RESEARCH ARTICLE

Clinical Outcomes of Intracranial Nonvestibular Schwannomas Treated with Linac-Based Stereotactic Radiosurgery and Radiotherapy

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Abstract

Background: Intracranial nonvestibular schwannomas arising from various cranial nerves excluding CN VIII are uncommon. Recently, stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (SRT) have been widely reported as effective treatment modalities for nonvestibular schwannomas. The purpose of this study was to study the long term clinical outcome for nonvestibular schwannomas treated with both X-Knife and CyberKnife (CK) radiosurgery at one institution. Materials and Methods: From 2004 to 2013, fifty-two nonvestibular schwannoma patients were included in this study, 33 patients (63%) were treated with CK, and 19 (37%) were treated with X-Knife. The majority of the tumors were jugular foramen schwannomas (38%) and trigeminal schwannomas (27%). HSRT was given for 45 patients (86%), whereas CSRT was for 6 (12%) and SRS for 1 (2%). Results: The median pretreatment volume was 9.4 cm^3 (range, 0.57-52 cm^3). With the median follow up time of 36 months (range, 3-135), the 3 and 5 year progression free survival was 94 % and 88%, respectively. Tumor size was decreased in 13 (25%), stable in 29 (56%), and increased in 10 (19%). Among the latter, 3 (30%) required additional treatment because of neurologic deterioration. No patient was found to develop any new cranial nerve deficit after SRS/SRT. Conclusions: These data confirmed that SRS/SRT provide high tumor control rates with low complications. Large volume tumors and cystic expansion after radiation should be carefully followed up with neurological examination and MRI, because it may frequently cause neurological deterioration requiring further surgery.

Keywords: Nonvestibular schwannoma - radiosurgery - stereotactic radiodiotherapy - clinical outcomes

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Introduction

Intracranial schwannomas are slow growing benign tumors, arising from schwann cells of the nerve sheath. The incidence of nerve sheath tumor accounts for 12 % of primary brain tumor. More than 90 % of intracranial nerve sheath tumor are vestibular schwannomas. Nonvestibular schwannomas are therefore less common, accounting only for 5% of all cranial nerve schwannomas (Ostrom et al., 2015).

Surgical removal has been considered as the standard of care. Nevertheless, total tumor removal is not always feasible without neurological complications, because the tumor is usually located close to the critical structures such as cranial nerves, brainstem and vessels. In this circumstance, stereotactic radiation technique including single fraction radiosurgery and fractionated stereotactic radiotherapy (SRT) has emerged as an alternative treatment to surgical resection. Its use includes primary or adjuvant treatment of large-volume tumors closed to critical structures, patients who are not suitable for surgery, residual postoperative disease, and recurrent tumors. Although the usage of stereotactic radiation technique in benign brain tumors is currently accepted worldwide, most of the reports are from the western countries, and there are relatively few studies from Asian countries. In addition to the rarity of nonvestibular schwannoma, the reports on a large number of patients with long-term follow up is still limited. The objective of this study was to report a long term clinical outcome for intracranial nonvestibular schwannomas treated with both frame-based Linac radiosurgery (X-Knife) and more recent advanced stereotactic system, frameless Robotic whole body radiosurgery (CyberKnife, CK) at one institute.

Materials and Methods

Patients

This study was approved by our institution review board. Informed consent was obtained from all patients.

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Before treatment, the management for all patients were discussed in the radiosurgery board conference. Generally, a patient who had a large tumor with brainstem compression (Koos grade IV) (Koos et al., 1998) was usually selected to undergo a maximum safety resection and considered adjuvant SRS/SRT for the residual tumor. In small to medium size tumor, definitive SRS/SRT was usually offered. The inclusion criteria for SRS/SRT included the following: (1) a small to medium size (</=3 cm) nonvestibular schwannoma diagnosed based on accepted characteristics imaging on MRI or by pathology; (2) a postoperative residual or recurrent tumor; (3) surgical or medical inoperable; and/or (4) patient preference.

