Fractionated Stereotactic Radiotherapy for Bilateral Vestibular Schwannomas Associated with Neurofibromatosis Type 2: Early Experiences in Ramathibodi Hospital

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Purpose : *To evaluate the rates of tumor control and useful hearing preservation in patients with bilateral vestibular schwannomas (VSs) associated with neurofibromatosis type 2 (NF-2) treated with fractionated stereotactic radiotherapy (FSRT).*
Material and Method : *From August 1998-December 2002 there were 5 patients with NF-2 who underwent FSRT (Linac-based system) for bilateral CP angle tumors. Median age was 28 (18-47) years. Median tumor volume was 5.4 (2.2-9.4) cc. Eight lesions received a marginal dose of 44.2-59.9 (median = 46.2) Gy in 25-33 fractions. The other 2 lesions received 4.4 and 4.9 Gy / fraction for 6 fractions in 3 and 2 weeks. Median follow-up was 19 (14-44) months.*
Results : *Radiographic and clinical tumor control rate was 90%. One lesion progressed at 7 months after FSRT and was completely resected. Of the 5 lesions with Gardner-Robertson class I-II hearing before FSRT, 2 (40%) retained useful hearing at the last follow-up. One patient had left facial spasm at 10 months after FSRT which gradually improved. No patient had facial palsy, facial numbness or pain.*
Conclusions : *FSRT provided good tumor control and hearing preservation rate in NF-2 patients with minimal morbidity. However, a longer follow-up is needed to evaluate long term results.*

Keywords : *Neurofibromatosis type 2, Stereotactic Radiotherapy, Vestibular Schwannoma*

J Med Assoc Thai 2004; 87(9): 1076-81

The aims of treatment in patients with vestibular schwannoma usually include both tumor control and preservation of neurological function. With modern treatment techniques, tumor resection, stereotactic radiosurgery (SRS), or fractionated stereotactic radiotherapy (FSRT), all achieved high tumor control rates. Surgical resection is preferred for patients with larger tumors compressing the brainstem. Controversies exist, however, about the proper treatment modality for smaller tumors especially those with useful hearing. In many SRS and FSRT series, patients with Neurofibromatosis Type 2 (NF2) formed a distinct subgroup with a lower rate of hearing preservation after irradiation[1-3]. Theoretical radiobiologic models suggested a direct relationship between late normal tissue damage and dose per treatment delivered to the tissues, but results from clinical series were unclear regarding what was the best fractionation schedule[4]. The purpose of this study was to evaluate rates of tumor control and useful hearing preservation in patients with vestibular schwannomas associated with NF-2 treated with FSRT in our institute.

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Material and Method

Patient characteristics

From August 1998-December 2002 there were 5 patients with NF-2 who underwent FSRT for bilateral

CP angle tumors at Ramathibodi Radiosurgery Unit. Median age of the patients was 28 (18-47) years. Decreased hearing was the presenting symptom in 4 patients (7 lesions). Four patients also had mild ataxia. Two patients had prior resection of spinal cord lesions (1 ependymoma, 1 neurilemmoma). One patient had partial resection of left vestibular schwannoma before FSRT. Median tumor volume was 5.4 (2.2-9.4) cc. Before FSRT there were 5 lesions in 4 patients with serviceable hearing (Gardner-Robertson grade 1-2). All patients had normal facial sensation and facial-nerve function (House-Brackmann grade 1).

FSRT technique

Treatments were performed using the linear accelerator base system (6 MV dedicated LINAC, Varian; with X-Knife planning system version 3 & 4, Radionics). The relocatable Gill-Thomas-Cosman frame was used for patient immobilization and target localization. Individual treatment planning was done based on a contrast-enhanced CT scan, 1.5-mm-slice thickness, with gadolinium-enhanced MRI. Written informed consent was obtained before FSRT in every case. Eight lesions received a marginal dose of 44.2-59.9 (median = 46.2) Gy in 25-33 fractions. The other 2 lesions received 4.4 and 4.9 Gy / fraction for 6 fractions in 3 and 2 weeks. There were 3 patients who also received FSRT for other growing tumors (1 for bilateral trigeminal schwannomas, 1 for right parietal meningioma, and 1 for meningioma in right lateral ventricle and the cervical cord tumor) in the same treatment course.

