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ORIGINAL ARTICLE

Long-term follow-up confirms the efficacy of Linac radiosurgery for acoustic neuroma and meningioma patients. A single institution's experience

M.A. Kalogeridi[1], P. Georgolopoulou[2], V. Kouloulias[1], J. Kouvaris[1], G. Pissakas[3]

[1]Radiotherapy Unit, Medical School, National University of Athens, Athens; [2]Department of Medical Physics, St. Savvas Anticancer Hospital, Athens; [3]Department of Radiotherapy, Alexandra's General Hospital, Athens, Greece

Summary

Purpose: *To investigate the long-term efficacy and toxicity in a group of consecutive patients treated with linear accelerator (linac) radiosurgery for acoustic neuromas and meningiomas.*

Methods: *Between 2000 and 2004, 34 patients (median age 65.5 years, range 50-84) with acoustic neuroma or meningioma were treated with linac-based stereotactic radiosurgery with a surface dose of 11-15.5 Gy. The maximum lesion diameter ranged from 10 to 34 mm. Median tumor volume was 5.95cm^3. The follow-up consisted of repeated imaging studies and clinical examination in the first 6 and 12 months after the intervention and yearly thereafter.*

Results: *Follow-up time ranged from 50 to 99 months (median 75). Nineteen (59%) tumors decreased in size and 13 (41%) remained stable. None of the tumors increased in size in the long-term follow-up, resulting in an overall growth control of 100% for the small number of patients of our study. No patient developed new permanent facial or trigeminal neuropathy or deterioration of preexisting symptoms.*

Conclusion: *Long-term follow-up confirms the efficacy and low toxicity of linac radiosurgery for neuroma and meningioma patients.*

Key words: linac, meningioma, neuroma, radiosurgery

Introduction

Acoustic neuromas account for 6-10% of primary intracranial tumors [1] and arise from the Schwann cells lining the vestibular branch of the VIII cranial nerve. The usual site of their growth is the internal auditory canal or the cerebellopontine angle, while they can expand to both of these sites. The sporadic form of neuromas makes up 95% of the cases, is usually unilateral and mainly occurs during the 5th and 6th decade of life. The other 5% is associated with type 2 neurofibromatosis, is typically bilateral and occurs in younger patients.

Meningiomas are estimated to be twice as frequent as neuromas (13-26%) with most of them being benign lesions[2]. They originate from non- neuroepithelial progenitor cells, the arachnoid cap cells. Meningiomas mainly occur during the 6th and 7th decade of life. Most of them are located at the convexity, the cerebellopontine angle, the cavernous sinus, the falx cerebri or the tentorium cerebelli.

In the past, these tumors were usually diagnosed after they have given rise to symptoms such as headache, tinnitus, hearing loss, vertigo or neurologic deficits mainly from the facial or trigeminal nerves [3,4]. During the last decades, however, advances in imaging have increased the chance of finding a neuroma or a meningioma that has not yet become clinically significant. In combination with the development of competing treatment modalities this gave rise to a lot of discussion about the need as well as the optimal method to treat these tumors.

In the past, surgery was the recommended treatment for neuromas and meningiomas. Despite the high rate of tumor control, surgery is not always feasible due to medical comorbidities. The non-invasive nature of radiotherapy (RT) makes it a valuable alternative for patients with benign tumors given the side effects of surgery. Pollock et al. reported the results of a prospective comparison of microsurgical resection and radiosurgery for neuroma patients after a mean follow-up period of 42 months. There was no difference in tumor control while normal facial movement and preservation of serviceable hearing was more frequent in the radiosurgi-

Correspondence to: Dr. Maria-Aggeliki Kalogeridi, MD. 12 Karaiskakis Street, GR-155 62 Holargos, Greece. Tel: +30 210 6516915, Fax: +30 210 6546845, E-mail: ma_kalogeridi@yahoo.com

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cal group [5]. Comparison between complete resection and radiosurgery for meningiomas patients favors the latter, giving equivalent progression-free survival (PFS) rates with less complications (22 vs. 10%; p=0.06) and less subsequent tumor treatments (15 vs. 3%; p=0.02) [6]. Fractionated stereotactic RT and stereotactic radiosurgery have been extensively studied and have shown high efficacy with low toxicity [7-10].

Based upon the data published in the 1990s we started to treat acoustic neuromas and benign meningiomas of the brain with linac-based stereotactic radiosurgery in our institution. We report herein the results on tumor control and toxicity after a minimum follow-up of 4 years.