From 2004 to 2012, a total number of 52 consecutive nonvestibular schwannoma patients treated with Linac-based SRS/SRT at the radiosurgery center, Ramathibodi Hospital were included in this study. The median follow up time was 36 months (range, 3-135 months). There were 24 males (46%) and 28 females (54%), with the median age of 50.5 years (range, 22-80 years). The median pretreatment Karnofsky performance status (KPS) was 90 (range, 100–70). The details of all patient characteristics are shown in Table 1.

Radiation technique

Frame-based Linac radiosurgery (X-Knife): In 1997, the Radiosurgery Center at Ramathibodi Hospital established the first dedicated Linac-based stereotactic radiation machine in Thailand. The system included a 6-MV dedicated Linac with fixed circular cones (Varian). The planning software was the X-Knife forward-planning system, versions 3 & 4 (Radionics). For single fraction treatment, the Brown–Robert–Wells (BRW) stereotactic head frame was applied (with the assistance of a neurosurgeon), while the relocatable Gill–Thomas-Cosman frame was used for the fractionated SRT technique. A collimator size that covered ≥ 90% of the target volume was selected. Multiple isocenters were used in irregularly shaped targets. High conformity was established by using a non-coplanar arc with different beam weighting.

Frameless robotic radiosurgery (CyberKnife, CK): In 2009, the first robotic radiosurgery (CK) in Thailand became operational at our hospital. The CK model G4 (Accuray Inc., Sunnyvale, CA, USA) uses a 6-MV lightweight

linac mounted on a fully articulated robotic arm. Multiplan (Accuray) software was used for inverse planning. Patients were immobilized in the supine position with a thermoplastic facemask.

Target delineation and treatment planning

Individual treatment planning was done at a workstation using an image set from a contrast-enhanced CT scan, 1.25 mm-slice thickness, with or without gadolinium-enhanced MRI. Target and critical organ contouring was done by physicians, and a treatment plan was generated by medical physicist. Gross tumor volume (GTV) and critical structures were contoured in each consecutive slice of CT and MRI. No additional margin was added to the GTV to obtain the planning target volume (PTV). Various dose fractionation and dose prescription were determined by the tumor volume, location, nearby critical structure, individual physician preference and patient expectation. The prescribed radiation dose was delivered to the isodose surface that covers, ideally, >95% of the target volume. Finally, the treatment planning was evaluated by our radiosurgery team consisting of a neurosurgeon, a radiation oncologist and a medical physicist.

Nineteen patients (37%) were treated with X-Knife and 33 (63%) were treated with CK. Hypofractionated SRT was selected for 45 patients (86%), conventional SRT for 6 patients (12%) and SRS for 1 patient (2%) respectively. The details of treatment are summarized in Table 1.

Clinical follow- up

All patients were routinely followed at 3, 6, and 12 months during the first year. The interval of 6 to 12 months was continued thereafter. MRI was performed annually. Tumor progression and regression was defined as at least 15 % tumor volume change, and stable, if the tumor volume change was not more than 15 % (Snell et al., 2006). Tumor expansion was classified into three types as described in the previous study (Hasegawa et al., 2006): 1) Type A- tumor expansion with loss of central enhancement, 2) Type B-solid expansion and 3) Type C- cyst formation or enlargement of a preexisting cyst.

Statistical analysis

Progression-free survival (PFS) was the time from radiation to treatment failure or death whichever came first or the most recent follow up. Treatment failure was defined as tumor expansion with worsening neurological symptoms and requiring additional treatment.

Statistical analyses were performed using Statistical Package for Social Sciences for Windows version 18.0 (SPSS V.18.0; SPSS Inc., Chicago, IL., USA).

