lymphoma), stereotactic radiosurgery as a boost dose was followed by conventional irradiation (Table 1).

Table 1. Role of Radiosurgery in the Treatment for 24 Intracranial Tumors

Primary treatment (RS alone: 10 cases)	meningioma	2
	low grade astrocytoma	2
	oligodendroglioma	1
	mixed glioma	1
	choroid plexus papilloma	1
	pineal teratoma	1
	metastases	2
RS for post-op residual tumor (9 cases)	meningioma	3
	acoustic neurinoma	2
	craniopharyngioma	2
	low grade astrocytoma	2
Combined with ERT as a boost dose (2 cases)	malignant astrocytoma	1
	Non-Hodgkin's lymphoma	1
Salvage treatment for recurrence after ERT (3 cases)	Ependymoma	1
	pineal tumor	1
	craniopharyngioma	1

RS: radiosurgery ERT: external irradiation

All patients were treated with modified linear accelerator radiosurgery technique using multiple non-coplanar converging arc irradiation from a 10 MV X-ray. Details of radiosurgery technique were described in our previous reports[4,5]. Secondary collimaters were used to reduce surrounding normal tissue dose with field diameters ranging from 14 to 35 mm. Maximum target dose was 15 to 25 Gy range with median dose of 20 Gy. Prescribed dose selection depended on tumor volume, tumor location, and radiosensitivity of critical structures in the vicinity of the tumor.

No patients received a prophylactic administration of steroids. Patients were discharged from the hospital in 2 days after treatment. Patients were followed to examine every 3 to 6 months. A CT scan and/or MRI was taken every 6 months. Two patients were lost to follow-up after radiosurgery. twenty two patients were followed for 1-41 months and median follow-up time was 22 months.

RESULTS

In sixteen patients, follow-up neuroimage after radiosurgery were obtained. Among them, seven patients showed complete disappearance of tumors (CR) on CT scan or MRI, 2-6 months after RS. The clinical characteristics and treatment results of 7 patients with CR were summarized in Table 2. Two patients with meningiomas (No. 1 & 2) received radiosurgery for residual tumor after surgical resection and showed CR on 6 months follow-up CT scan. They are alive on 30 and 31 months after RS without evidence of tumor recurrence or any complication. Three patients (No. 3, 4, 5) received radiosurgery as a sole treatment modality for their newly diagnosed tumors. Although they spent a symptom-free period for a while after CR, tumors recurred at margin of previous tumor sites at 21-23 months after RS (Fig. 1, 2). In a case with primary CNS non-Hodgkin's lymphoma, RS was performed prior to external irradiation as a boost for left thalamic tumor with a pathologic diagnosis of glioblastoma multiforme by stereotactic biopsy. After RS, permanent pathologic diagnosis was turned out as non-Hodgkin's lymphoma. At completion of radiotherapy (whole brain, 4500 cGy in 5 weeks and 540 cGy on tumor area), he was completely free of disease clinically and radiolographically. Fourteen months after RS, he experienced right side sensory change and weakness and CT scan revealed contrast enhancement on primary tumor site with extensive sur-

Table 2. Summary of Seven Patients with Complete Response after Radiosurgery

Patient No.	Age (yr)	Sex	Tumor Location	Histology	Tumor diameter (mm)	Combined therapy	RS dose (Gy)	Interval RS to CR	Compli-cation	Current status
1	40	M	Left deep temporal	meningioma	30	surgery 3 times	15	6 Mo.	none	31 Mo. No evidence of recurrence
2	53	F	torcular	meningioma	22	surgery	18	6 Mo.	none	30 Mo. No evidence of recurrence
3	13	M	Rt. basal ganglia	oligodendro-glioma	25	none	20	3 Mo.	none	22 Mo. marginal tumor recurrence 34 Mo. alive with disease
4	29	M	pineal	mixed glioma	22	none	20	2 Mo.	none	21 Mo. marginal recurrence with CSF seeding
5	29	M	trigone of Rt. lat ventricle	none (choroid plexus papilloma)	25	none	20	4 Mo.	none	23 Mo. marginal recurrence
6	53	M	Lt thalamus	Non-Hodgkin's lymphoma	25	Ext. RT	15	2 Mo.	perifocal edema (14mo)	29 Mo. alive without tumor recurrence
7	17	F	mid-brain	low grade astrocytoma	21	surgery Ext. RT	20	6 Mo.	perifocal edema (6 Mo.)	29 Mo. alive without tumor recurrence

