The Effect of External Radiation Therapy for Intracranial Arteriovenous Malformation

— Conventional Radiation Therapy vs Stereotactic Radiosurgery —

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From February 1987 through July 1990, the seventeen cases of inoperable intracranial arteriovenous malformation (AVM) were treated using 6 MV linear accelerator at the Division of Therapeutic Radiology, Kang Nam St. Mary's Hospital.

Of seventeen cases, fourteen were male and three were female. Ages ranged from 10 to 51 years (median age of 26 years). The main symtoms were headache, epilepsy and hemiparesis in decreasing order of frequency.

The middle cerebral artery is the most common origin of the feeding vessel (41.2%).

Four were treated by conventionally fractionated radiation therapy (CRT), thirteen were treated by stereotactic radiosurgery (RS). Duration of follow-up in CRT and RS group were 4 to 43 months (median 33 months) and 3 to 12 months (median 13 months), respectively.

When the response was assessed by radiologic follow-up study, two of four CRT group showed minimal response.

Of thirteen cases of RS group, two (15.4%) showed complete response, five (38%) partial response, two (15.4%) minimal response and four (30.7%) no response by the same assessment. There was no statistical significance in terms of follow-up period ($p=0.22$), size of lesion ($p=0.82$) and treated dose ($p=0.65$).

Further accumulation of experience is recommended with proper case selection and sufficient follow-up period.

Key Words: Arteriovenous malformation, Linear accelerator, Stereotactic radiosurgery, Conventional radiation therapy

INTRODUCTION

Generally, there is no question that neurosurgical approach is the choice of treatment for arteriovenous malformation (AVM) wherever it is. For the managment of the inoperable AVM, the radiotherapy has been used as a last assessment, despite some occasional successes until 1970 it had been considered ineffective and had been abandoned[1~3].

During the last three decades, a wealth of radiobiologic evidence concerning the sensitivity of vessels to irradiation accumulated. Furthermore, there were attempt to supplant instrument used in neurosurgery with stereotactically directed narrow beams of ionizing radiation[4~6].

The radiation therapy was accepted as one of the tool for the management of intracranial AVM using both conventionally fractionated radiation therapy and stereotactic radiosurgery, recently.

The most important factor in radiosurgery is the physically determined concentration of radiation on the target in contrast to fractionated radiotherapy, which is based on difference in radiosensitivity between tumor cells and cells of adjacent healthy tissue[1].

The aim of this paper is to investigate the clinical and radiologic response of AVM which was treated by stereotactic radiosurgery comparing it with conventionally fractionated radiation therapy and to find any prognostic factors to affect the treatment response.

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MATERIALS AND METHODS

From February 1987 through 1990 (41 months), the 17 patients of inoperable AVM were treated using 6 MV linear accelerator (NELAC-6) at the Division of Radiation therapy, Kang Nam St. Mary's Hospital. Of seventeen patients, 14 were male and 3 were female. A median age of 17 patients was 26 years which ranged from 10 to 51 years.

Of 17 patients, 4 were treated with conventionally fractionated radiation therapy (CRT) and remaining 13 were treated with stereotactic radiosurgery (RS). In the CRT group, the total dose varied from 3020 to 4400 cGy and treated with 170 to 200 cGy of daily dose for 3 to 4.5 weeks (Table 1).

In the RS group, treated dose ranged from 12 Gy to 30 Gy (median 25 Gy) and field size varied from 0.8 to 2.0 cm. The number of arcs used was 6 to 7, the length of each arc varied from 30 to 180 degree in the preset plane and total length of arc ranged from 600 to 930 degrees (Table 2).

The technique of stereotactic radiosurgery was described in the previous report[7]. In the CRT group we used parallel two opposing or three fields technique (SAD 80 cm).