Results

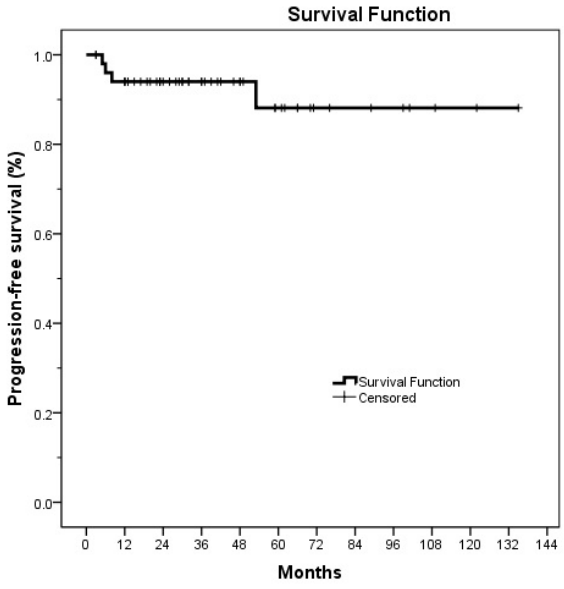

Figure 1. Kaplan-Meier curve demonstrating progression free survival in 52 patients

Progression free survival

With the median follow-up time of 36 months (range, 3-135), 4 patients were calculated as treatment failure that included 1 patient who died with unknown cause at 53 months after radiation and 3 patients who developed tumor expansion with neurological deterioration that required additional treatment at 5, 6 and 7 months post radiation .

Table 1. Summarizes baseline and treatment characteristics of 52 nonvestibular shcwannoma patients

Sex, no (%)	
Male	24 (46)
Female	28 (54)
Median age ,years (range)	50.5 (22-80)
Median follow-up time, months (range)	36 (3-135)
Previous surgery, no. (%)	14 (27)
PreRT neurodeficit, no. (%)	38 (73)
Location of tumor, no. (%)	
CN II	3 (6)
CN III	2 (4)
CN V	14 (27)
CN VI	1 (2)
CN VII	9 (17)
CN XII	2 (4)
Jugular foramen	20 (38)
Cavernous sinus	1 (2)
Imaging pattern, no. (%)	
Mixed cystic-solid	37 (71)
Pure solid	15 (29)
Brainstem compression, no (%)	9 (17)
Machine, no. (%)	
CyberKnife	33 (63)
X-Knife	19 (37)
RT technique, no. (%)	
HSRT	45 (86)
CSRT	6 (12)
SRS	1 (2)
Median prescribed isodose (range)	80 (62-90)
Median volume, cm3 (range)	9.4 (0.57-52)
Prescribed dose X no. of fraction, no (%)	
21-25 Gy X 5 (BEDGy3= 50.4-66.7)	26 (50)
30 Gy X 10 (BEDGy3= 60)	11 (21)
18 Gy X 3 (BEDGy3= 54)	7 (13)
45 Gy X 25 (BEDGy3= 72)	6 (12)
12 Gy X 1 (BEDGy3=60)	1 (2)
20 Gy X 4 (BEDGy3= 53.3)	1 (2)

*CK= CyberKnife; Gy =Grays; SRS= radiosurgery, single fraction; HSRT= hypofractionated stereotactic radiotherapy; CSRT= conventional stereotactic radiotherapy; BEDGy3= Biological effective dose

The 3- and 5- year PFS rates were 94 % and 88%, respectively (Figure 1). Factors associated with PFS were analyzed by univariate testing. However, there is no factor affecting PFS significantly.

Imaging response

Based on the serial MRI follow-up, thirteen patients (25%) had a decrease in tumor size, while 29 patients (56%) had tumor stable. Tumor expansion was observed in 10 (19%) patients. Type A pattern (tumor expansion with loss of central enhancement) was found in 4 (40%) patients, type B pattern (solid expansion) was found in 4 (40%) patients, and type C pattern (cystic formation) was found in 2 patients (20%). In the type A tumor group, all of them achieve tumor regression without any additional treatment. In the type B group, 1 of them showed gradual tumor enlargement with eventual neurologic deterioration that required craniotomy at 7 months post radiation. In the type C group, patients required craniotomy because of symptomatic brainstem compression at 5 and 6 months post radiation. Table 2 shows the characteristics of the patients who developed tumor expansion.

Clinical response

Thirty-eight patients (73%) had neurologic deficit before SRS/SRT and 14 (27%) were asymptomatic. During their F/U period, 20 patients (38%) reported some degree of improvement in their neurologic deficit, but 29 patients (56%) reported no change of any preexisting symptoms. Three patients (6%) who had tumor expansion developed neurologic deterioration because of massive brain stem compression. All of them received further surgery. After surgery, they had improvement of preexisting symptoms. However, some new cranial nerve deficits developed. All patients were still alive at the last follow up. There was no other late complication in this study.