After FSRT all patients were clinically evaluated every 3-6 months. MRI and audiogram were performed at varying intervals depending on the patients' symptoms.

Table1 shows baseline characteristics and treatment results of each patient.

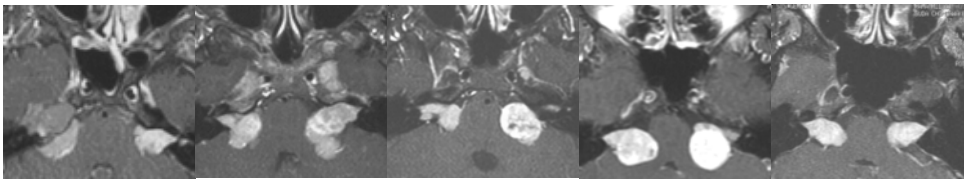
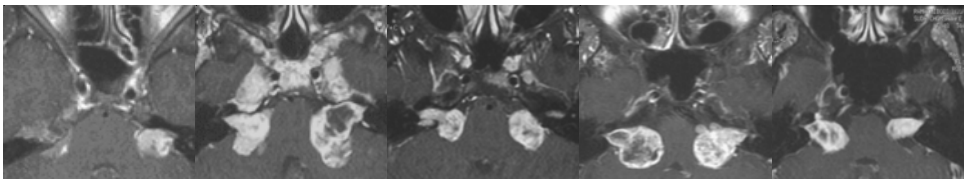
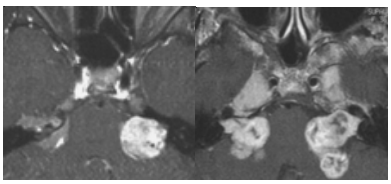
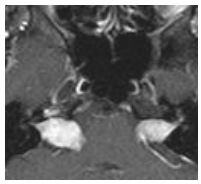
Results

Median follow-up time was 24 (14-44) months. Radiographic and clinical tumor control rate was 90%. Patient no. 1 had left-sided tumor removal 12 months before FSRT, pathologic diagnosis was schwannoma. He received FSRT for tumor progression. His right-sided tumor responded well to radiation, under retrospective review it was thought to be a meningioma. His left tumor continued to progress 7 months after radiotherapy, complete tumor resection was performed at 24 months after FSRT. Pathologic diagnosis was the same and he had left facial palsy and complete left-sided deafness after surgery. Of the 5 lesions with Gardner-Robertson class I-II hearing before FSRT, 2 (40%) retained useful hearing at the last follow-up. No patient had improved hearing class after FSRT. Patient no.4 had left facial spasm at 10 months after FSRT which gradually improved. No patient had facial palsy, facial numbness or pain from FSRT.

Discussion

Many challenges are encountered in treating NF2 patients. Uncontrolled bilateral VSs would lead to deafness and other functional disabilities or even death from brainstem compression. Other patients might have associated multiple intracranial and/or spinal tumors which further compromised the prospects of the quality of life and survival of the patients. However, over the years there has been much progress in the treatment of VS. Apart from modern surgical techniques which have yielded a high tumor control rate with decreasing morbidity[5-10], radiation now has an increasing role in this group of patients. Tumor control rate of more than 95% has been reported in multiple large SRS series[2,11-13]. Data has supported the use of SRS in NF2 patients as well. Subach et al (1999) reported results of 40 patients with NF2 treated with radiosurgery at the University of Pittsburgh, tumor control rate was 98% with a median follow-up of 36 months[14]. Nevertheless, cranial nerve complication rates in NF2 patients seemed to be higher when compared with other VS patients. In analyses of neurological complications in 138 VS patients, including 6 NF2 cases, treated with SRS at Tokyo University Hospital, Ito et al (2000) reported NF2 as the risk factor for both total hearing loss and pure tone threshold elevation[2]. Useful hearing preservation rate in the Pittsburgh's NF2 series was 43%, normal facial nerve function preservation rate was 81% and normal trigeminal nerve function preservation was 94%. Rate of useful hearing preservation was improved from 0 to 67% after the use of MRI for treatment planning and the changes of treatment technique in 1992. In another NF2 series, Kida et al (2000) reported 100% tumor control rate in 20 cases and preservation of serviceable hearing in 33.3% after SRS [15]. Roche et al (2000), in treating 27 NF2 patients with SRS, reported a tumor control rate of 74%, 57% of serviceable hearing preservation and 9% of facial nerve deficit [16]. In SRS series with non-NF2 VS patients, on the other hand, the rate of serviceable hearing preservation ranged from 33-71%, for facial nerve preservation from 64 to

