The Laryngoscope

Contemporary Review

Malignancy in Vestibular Schwannoma after Stereotactic Radiotherapy: A Case Report and Review of the Literature

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Objectives/Hypothesis: A relation between conventional radiotherapy and the development of intracranial neoplasma is well known, but radiation-associated tumor following stereotactic radiotherapy of vestibular schwannoma is underestimated.

In this article we will study this relation by doing a complete literature review on all the malignant intracranial tumors that appeared following radiosurgery and adding a case of malignant vestibular schwannoma following stereotactic radiotherapy in a Neurofibromatosis type 2 patient.

Methods: Literature review and discussion.

Results: We found 26 cases of malignant brain tumor following stereotactic radiotherapy including our case. In 13 cases the tumor occurred in context of Neurofibromatosis type 2. None of the patients had a tumor size less than 2.5 cm. and the mean latency period between the radiotherapy and malignant tumor development was 5.8 years.

Conclusion: Patients with vestibular schwannoma should be made aware of the low incidence of the radiation-induced malignant changes and long-term follow-up is mandatory.

Key Words: Malignant schwannoma, malignant peripheral nerve sheath tumor, neurofibromatosis type 2, neurosarcoma, triton, radiosurgery, vestibular schwannoma, radiation therapy, Gamma knife, malignant transformation.

Laryngoscope, 121:923–928, 2011

INTRODUCTION

Vestibular schwannoma (VS) is a tumor that arises from Schwann cells of the vestibular nerve. The incidence is about 20 per million/year and it accounts for 10% of intracranial tumors, 75% of cerebellopontine angle (CPA) tumors, and 5% of such tumors occur in patients with Neurofibromatosis type 2 (NF2).[1]

These tumors are benign, but rare malignant variants have been described in the literature especially after the widespread use of stereotactic radiation for the treatment of VS.

The criteria of radiation-induced tumor was first established by Cahan et al.[2] in 1948 when he reported 11 cases of secondary sarcoma following radiation therapy for breast cancer and bone tumors.

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Editor's Note: This Manuscript was accepted for publication November 16, 2010.

The authors have no financial disclosures for this article.

The authors have no conflicts of interest to declare.

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DOI: 10.1002/lary.21448

We hereby describe a case of a malignant VS in a NF2 patient who underwent a previous stereotactic radiotherapy. This case was the only malignant tumor found during a 23-year experience in VS surgery at the Gruppo-Otologico until June 2010 (2,342 cases operated).

CASE REPORT

A 15-year-old male, known to have NF2, presented to our group in 2001 with a left mild sensorineural hearing loss (SNHL). The patient had bilateral VS diagnosed in 1994 when a magnetic resonance imagine (MRI) showed a 1-cm left CPA tumor and a right intracanalicular lesion.

The tumors were followed up with annual MRIs, the last one was done 1 week prior to his presentation and showed growing of both tumors, with the left side tumor size of 2.2 cm and the right side of 1.8 cm in the largest diameter; the MRI revealed also an infracentimetric right lower cranial nerve tumor.

We recommended removal of the left side tumor with eventually auditory brainstem implant (ABI), but the family refused and decided to undertake stereotactic radiotherapy.

The patient underwent in another center Gamma knife (GK) treatment on the left side (13.5 Gy at 50% isodose line were delivered to the tumor margin).