Discussion

The standard management for intracranial nonvestibular schwannomas is surgical resection. With improvement of advanced surgical technique, total tumor removal is accomplished in 40% -80 % (Sharma et al., 2008; Zhang et al., 2009) with the tumor control rate of 81%-100% (Lee et al., 2001; Al-Mefty et al., 2002; Goel et al., 2003; Kadri et al., 2004; Bulsara et al., 2008). While a consistently high rate of local control with total tumor

Table 2. Characteristic of Patients who Developed Tumor Expansion After Radiation

No	Sex	Age (yr)	Pre RT vol (cm3)	Machine	Tech	Pattern of tumor expansion	Worsening of neurologic symptoms	Management after expansion
1	M	36	17.12	X-Knife	CSRT	Type C	Yes	Surgery due to BS compression
2	F	53	34.2	X-Knife	HSRT	Type C	Yes	Surgery due to BS compression
3	F	49	32.25	X-Knife	HSRT	Type B	Yes	Surgery due to progression
4	M	53	41.6	X-Knife	CSRT	Type A	No	Observe
5	F	45	11.05	CK	HSRT	Type A	No	Observe
6	F	39	12.9	CK	HSRT	Type A	No	Observe
7	M	57	34.2	CK	HSRT	Type A	No	Observe
8	F	58	10.63	CK	HSRT	Type B	No	Observe
9	F	51	9.4	CK	HSRT	Type B	No	Observe
10	F	61	9.73	CK	HSRT	Type B	No	Observe

CK= CyberKnife; HSRT= hypofractionated stereotactic radiotherapy; CSRT= conventional stereotactic radiotherapyv

Table 3. Summary of the Local Control Rates from the Previously Reported Studies of Non-Vestibular Schwannoma Treated with Stereotactic Radiotherapy

Author	No of pts	Median F/U (range)(months)	tech	Median Volume (cm3)	Tumor control (%)	Complication (%)
Elsharkawy et al, 2012	36	37 (2-108)	SRS	2.9 (0.07-8.8)	91 % (2-yr PFS)	None
Showalter et al, 2008	39	24	SRS/CSRT	NA	95%	4% worsened CN
Zabel et al, 2001	13	33(13-70)	CSRT	19.8(4.5-76)	100%	None
Mabanta et al, 1999	18	32(5-75)	SRS	5.5(0.7-15.4)	100%	17%
Choi et al, 2011	40	29 (6-84)	SRS/HSRT	3.2 (0.1-23.7)	97.60%	2 new or worsened CN deficit
Kimball et al, 2011	49	37 (6-210)	SRS	5.3 (0.3-24.5)	97 % (1 yr)	4 new cranial deficit (9%)
Our study	52	36 (3-135)	SRS/HSRT/ CSRT	9.4(0.57-52)	83% (5 yr)	none
Hamm KD et al, 2008	19	35 (11-63)	SRS/HSRT/ CSRT	14.1(4.2-43.1)	88% (5yr PFS)	None
Nishioka et al, 2009	17	59.5(7.4-122.6)	CSRT	8.2(0.3-31.3)	95%	None

SRS= radiosurgery, single fraction; HSRT= hypofractionated stereotactic radiotherapy; CSRT= conventional stereotactic radiotherapy; PFS= Progression free survival

removal has been reported in the previous literatures, the local control rates in subtotal tumor removal still vary widely. For the example, (Pollack et al., 1989) revealed regrowth of all residual tumor within 3 years after the initial surgery, while other study reported low rate of tumor recurrence and acceptable in clinical outcome (Bordi et al., 1989). Despite improvement of surgical technique, risk of surgical complication involving cranial nerve deficit is still high ranging from 0%-50% (Samii et al., 1995; Lee et al., 2001; Sarma et al., 2002; Sanna et al., 2006; Bulsara et al., 2008). Other rare complications such as meningitis, cerebrospinal fluid leak, hydrocephalus, hemiplegia and death are occasionally reported (Sarma et al., 2002; MacNally et al., 2008; Safavi et al., 2010).