Table 1. Baseline characteristics and treatment results of each patient

Patient no.	1		2		3		4		5	
Gender	M		F		M		M		F	
Age	18		34		20		28		47	
Side	rt	lt	rt	lt	rt	lt	rt	lt	rt	lt
Dose (Gy)										
Minimum	45.4	47	44.3	47.5	45	50.2	44.2	29.2*	59.9	26.6*
Average	54.6	52.6	54.1	54.9	59	62.2	58	35.5*	67.1	33.9*
Maximum	56.8	54.3	62	62	65	73	76	53	72	54
no. of fractions	27	27	28	28	25	25	26	6/2wk	33	6/3wk
Follow-up (mo)										
clinical	44		35		19		14		24	
audiogram	23**		8		14		7		13	
Lesion volume (cc)										
pre-FSRT	9	2.2	4.7	9.4	3.2	6.6	6.1	8.5	2.7	4.1
post FSRT (last FU-MRI)	6.4	6**	5.6#	10.7#	3.3#	6.2	8.2#	7.1	2.0	3.3
Imaging										
Pre-FSRT										
follow-up										
	8 mo		12 mo		16 mo		9 mo		12 mo	
										
	20 mo		24 mo					24 mo		
Hearing***										
pre-FSRT	N	S	S	N	S	S	S	N	N	N
post-FSRT	N	N	N	N	S	S	N	N	N	N

* Hypofractionation

** At the time of tumor progression, before salvage surgery

*** Gardner-Robertson classification of hearing; S = serviceable hearing, PTA ≤ 50 dB HL, SDS ≥ 50%: N = nonseviceable hearing, PTA > 50 dB HL, SDS < 50%

\# The tumors were considered stable because they had central lucency, which was supposed to reveal response to radiation. However longer follow-up is necessary

98%, and for trigeminal nerve preservation from 85 to 97.4%[2,3,13,17-24].

Factors identified as relating to increased cranial nerve complications after SRS included tumor diameter, marginal tumor dose, the use of CT in treatment planning, and higher number of isocenters [2, 12, 17, 20]. With a larger tumor, in order to avoid normal tissue injury the dose given to the tumor usually would be decreased which raised the concern of decreasing tumor control. In an attempt to lower the treatment complications without compromising the tumor control, many institutes have used fractionated irradiation with stereotactic technique[1,3,25-30]. There was evidence that fractionated conventional radiotherapy was effective in controlling VS[31,32], and theoretically with fractionation normal tissue injury was expected to be less. With a tumor control rate of 86.2-100% along with CN VIII, VII, V preservation rates of 53-100%, 97-100%, and 84-100%, respectively, FSRT seemed to be a good treatment alternative for patients with VS. However, there remains the question of the optimal dose and fractionation in this group of patients[4,33]. In comparison between SRS (single 12 Gy-fraction) and FSRT (2 Gy/fraction, 25 fractions/5 weeks), Andrews et al(2001) reported a high tumor control rate in both groups($\geq$ 97%) and functional hearing preservation 2.5-fold higher in the FSRT group[3]. But in 14 NF2 patients both tumor contol and the hearing preservation rate were lower than the sporadic cases (67% and 67%). They suggested that in order to achieve a higher tumor control rate in NF2 patients higher total dose might be needed but hearing preservation rate might fall. Also, it was observed that there was a greater probability of hearing preservation if FSRT was given early when the patient still had Gardner-Robertson hearing grade I. At our institute the decision was made to treat both sides of the VSs in patients with NF2 with the hope of preserving any hearing the patients might have, and dose 1.8 Gy/fraction, 5 fractions/week with multiple isocenters for isodose conformality was selected for the serviceable-hearing lesions. Hypofractionation using a dose of 4-5 Gy/fraction, 6 fractions in 2-3 weeks was selected for lesions with no serviceable hearing in contact with the brainstem. Though a tumor control rate of 90% with no permanent dysfunction of the facial nerve and no complication of the trigeminal nerve in the present series might be comparable with the others, there is still a need for improvement of useful hearing preservation. Since failure to control the tumor would eventually lead to hearing impairment, after failing to control the tumor in the first case (patients No.1) the average and maximum tumor dose was raised in the 3 last cases (patients no.3-5), and this might in part explain the hearing drop in patient no.4 though the tumor was still controlled. Another possible reason was the tumor volume, with the long phase of tumor necrosis and enlargement before shrinkage, treating large tumors might have less chance of hearing preservation than the smaller ones. Longer follow-up along with more patients and further modification of the radiation dose would provide further insight into the usefulness of FSRT in this group of patients.