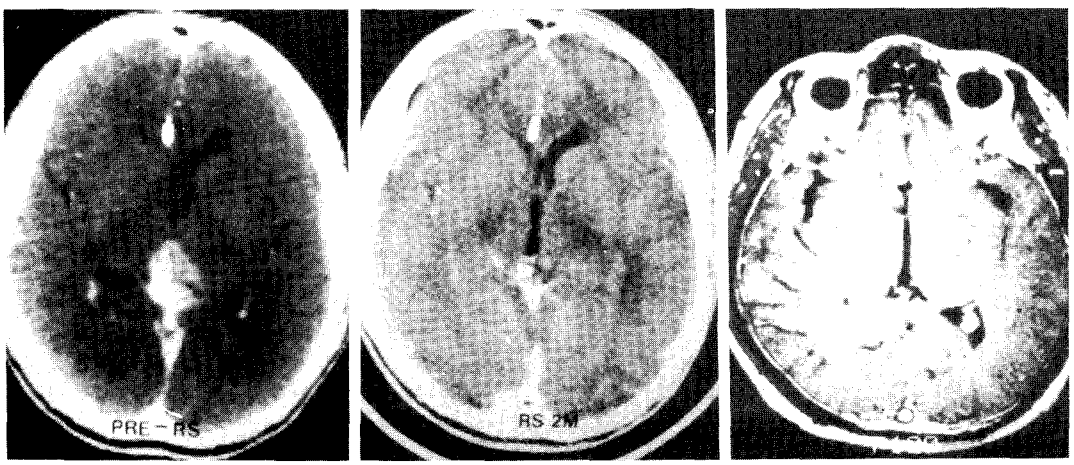

Fig. 1. Pre-radiosurgery contrast enhanced C-T scan showed pineal tumor. Pathology was confirmed as mixed glioma by stereotactic biopsy (left). C-T scan at 2 months after radiosurgery revealed complete disappearance of tumor (middle). Newly developed small nodule on pineal area was shown on MRI at 21 months after RS (right).

rounding brain edema. However, several months of steroid therapy, CT lesion and clinical symptoms and signs were disappeared.

Among five patients with meningiomas, as mentioned above, two revealed CR and one obtained partial response without evidence of regr-