Table 1. The Treatment of Conventional Radiotherapy Group

Case	Dose (cGy)		Duration (wks)
	Total	Daily	
1	3020	200	3
2	3150	170–180	4
3*	4500	180	4.5
4	4400	200	4

* initially 3240 cGy/18 fx/3wks
boost up to 4500 cGy/7 fx/1.5wks
after 20 months follow-up

Table 2. Treatment of Radiosurgery Group

Case	Dose (cGy)	Field size (cm)	No. of arc
1	3000	2x2	7
2	1200	0.8x0.8	7
3	3000	1.5x1	7
4	2900	2x2	7
5	1900	2x2	7
6	2500	2x2	7
7	2000	0.5x0.5	6
8	1800	1x1	7
9	3000	1x1	6
10	3000	1x1	6
11	3000	1x1	6
12	2200	1x1	7
13	2000	1x1	6

RESULTS

The clinical and radiologic response of 17 patients of AVM were analysed as followings. Duration of median follow up in CRT and RS group were 33 months (ranged from 4 to 43 months) and 13 months (ranged from 3 to 21 months), respectively.

Table 3. Clinical Manifestation

Main symptoms	No. of cases (%)
headache	12 (70.1)
epilepsy	5 (29.4)
hemiparesis	4 (23.5)
episode of bleeding	5 (29.4)

Table 4. Origin of Feeding Artery

	No. of cases (%)
MCA	7 (41.2)
ACA	3 (17.6)
PCA	2 (11.8)
ACA & MCA	2 (11.8)
MCA & PCA	2 (11.8)
ACA, MCA & PCA	1 (5.8)
Total	17 (100.0)

Table 5. Size of AVM

Diameter	Conventional RT	Radiosurgery
< 2 cm	0	4
2 – 4 cm	1	9
> 4 cm	3	0
Total	4	13

The main symptoms were headache, epilepsy and hemiparesis in decreasing order of frequency. The five complicated AVMs were observed (Table 3).

In view of feeding arteries, middle cerebral artery is the most common origin and one case has shown multiple feeding arteries (Table 4).

Considering the size of AVM treated, 9 out of 13 RS group showed moderate size (2~4 cm in diameter) and remaining 4 cases were small ones (below 2 cm in diameter). Whereas in CRT group, 3 out of 4 showed large size (over 4 cm of lesions) (Table 5).

To evaluate the clinical response, symptomatic and neurologic improvment were considered. In the CRT group 3 of 4 cases revealed symptomatic and neurologic improvement and remaining one noted stationary or unchanged condition. But all of the RS group showed definite symptomatic and neurologic improvement (Table 6).

Table 6. Therapeutic Response

Response	Conventional RT	Radiosurgery
Clinical		
improved	3 (75%)	13 (100%)
not improved	1 (15%)	0 (0%)
Radiologic		
CR	–	2 (15.4%)
PR	–	5 (38.5%)
MR	2 (50%)	2 (15.4%)
NR	–	4 (30.7%)

CR (complete response) : 100% disappearance of lesion
PR (partial response) : over 50% disappearance of lesion
MR (minimal response) : less 50% disappearance of lesion
NR (no response) : no interval change

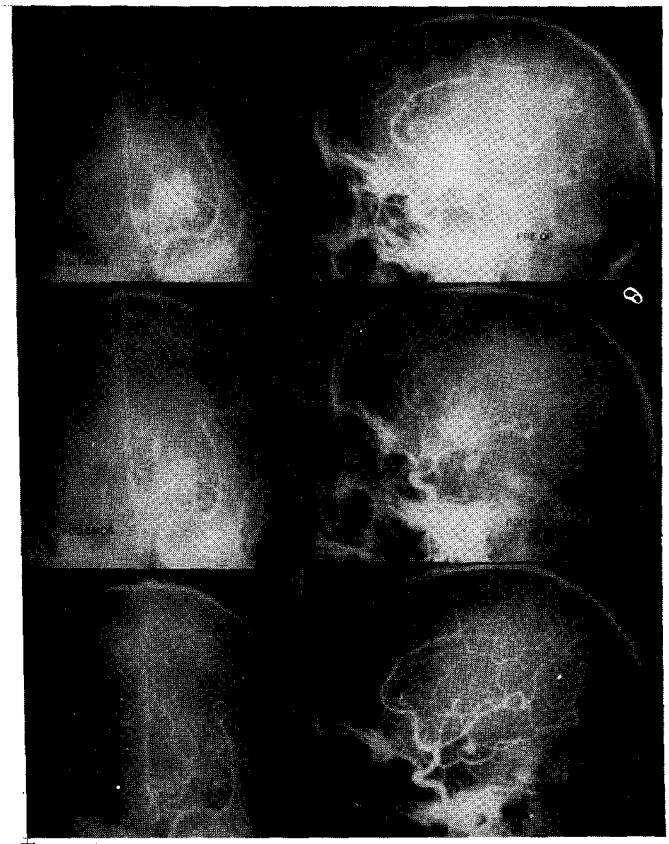

Fig. 1. deep temporal AVM, 40 years old male: CR after RS (19 Gy, field size 2×2 cm) on 6 & 18 months follow-up angiogram.