Stereotactic irradiation is the advanced radiation technology that demonstrates excellent efficacy and safety in various brain tumors. The stereotactic concept delivers an impressively accurate, highly conformal and large radiation dose to a target while limiting beam exposure for nearby critical structures. For single-fraction treatment (SRS), the treatment targets should ideally be small (<30 mm) because of the dose–volume-dependent risk of delayed radiation injury. In contrast, fractionated SRT using a relocatable head frame or frameless technology allows larger radiation volume.

In Thailand, the first dedicated Linac-based stereotactic radiation machine including X-Knife and more recent advance stereotactic system, CyberKnife, were installed at the Radiosurgery Center of Ramathibodi Hospital. Until now, we have provided treatment for many patients with a wide variety of tumor types by using both frame-based radiosurgery and frameless radiosurgery. Our previous studies showed a high control rate with low complication of stereotactic radiation in various brain tumors (Puataweepong et al., 2014; Puataweepong et al., 2015). In this study, we reported the long term results in nonvestibular schwannoma treated with SRS/SRT in one institute.

Published studies of SRS and SRT in vestibular schwannoma showed 93-98% tumor control (Andrews et al., 2001; Chung et al., 2004; Collen et al., 2011; Fong et al., 2012; Puataweepong et al., 2014). Due to its rarity, the data on intracranial nonvestibular schwannomas treated with radiation are limited. Recent published reports on nonvestibular schwannoma treated with SRS and fractionated SRT revealed similarly high tumor control with low complication. The results from previous studies of SRS have been reported with the tumor local control rates ranging from 88-100% (Mabanta et al., 1999; Pollock et al., 2002; Kimball et al., 2011; Elsharkawy et al., 2012), and this was similar to the results of SRT, conventional fraction that reported 99-100% local control rate (Zabel et al., 2001; Showalter et al., 2008; Nishioka et al., 2009). From the radiobiology knowledge, fractionation provides the advantage of radiobiological effect that spares normal tissues by allowing for repair of damage between fractionation. Nevertheless, 4-6 weeks of total treatment, patient inconvenience and a daily expense have to be considered. More recently, hypofractionated SRT became an interesting option for various types of benign intracranial tumor, because this technique maintains radiobiological advantage of fractionation while providing the short total treatment time (3-5 fractions). The previous results of hypofractionated SRT in nonvestibular schwannoma including our study have reported the local control rate ranging from 88-97%, which were comparable of the local control rate of SRS and CSRT (Hamm et al., 2008; Choi et al., 2011). Table 3. summarizes the local control rates from the previously reported studies of non-vestibular schwannoma treated with stereotactic radiotherapy

Tumor expansion is a common finding after SRS/SRT in vestibular schwannoma, ranging from 17-74% (Pollock, 2006; Hasegawa et al., 2006; Nagano et al., 2008). However, there are limited data regarding tumor expansion in nonvestibular schwannoma. From our study, we found10 patients (19%) with tumor expansion. Three patients (30%) required additional surgery mainly because of neurological deterioration. Our results also showed that large tumors with cystic expansion after radiation were

more likely to require additional surgery. In large tumor patients, this is an unsophisticated aspect because the neurological deterioration easily developed, even with slight tumor enlargement. In addition to cystic expansion post radiation, the cause still remains unclear, but it may be caused by repeated intratumoral hemorrhages or increased vascular permeability induced by irradiation.

There were some limitations of our study including a retrospective nature with no regular and routinely performing imaging for follow up evaluation. Nevertheless, the results of our study did provide the additional and important data to support the use of SRS and FSRT for patients with intracranial nonvestibular schwannomas

In conclusion, this study showed excellent long term outcomes of intracranial nonvestibular schwannoma patients treated with Linac-based stereotactic radiation. With regard to our finding, large volume tumors and cystic expansion after radiation should be carefully followed up with neurological examination and MRI, because it frequent causes neurological deterioration requiring further surgery.

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