Methods

Between 2000 and 2004, 34 consecutive patients (9 men and 25 women) received linac-based stereotactic radiosurgery for a benign intracranial tumor. The median patient age was 65.5 years (range 50-84). All patients had a unilateral, well circumscribed tumor with imaging characteristics of acoustic neuroma or benign meningioma. Patient characteristics are shown in Tables 1 and 2. Six patients had previously undergone attempts of surgical removal and were referred for radiosurgery because of residual or recurrent tumor. None of the neuroma patients had useful hearing.

Tumors considered for radiosurgery had a maximum diameter of 35 mm. Median tumor volume was 5.95cm^3. Patients with larger tumors were offered surgery or fractionated RT.

In all patients stereotactic radiosurgery was performed using an Elekta SL-18 linac converted for radiosurgery with the attachment of an isocentric subsystem (Philips SRS200XK) and non-coplanar arc irradiation with circular collimators.

The whole procedure was carried out in 8-9 h. On the treatment day a Brown-Roberts-Wells stereotactic head-frame with 4 sharp stereotactic pins was screwed onto the patient's scull under local anesthesia. With the stereotactic head-frame attached, a contrast-enhanced CT scan was performed using a stereotactic localizer. The patient's entire head was scanned using 1-3 mm contiguous slices. Tumor delineation was made on this contrast-enhanced CT scan. Organs at risk such as the optic nerves, optic chiasm, lenses and brain stem were outlined on the treatment planning CT.

A treatment plan was achieved using 1-8 isocenters. The dose for neuroma and meningioma patients was 11-12 Gy and 12-15.5 Gy respectively to the prescription isodose which covered 95-100% of the tumor. High conformality of the treatment dose to the borders of the tumor was established by different combinations of number, span and weight of noncoplanar arcs, as well as weight and collimator size of each isocentre. The circular collimators used ranged in diameter from 10-30 mm. Every effort was made to achieve homogeneity in dose distribution across the tumor while keeping the dose to the stem as low as possible. The dose to the optic chiasm was kept strictly under 8 Gy.

Table 1. Pretreatment neuroma patient characteristics (n=20)

Characteristics	*Patients, no.*	*%*
Gender		
Men	5	25
Women	15	75
Age (years)		
Median (range)	66 (57-80)	
KPS		
≥ 90	18	95
60	1	5
Tumor location		
Right	9	45
Left	11	55
Intracanalicular	0	0
Cerebelopontine angle	7	35
Intracanalicular and cerebelopontine angle	13	65
Tumor size (cm)		
Small (<2)	7	35
Medium (2-3.9)	13	65
Prior treatment		
Surgery	4	20
Radiotherapy	0	0

KPS: Karnofsky performance status

Table 2. Pretreatment meningioma patient characteristics (n=14)

Characteristics	*Patients, no.*	*%*
Gender		
Men	4	27
Women	10	71
Age (years)		
Median (range)	65.5 (35-84)	
KPS		
≥80	13	93
Tumor location		
Right	7	50
Left	7	50
Convexity	7	50
Cerebelopontine angle	7	50
Tumor size (cm)		
Small (<2)	3	21
Medium (2-3.9)	11	79
Prior treatment		
Surgery	2	14
Prior radiotherapy	0	0

KPS: Karnofsky performance status

Treatment duration was 30 to 60 min once the machine was set up. After the irradiation was completed patients had their frame removed, remained in the department for an observation period of an hour and were then discharged from the hospital.

Corticosteroids were routinely prescribed starting at 8 mg of dexamethasone with 25% reduction every 4 days.

Endpoints and follow-up

The primary study endpoint was tumor control and the secondary was low toxicity.

Pre-treatment evaluation included neurologic examination with a focus on cranial nerves function.

Clinical follow-up was obtained from the patients or from their referring doctors if they lived at a significant distance from our institution. When necessary, patients were contacted by telephone to update their outcomes for the purposes of this study.

Our follow-up protocol consisted of repeated imaging studies and clinical examination with assessment of facial and trigeminal nerve function at 6-month intervals for the first year and yearly thereafter (Figures 1-4).

Verification of tumor control after radiosurgery requires a more extended follow-up period because there is no easily accessible imaging modality with which clinicians can assess the tumor's biological viability [11]. An actuarial follow-up of at least 3 years is considered necessary for any meaningful conclusions to be drawn [12]. In our study tumor growth control was defined as absence of permanent increase in tumor dimensions more than 2 mm and was judged by assessing tumor dimensions over time on contrast enhanced scans (CT or MRI).