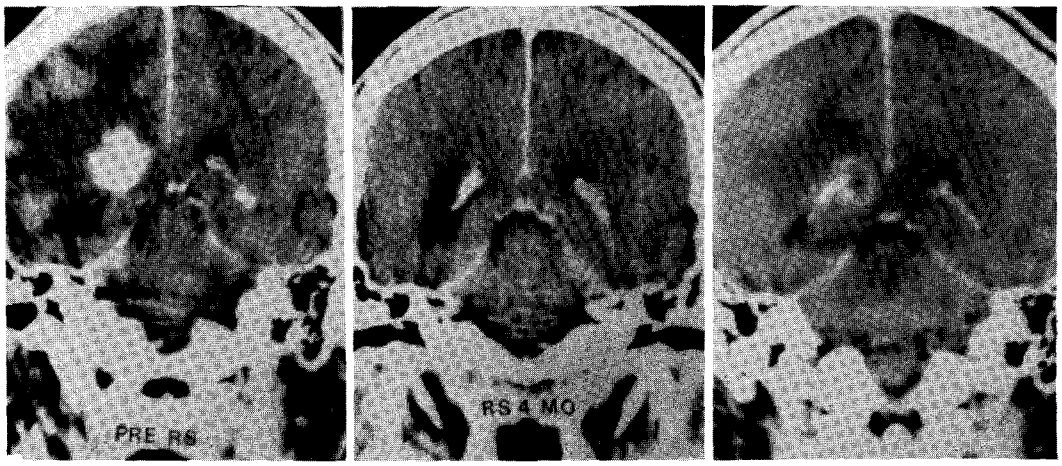

Fig. 2. Pre-radiosurgery CT scan revealed well demarcated mass on trigone of right lateral ventricle and surrounding brain edema. RS was done with an impression of choroid plexus papilloma by neuroimage alone (left). Complete disappearance of mass without brain edema on CT Scan at 4 months after RS (middle). CT Scan at 23 months after RS revealed contrast enhancing lesion on previous tumor site with brain edema. This finding should be differentiated between tumor recurrence and brain necrosis (right).

owing at 41 months after RS. Recent two patients didn't get a follow-up CT scan.

There were nine glial tumors and six patients among them didn't received external beam irradiation as a initial treatment. Among five patients who were followed more than 2 years, three patients obtained CR (Table 2) and two obtained PR. All except one revealed focal enhanced lesion around original tumor site at 21~23 months after RS which were considered as tumor recurrence, but could not be completely differentiated from brain necrosis in 2 cases.

There were 2 cases of solitary brain metastasis (renal cell carcinoma and adenocarcinoma of lung). Their primary tumors were resected 17 and 20 months before and both of them had no evidence of systemic disease at the time of RS. In a patient with renal cell carcinoma, 2 months follow-up brain CT scan revealed central tumor necrosis, but peripheral rim enhancement was enlarged. We added external beam irradiation with impression of progressive disease and he was in stable disease at the time of last follow-up, 8 months after RS. In the other patient with lung cancer, solitary cerebellar metastatic nodule was decreased in size but another cerebral metastatic nodule was newly developed 4 months after RS. She received 30 Gy of whole brain irradiation and stable now, eight months after RS.

There was no acute treatment related discomforts. One patient with peripherally located meningioma experienced focal area of alopecia. Among sixteen patients who were followed more than 6 months with neuroimage, three patients experienced neurologic symptom with peritumoral edema on CT scan, 6, 6, 14 months after RS. One patient with parasagittal meningioma had a largest tumor in our series (3.5 cm in diameter) and the other two patients received external irradiation in addition to RS. One patient with craniopharyngioma who received RS for post-op residual tumor developed decreased bilateral visual acuity which was considered as optic chiasmal injury by radiation. One patient with acoustic neurinoma developed ipsilateral facial weakness at 4 months after RS and persisted until last follow-up, 14 months after RS.

DISCUSSION

With development of linac (linear accelerator) radiosurgery technique, more radiation oncologists could participate radiosurgery program and radiosurgery has increasingly been applied to the treatment of malignant tumors as well as benign tumors. In many large radiosurgery centers, the most common treatment categories were AVM (44~55%) followed by acoustic neurinoma (19%),

meningioma, and pituitary tumors[6,7,8]. Although many investigators agreed that radiosurgery is effective for inoperable AVM, the indications of radiosurgery for many other lesions have not been clearly established. Nowadays, most groups had tried radiosurgery for intracranial tumors with several indications such as a sole treatment for small, benign tumors, adjuvant therapy with radiotherapy for malignant tumors, salvage therapy for previously irradiated recurrent tumors, and preoperative therapy for vascular tumors[9].

In benign tumors, acoustic neurinoma was most common indication of radiosurgery followed by meningioma and pituitary adenomas. Microsurgical removal remained the preferred treatment for patients with acoustic neurinomas. Although complete surgical removal is curative in vast majority of patients, there is a limitation in preservation of hearing and facial nerve function. RS has been an alternative treatment method in patients who are elderly or have significant medical problems that would increase the operative risks, in patient with bilateral tumors, and in patients with tumors in the only hearing ear[9,10,11]. Usual prescribed doses were 16~20 Gy on tumor margin. At Karolinska hospital in Sweden, radiosurgery has been the standard treatment for last 16 years[11]. They treated 325 acoustic tumors from 1969 until 1990 and reported the results of 227 cases. In 85% of patients showed decrease or no change of tumor size after RS. Unilateral tumors were more favorably responded than bilateral tumors (88% vs 75%). Hearing was preserved in 77% of patients. Loss of hearing seemed to be associated with average tumor diameter. Facial weakness can occur in 16~30% of patients usually 6~8 months after RS. Almost all facial weakness were recovered 6~12 months after onset. Trigeminal neuropathy occurred 10~20% of cases and tended to be more permanent. In Pittsburgh experience, all trigeminal neuropathy improved at 17 months[10].