To evaluate the radiologic response, follow up CT scan and angiograms were obtained. Complete response (CR), partial response (PR) and minimal response (MR) were defined as 100% disappearance, over 50% disappearance and less than 50% disappearance of lesion, respectively. No response (NR) meant no interval change in size.

In the 4 cases of CRT group, only 2 cases were able to have follow-up studies. One case was examined with follow-up CT scan and the other case was performed with follow-up CT scan and the other case was performed with angiographic follow-up. All 13 cases of RS group were able to have follow-up angiographic studies. Nine cases had definite radiologic response, which were CR in 2 cases (15.4%), PR in 5 cases (38.5%), and MR in 2 cases (15.4%). Therefore the radiologic response rate of RS group was 69.3%. NR was noted in 4 cases (30.7%). However the follow-up periods of 2 cases were not long enough to expect the radiologic response.

The Fisher's exact test was used to determine statistical significance of difference in radiologic response of RS group within the following variable; duration of follow up ($p=0.22$), size of lesion ($p=0.82$) and radiation dose ($p=0.65$). No statistical significance is identified in this analysis. It was impossible to compare the result of RS group with CRT group statistically because of too small number in the latter.

DISCUSSION

In the publication of radiotherapy for AVM, the detail of treatment were often lacking. The field of irradiation was approximate and accuracy in dosimetry usually was absent. Evaluation of results, usually based on clinical criteria and follow-up with angiography was unsystematic.

Since the pioneering work of Leksell in 1951, radiosurgery has become attractive form of therapy for AVM[4,8].

Initially, radiosurgery was performed with heavy charged particle beam from cyclotron and later by the gamma unit[8,9]. The well proven efficacy of radiosurgery has led to the development of 1inear accelerator-based RS technique[5,6].

Radiosurgery differ from conventional fractionated RT in principle and technique. Generally speaking, CRT is based on the biologic difference in radiosensitivity between the cell of pathologic and surrunding normal tissue[1,7].

In radiosurgery, accurate stereotactic localization combined with steep dose gradient makes the biologic differentiation less critical and the physically determined concentration of the radiation on the target becomes one of the important factors of treatment. Thus a high single dose with a sharp gradient can be focused on well delineated volume of tissue with little effect on the surrounding normal tissue. The degree of histopathologic damage will depend on the treatment dose, volume and time factor.

The optimal irradiation dose needed to provide the maximal therapeutic effect continue to be the subject of discussion. Steiner, in his series of 300 cases treated with gamma unit, has suggested that a minimum dose of 20~25 Gy delivered to AVM gave a good chance for a full obliteration[2].

Colombo et al have treated with 97 cases with AVM using multiple are irradiation technique. Doses varied from 18.7 to 40 Gy prescribed at the isodose contour which would coincide with the periphery of the target (60~90%)[5].

They suggested that for AVM up to 1.5 cm in diameter, dose of 22~30 Gy should be delivered at the edge of lesion[3]. Luis et al experienced that 25 Gy given the periphery of AVM is sufficient to obliterate the malformation completely[4]. It is not apparent that there is the limit of dose (median 25 Gy, range from 12 to 30 Gy) which affect response rate in our series.

Between the group using more than 25 Gy and that using below 25 Gy, statistically significant difference is not noted. The definition of target volume appears to be of special importance as well. Luis et al reported better response rate to prescribe the 25 Gy at the edge of the nidus with 90% than 50% isodose contour. It appears that a potential coverage of AVM will result in less optimal obliteration.

The target volume should include the entire cluster of pathologic vessels corresponding the nidus according to the investigation from the Lawrence Berkely Laboratory[4,8].

Our policy is to cover the nidus with dose prescribed at the 80~90% isodose contour[10].