In our series the follow-up period ranged from 50-99 months (median 75).

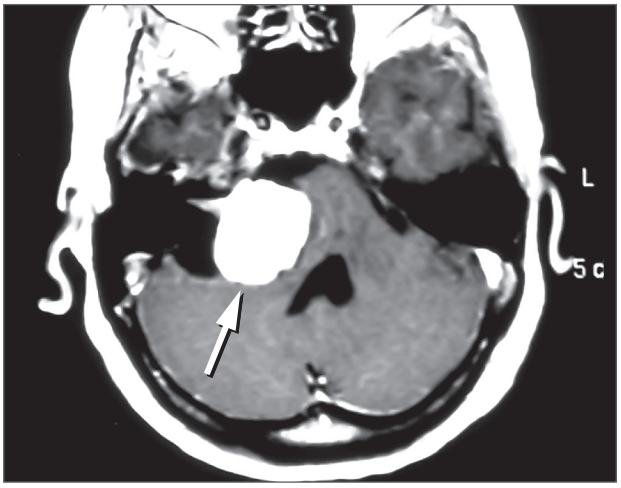

Figure 1. CT of a patient with neuroma before stereotactic radiosurgery (arrow).

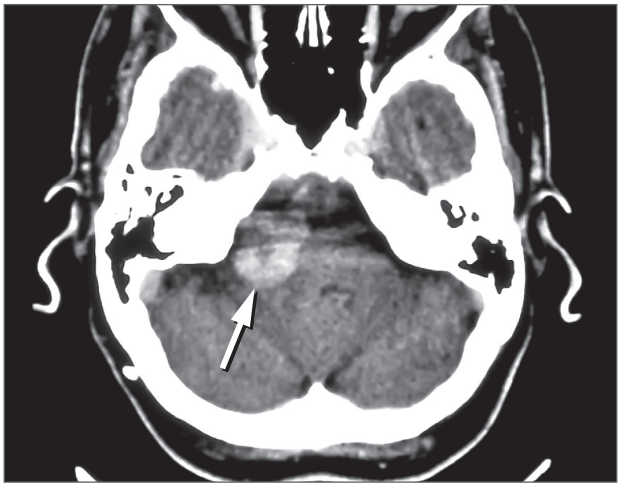

Figure 3. Same patient. Four years after stereotactic radiosurgery; shrinkage of the tumor is obvious (arrow).

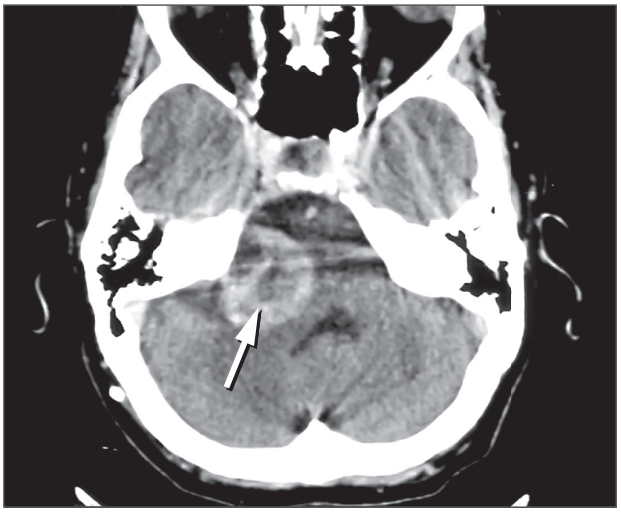

Figure 2. Same patient. Loss of central enhancement 6 months after stereotactic radiosurgery (arrow).

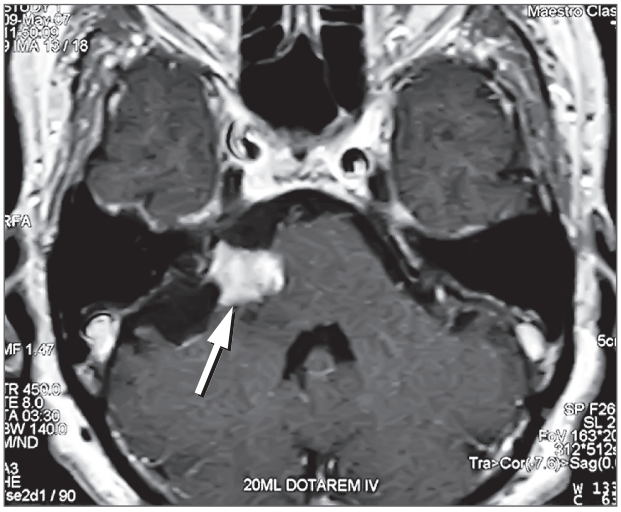

Figure 4. Same patient. Eight years after stereotactic radiosurgery significant shrinkage of the tumor is apparent (arrow).