In the management of meningioma, RS has been used for only selected cased such as; residual or recurrent meningiomas after surgical resection, tumors in high risk location, and medically inoperable cases[12,13]. With increasing experience and improving techniques, RS became not only an important adjuvant treatment modality after surgery but also an effective primary treatment modality[12]. In Pittsburgh experience, RS was the primary treatment modality in 32% of meningioma patients who received RS. They had a symptomatic tumors demonstrated by neuroimage and received RS without tissue diagnosis. Only two patients among 50 patients had delayed tumor growth and actuarial 2-year tumor contral rate (decrease or no change in tumor size) was 96%. Most investigators selected treatment dose according to the tumor size and location, between 15-25 Gy on periphery of the tumor, but optimum dose is still unclear.

In treating a sellar, suprasellar, and parasellar tumors such as pituitary adenoma, craniopharyngioma, or parasellar meningiomas, clear delineation of tumor volume and adjacent normal structures, especially optic nerve/chiasm and precise dose planning are crucial for RS. Tolerance of optic chiasm to large single dose is uncertain, but many investigators believed roughly 8~10 Gy[9,13].

Theoretically, radiosurgery, with its dose localization characteristics, is inappropriate for the treatment of low grade astrocytoma or malignant intracranial lesions in which tumor cells are known to infiltrate beyond the borders of abnormalities seen on neuroimage. Some investigators had tried radiosurgery for gliomas with a rationale of its radioresistance to conventional radiotherapy, especially type I lesions defined by Daumas-Dupont which are consisted of circumscribed tumor tissue with no isolated tumor cell invasion into surrounding parenchyma[14]. Pozza et al from Vincenza, Italy reported their radiosurgery experience with low-grade astrocytomas[15]. A total dose of 16-50 Gy was administered in either one fraction or two fractions 8 days apart. Twelve of fourteen patients revealed a partial or complete radiographic response to treatment. Their follow-up period was 11 to 48 months. In our series, all but one patients with low grade gliomas followed more than 2 years recurred on margin of the original tumors, even they were well circumscribed tumors and needed external irradiation. We thought that RS alone is insufficient to these marginally infiltrative tumors and should be combined with external irradiation. Therefore the ultimate role of radiosurgery in these tumors would probably be as an adjuvant (boost) to conventional radiotherapy in the initial management and as a palliative tool for small, previously irradiated lesions[16]. In these situation, RS boost dose usually depend on tumor size, for instance, inversely proportional to the size of the collimator to reduce normal brain damage.

Metastatic brain tumors were the most common indications of RS among the malignant tumors. As opposed to malignant brain tumors, metastases are often well circumscribed and more or less spherical which makes them amenable to treat with

radiosurgical techniques. At first, RS was used as an alternative method of surgical resection for inoperable and radioresistant solitary brain metastasis[17], because recent literatures indicated that surgical resection in addition to whole brain irradiation improved survival and quality of life[18]. Also, RS has used in the management of recurrent or persistant tumors after external irradiation with or without surgery[19]. Sturm et al at Tumor Centre Heidelberg-Manheim reported a series of 12 lesions that were considered as radioresistant tumors (renal cell carcinoma, fibrosarcoma, papillary thyroid carcinoma) and inoperable[17]. Patients received 20~30 Gy in a single fraction. All seven patients followed for more than 3 months achieved arrest of tumor growth. In JCRT (Joint Center for Radiation Therapy in Boston) experience with RS for the treatment of brain metastases that have recurred following prior radiotherapy, all 21 lesions were controlled by radiosurgery as defined by a decreased size of the lesion on CT or stabilization of enhancing volume. Complications were limited and transient in nature and no cases of symptomatic radiation necrosis occurred in any patient despite previous exposure to radiotherapy. They suggested that RS is an appealing technique for the initial management of deep seated lesions as a boost to whole brain radiotherapy[19]. Coffey et al at Pittsburgh also reported 24 patients with solitary brain metastases treated with Gamma unit[20]. They proposed that in cases of solitary brain metastses less than 3 cm in diameter, stereotactic radiosurgery plus fractionated whole brain irradiation is preferable method. Recently, many investigators tried RS for multiple metastatic tumors[21]. We experienced a patient (not included in this series) with two metastatic brain tumor nodules from lung cancer treated with 30 Gy whole brain radiotherapy and radiosurgical boost without any acute or subacute side reaction.