It is now agreed that vessels are moderately sensitive to radiation. Endothelial tissue of small vessels appears to be more responsive to radiation than that of large vessels.

An excessive proliferation of endothelial cells following irradiation with narrowing or total occlusion of small vessel may occur. Although the precise mechanism of damage to the large vessel is unclear there is physiologic and pathologic

evidence suggesting that progressive sclerosis with subsequent occlusion of vasa vasorum after irradiation interfere with nutrition of vessel wall and lead to failures reminiscent of an endarteritis obliterance[2,3,5].

The main drawback of radiotherapy in AVM is the long latent period before the effect can be assessed. Hemodynamic change can be seen already 3 months after treatment. The latency between time of treatment and complete angiographic disappearance of malformation varies from 6 to 22 months.

The long latency corresponds presumably to the slow development of histologic changes of the irradiated vessel wall. The changes are scarce and spotty in early postirradiation phase while the obliterative endothelial damage being a late event.

From the analysis of our experience, the group with longer duration of follow-up had a tendency of better response rate. But statistical significance is not identified.

The overall response rate of RS group was better than that of CRT group despite of shorter duration of follow-up. Only 50% of MR was noted CRT group. Whereas, more than one half of patients in RS group show CR or PR within 3~21 months (median 13 months). It appears that this poor outcome in CRT Group is partially attributable to insufficient radiation dose.

With consideration for the characteristic long latency, the more patients are expected to be responder as time passes by. Our priliminary results for AVM treated by RS are encouraging, while the results of CRT group are disappointing.

Several questions remain unanswered in radiosurgery and the further experience with longer follow-up is required. A number of parameters need to be properly established to facilitate meaningful comparision among different center and techniques. These include imaging evaluation of AVM, dose prescription, definition of target volume, criteria to assess response to treatment, size and location of lesion.

Although there are still unsolved problems and failures RS seems to have already acquired an established place in the treatment of AVM. This closed treatment method of AVM will be of benefit to the group of patients judged to be unsuitable for conventional open surgery.

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= 국문초록 =

뇌동정맥성 기형의 외부방사선 치료 효과

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가톨릭의대 방사선치료실에서는 1987년 2월부터 1990년 7월까지 41개월 동안에 뇌동정맥성 기형으로 확진된 17예에 대해서 6 MV 선형가속기를 사용하여 SAD법으로 외부방사선 치료를 시행하였다.

치료방법은 총 14예중 4예(24%)에 대해서는 보통분할방식으로, 13예(76%)는 정위다방향 고선량 단일 조사로 치료하였다. 이들의 임상적 및 방사선학적 추적검사를 분석하여 다음과 같은 결과를 얻었다.

1. 연령분포는 10~51세(중앙값 26세)였고, 남녀비는 14 : 3으로 나타났다.

2. 주증상은 두통이 12예(70.1%), 경련 5예(29.4%), 편부전마비 4예(23.5%) 등의 순이었고, 파열에 따른 출혈을 동반한 경우가 5예(29.4%)있었다.

3. 각 뇌동정맥성 기형은 중뇌동맥 분지에서 기원한 경우가 7예(41.2%), 전뇌동맥 3예(17.6%), 후뇌동맥 2예(11.8%), 전뇌 및 후동맥 1예(5.9%)순으로 나타났다.

4. 보통 분할방식 치료군의 조사량은 3,020~4,500 cGy/3~4주, 정위다방향 단일고선량 치료는 1,200~3,000 cGy를 조사하였다.

5. 추적조사기간은 보통분할방식 치료군이 4~43개월(중앙값 33개월), 정위다방향 단일고선량 치료군이 3~21개월(중앙값 13개월)이었다.

6. 보통분할방식 치료군중 방사선학 추적검사를 실시한 2예에서는 경미한 반응을 보였고, 임상적 추적만을 실시한 2예 중 1예에서는 임상증상의 호전을 보였다.

7. 정위다방향 고선량 단일치료군은 13명 전예에서 방사선학적 추적검사상 완전반응 2예(15.4%), 부분반응 5예(38.5%), 경미반응 2예(15.4%), 무반응 4예(30.7%)로 각각 나타났으며, 임상증상의 호전을 보였다.