Results

Thirty-four patients were treated and 32 were followed-up. Two patients were lost to follow-up. Nineteen (59%) tumors decreased in size and 13 (41%) remained stable. Shrinkage of the tumor was observed in 58% and 61.5% of neuroma and meningioma patients, respectively. None of the tumors increased in size in the long-term follow-up, resulting in overall tumor growth control of 100%. Only one tumor showed a marginal increase on MRI 6 months after radiosurgery in comparison with the pretreatment MRI. A subsequent decrease was noticed on the next radiographic assessment and the tumor remained stable ever after.

For tumors that showed a decrease in size the onset of change was 6 months after radiosurgery.

Tumors in 10 patients were noted to have a loss of central enhancement. The onset of this change was 6 months after linac-based stereotactic radiosurgery (Figure 2).

This change of central enhancement was not associated with temporary tumor diameter increase. The only tumor with a transient increase on MRI in our series never manifested such a necrosis. Since all 20 neuroma patients had no measurable or useful hearing before radiosurgery hearing level was not specifically assessed during follow-up and none of our patients reported a change in the hearing status.

Most patients (94%) had intact trigeminal nerve function before radiosurgery. In the immediate post-treatment period no treatment-related neuropathy was noticed. In the long- term follow-up (median 75 months) none of them developed any new pain or decrease in sensation within the ipsilateral nerve distribution. One patient out of two with facial numbness before SRS had clear improvement after therapy, while the other one remained stable. None of these two patients had undergone prior surgery.

Before treatment none of the patients had facial nerve neuropathy. In the immediate post-treatment period 3 patients had transient symptoms that could be related to facial nerve neuropathy. However, symptoms resolved in a few days without any medication. At long-term follow-up (median 75 months) no permanent deficits were reported.

In the immediate post radiosurgery period no toxicity was reported apart from new onset of headache in 6 patients which lasted less than 12 h and was successfully treated with paracetamol. Most patients attributed it to the head frame pins.

After completion of radiosurgery patients were able to return immediately to their everyday activities and none of them experienced any decrease in Karnofsky's performance status.

Discussion

Acoustic neuromas and benign meningiomas are intracranial tumors that are hardly life-threatening. However, they can affect quality of life causing symptoms relevant to their site of growth such as headache, tinnitus or ocular disturbances (visual field deficit, decreased visual acuity, diplopia). More often they are asymptomatic and are incidentally found on a CT or MRI of the brain. Since the chances of detecting a benign intracranial tumor before it becomes symptomatic have increased with the advances in imaging modalities the question was raised about the need to treat these tumors.

The behavior of these tumors has been studied in patients who recurred after surgical intervention [14] and more recently in patients who have not been offered any kind of treatment [15,16]. Long-term observations confirmed that these tumors remain stable or grow at a slow rate. Mean growth rate for untreated neuromas and meningiomas is 1.2 mm and 2.4 mm per year, respectively [15,16]. These data support conservative management with only close follow-up for asymptomatic patients as an alternative approach to immediate treatment.

In the past the standard therapeutic approach for acoustic neuromas and meningiomas was surgical excision. The more complete the removal of the tumor, the less the likelihood for recurrence and the greater the chance for cure. Tumor control rate for neuroma patients is 100% after total resection but decreases to 45-90% for subtotally resected tumors [17-19]. Many meningiomas cannot be totally excised because they are enveloping vital neural or vascular structures [20]. Even after total resection 19% of meningiomas recur by 20 years [21], while after incomplete resection the progression is 30% and 90% at 5 and 15 years, respectively [22]. Moreover, even with the more recent technical advances surgery is not always devoid of side-effects.

RT can be offered as an alternative to neuroma and meningioma patients who are not surgical candidates or are not willing to take the risks of surgery. Many authors have reported excellent results with primary RT [23,24] and 10-year recurrence-free probability up to 100% [9]. Fractionated RT is highly effective for neuroma patients as well, giving control rates up to 100% [7,25,26], and it takes up to 6 weeks to be completed. Consequently, it may have a negative impact on the patients' quality of life. A single fraction treatment such as radiosurgery would be more convenient for the patients and the busy radiotherapy departments. These reasons make stereotactic radiosurgery an appealing alternative to RT and the method has gained popularity the last 3 decades. Many authors have reported high local control rates up to 100%, comparable to surgical re-

section, with low toxicity from cranial nerves for both neuroma and meningioma patients [5,6,10,27-29].