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ผลการรักษาเบื้องต้นของเนื้องอก Vestibular Schwannoma 2 ข้างในผู้ป่วย Neurofibromatosis-2 ด้วยรังสีศัลยกรรมในรามาธิบดี

มัณฑนา ธนะไชย, วีระศักดิ์ ธีระพันธ์เจริญ, จิรพร เหล่าธรรมทัศน์, จันทร์ชัย เจรียงประเสริฐ, พวงทอง ไกรพิบูลย์, พรพรรณ ยงวิทิตสถิต

วัตถุประสงค์ : เพื่อศึกษาอัตราการควบคุมโรคและการคงการได้ยิน (useful hearing preservation) ของเนื้องอก Vestibular Schwannoma 2 ข้าง ในผู้ป่วย Neurofibromatosis-2 หลังการรักษาด้วยวิธีรังสีศัลยกรรม

วัสดุและวิธีการ : ตั้งแต่สิงหาคม 2541-ธันวาคม 2545 มีผู้ป่วย neurofibromatosis-2 5รายได้รับการฉายรังสีศัลยกรรมแบบแบ่งฉายรังสีหลายครั้ง (stereotactic radiotherapy) เพื่อรักษาเนื้องอก Vestibular Schwannoma ทั้ง 2 ข้าง อายุเฉลี่ย(median) 28 (18-47) ปี ขนาดเฉลี่ย (median) ของเนื้องอก 5.4 (2.2-9.4) cc เนื้องอก 8 ข้างได้รับปริมาณรังสีที่ขอบ (marginal dose) 44.2-59.9 (median = 46.2) Gy ใน 25-33 ครั้ง เนื้องอก 2 ข้างได้รับปริมาณรังสีที่ขอบ 4.4 และ 4.9 Gy ต่อครั้งเป็นจำนวน 6 ครั้งใน 3 และ 2 สัปดาห์ตามลำดับ ระยะเวลาในการติดตามผลการรักษา 19 (14-44) เดือน

ผลการศึกษา : อัตราการควบคุมโรคเท่ากับร้อยละ 90 จากการติดตามภาพถ่ายรังสีและอาการผู้ป่วย มีเนื้องอก 1 ข้างไม่สามารถควบคุมได้ด้วยรังสีและเริ่มขยายขนาดหลังฉายรังสี 7 เดือน ต่อมาได้รับการผ่าตัดออกได้หมด ในเนื้องอก 5 ข้างที่ยังมีการได้ยินก่อนการฉายรังสี (Gardner-Robertson class I-II) พบว่าร้อยละ 40 หรือ 2 ข้าง สามารถคงการได้ยิน(useful hearing)หลังการฉายรังสี ผู้ป่วย 1 รายมี hemifacial spasm ข้างซ้าย 10 เดือนหลังฉายรังสีและอาการดีขึ้นในภายหลัง ไม่มีรายใดที่เกิดอาการหน้าเบี้ยว หน้าชา หรือปวดบริเวณใบหน้า

สรุป : รังสีศัลยกรรมแบบแบ่งฉายรังสีหลายครั้งเป็นวิธีหนึ่งในการรักษาเนื้องอก Vestibular Schwannoma ในผู้ป่วย Neurofibromatosis-2 ที่ให้อัตราการควบคุมโรคสูงและผลข้างเคียงต่ำในระยะแรก ควรมีการติดตามผลต่อเพื่อประเมินผลการรักษาในระยะยาว