Despite more than five thousand patients worldwide were treated with stereotactic radiosurgery, little is known about the precise relationship of volume and radiation dose on complication for the relatively small brain volumes treated in RS with or without conventional radiotherapy. Recent literatures reported that more complications were noted in RS for intracranial tumors than AVM and of note was that less patients with metastatic lesions experienced complications[18,22]. In recent report about complications from RS of intracranial tumors, tumor dose inhomogeneity which was related to problems with multiple isocenter placement and maximum tumor dose were most significantly associated with toxicity. Sixty-seven percent of patients with primary tumors receiving maximum tumor doses >25 Gy experienced complication[22].

The use of stereotactic radiosurgery on intracranial neoplasms appears encouraging. However, there is a continued need for better dose-volume relationship and optimum combination method with external beam irradiation according to various histologies. In order to define the indications of radiosurgery in the management of intracranial tumors, we should get the long-term results available to demonstrate the benefits versus potential complicaitons of this therapeutic modality.

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= 국문초록 =

두개강내 종양에 대한 방사선 뇌수술의 역할

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연세대학교 의과대학 세브란스병원에서는 1988년 8월 10MV 선형 가속기를 이용한 방사선 뇌수술(radiosurgery, stereotactic external beam irradiation)을 시작한 이래 1991년 12월까지 총 24예의 두개강내 종양에 대하여 방사선 뇌수술을 시행하였다. 대상 환자들의 조직학적 유형은 뇌수막종이 5예, 두개인두종이 3예, 악성임파종이 1예, 전이성 뇌종양이 2예 있었다. 대상환자들은 몇가지 다른 질병상태에서 방사선 뇌수술을 받았는데, 10예는 뇌정위적 생검이나 신경방사선학적 영상만으로 진단을 한 후 일차적인 치료로 방사선 뇌수술을 시행했으며, 9예에서는 수술 후 잔류 종양에 대하여 방사선 뇌수술을 시행하였다. 또 3예에서는 방사선 치료후 재발한 종양에 대해 구제요법으로 시행하였고, 2예에서는 외부 방사선 조사와 함께 추가 방사선조사로써 시행되었다. 6개월 이상 추적 조사된 환자 16명 중에서 7명(뇌수막종 2예, 신경교종 4예, 악성임파종 1예)이 CT Scan 또는 MRI상 종양의 완전 소멸을 보였고 나머지 9예는 모두 종양 크기의 감소를 보였다. 방사선 수술시 급성 부작용은 없었고 4예에서 만성 합병증이 나타났는데 3예에서 신경학적 증상의 발현과 함께 CT Scan상 뇌부종이 나타났었고 1예의 두개인두종에서는 방사선에 의한 시신경 손상으로 생각되는 시력 소실이 있었다.

저자들의 경험 예들은 조직학적 유형이 다양하고 증례수가 많지 않고 추적 조사 기간이 짧기 때문에 결론을 얻기 어렵지만 정위적 방법으로 종양에 다량의 방사선을 일시에 조사함으로써 완전 관해까지의 우수한 종양 제어효과를 얻을 수 있었다. 그러나 여러가지 종류의 뇌종양의 치료에 있어서 방사선 뇌수술이 생존율 향상이나 삶의 질의 향상에 기여할 수 있는지를 알기 위해서는 더 많은 증례를 통하여 경험을 축적하여야 할 것이다.