Our study showed that linac-based stereotactic radiosurgery for neuroma and meningioma patients offers favorable tumor control with minimal toxicity. The small size of our sample does not allow comparison of the results with those of larger series. Gamma knife has been the first radiosurgical method offered to treat benign intracranial tumors and published series usually are much larger than ours or other linac-based series.

However, our study has a long follow-up period (median 75 months), longer than most recently published series of stereotactic radiosurgery for neuromas or meningiomas. This is an important remark for two reasons. First, the reported rate of radiological tumor response depends on the follow-up period after radiosurgical intervention. Nicolato A et al. reported a 43.5% radiologic response of meningiomas after radiosurgery with a follow-up period of less than 30 months, while this rate increased to 80% for longer follow up ($p<0.0002$) [30].

Second, radiosurgery-related toxicity, mainly from cranial nerves, becomes apparent 3-5 years after the intervention [28]. An actuarial follow-up of at least 3 years is considered to be meaningful and sufficient to exclude the possibility of later increase in tumor growth (except on the very long-term) or worsening of neurological symptoms [12].

A recent study by Radu A et al. reports the results of 22 neuroma patients treated with linac radiosurgery at a dose of 12 Gy [31]. Tumor growth control was obtained in all patients (100%). Trigeminal neuropathy was observed in one patient after a short median follow-up period of 18 months. The results are in agreement with another recently published study of 26 patients given 10-14 Gy who had a 95% of tumor control after a median follow up of 49 months [32]. Linac-based radiosurgery series for meningioma patients give tumor control more than 97% and low toxicity with median doses of 12.7 and 14 Gy [33,34].

The results of our study are in line with those in previous reports (Table 3). We limited the tumor dose to 11-15.5 Gy in keeping with the trend initiated at the end of 1980s to lower the radiation dose to the tumor in order to reduce neuropathic complications. None of the tumors increased in size in the long-term follow-up, resulting in an overall growth control of 100% for the small number of patients of our study. Only one tumor showed a marginal increase on the MRI 6 months after radiosurgery in comparison with the pretreatment MRI. A subsequent decrease was noticed on the next radiographic assessment and the tumor remained stable ever after. This is in agreement with previous reports stating that most patients with tumors that slightly increase in size after radiosurgery, either stabilize or regress afterwards [8,27].

The vast majority of tumors (89%) that decreased in size in our series had a pretreatment medium size. Decrease in tumor size was seen in 58% and 61.5% of neuroma and meningioma patients, respectively, and was closely related with the length of the follow-up period. Tumor decrease in size was reported in 10 patients the first year after intervention, in 13 patients the second year and in all 19 patients with tumor shrinkage the third year after radiosurgery.

Almost one third of our patients showed loss of central enhancement. We, like others, believe that loss of enhancement in the post-treatment period represents necrosis [34].

The follow-up period of our study is sufficient to estimate cranial nerve toxicity. No new permanent facial or trigeminal toxicity developed. Apart from transient headache in the immediate post-radiosurgery period no other acute side effects were noted.

In summary, our study confirms in a small number of patients with benign intracranial tumors that linac-based stereotactic radiosurgery provides excellent tumor control. After long-term follow-up (median 75 months) cranial nerve toxicity remains low, making this method a well-tolerated, appealing alternative to fractionated RT or microsurgery for neuroma and meningioma patients.

Table 3. Published studies on radiosurgery for acoustic neuromas and meningiomas

Authors [Ref. no]	*Tumor*	*Method*	*Number of patients*	*Follow-up (months)*	*Dose (Gy)*	*Local control (%)*
Hasegawa et al.[35]	neuroma	Gamma knife	317	93.6	13.2	93
Iwai et al. [36]	neuroma	Gamma knife	51	60	12	92
Rutten et al. [32]	neuroma	Linac	26	49	12	95
Radu et al. [31]	neuroma	Linac	22	18	12	100
Okugana et al. [37]	neuroma	Linac	46	56.5	14	81.6-100
Present study	neuroma	Linac	20	73	11-12	100
Flickinger et al. [38]	meningioma	Gamma knife	219	29	14	93.2
Spiegelmann et al. [33]	meningioma	Linac	42	36	14	97.5
Shafron et al. [34]	meningioma	Linac	70	23	12.7	100
Present study	meningioma	Linac	14	78.5	12-15.5	100

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