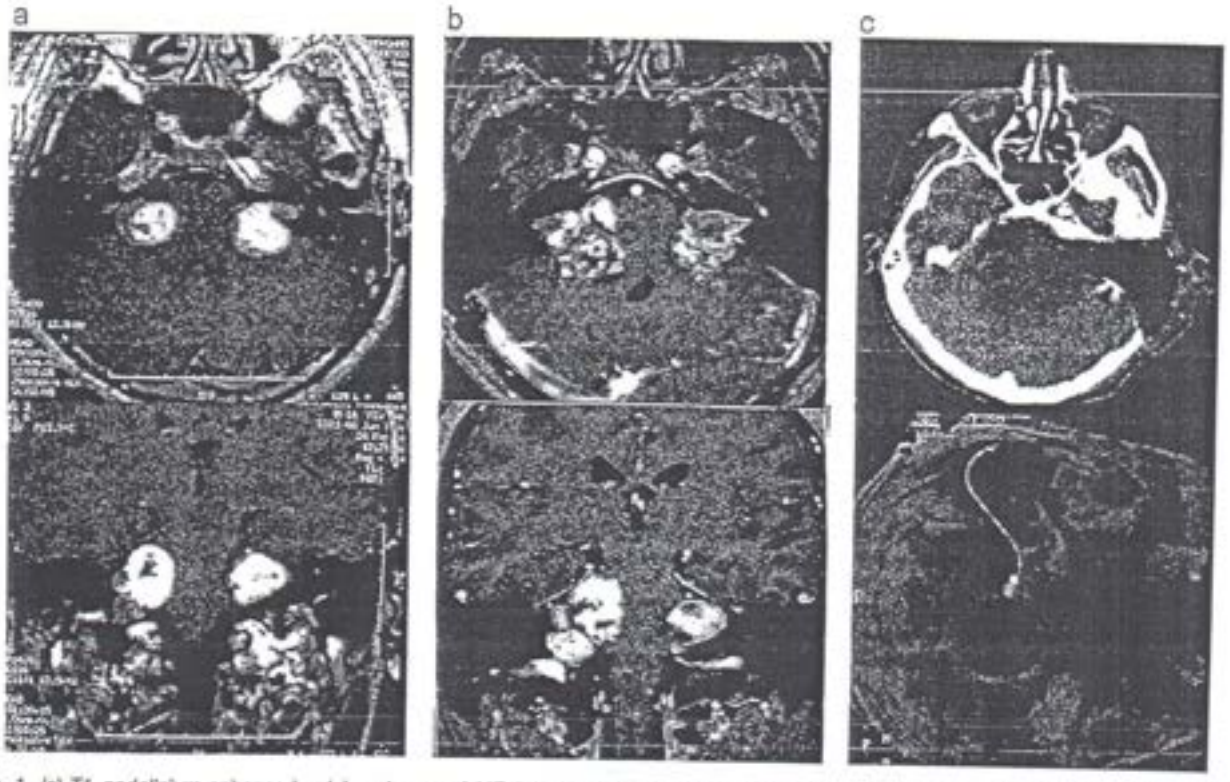

Fig. 1. (a) T1 gadolinium-enhanced axial and coronal MR images demonstrated bilateral VS and right lower cranial nerve tumor in NF2 patient (in 2001). (b) Gadolinium-enhanced axial and coronal MR images showing growth of bilateral tumors in 2006. (c) Postoperative CT scan with 3D reconstruction revealed total resection of the left side tumor with the ABI in place.

In 2003, the MRI showed a decrease in the size of the left-side tumor with central necrosis, but there was a growth of the right-side tumor, with appearance of new lesions in the cervical and lumbar spine in favor of meningiomas. We recommended the surgical treatment but the family refused again, and the patient received another stereotactic radiotherapy to the right sided tumor (13 Gy at 50% isodose line were delivered to the tumor margin).

In October 2006, the patient presented again to us with worsening of hearing and a new onset of left facial weakness (grade 4 House-Brackmann). An audiogram revealed a left dead ear with right moderate SNHL. MRI was done and showed enlargement of both tumors on the right more than the left side (Fig. 1).

At that time, the patient and his family agreed to undergo surgery. Decision was taken to remove first the left side tumor because of the hearing status and the patient symptoms.

A left transcochlear approach was performed in October 2006. The tumor had a very hard consistency and no plane of cleavage with the brainstem was identified. Meckel's cave and the facial nerve were involved by the tumor. A total resection of the tumor was achieved with insertion of an ABI.

The patient's immediate postoperative course was smooth with no complications, and he was discharged home after 5 days.

In December 2006, the patient was admitted to the intensive care unit (ICU) in another center following an intracerebral hemorrhage, and he passed away few weeks later secondary to a respiratory failure.

HISTOLOGY

The tumour specimen consisted of several fragments heterogeneous in appearance and texture, partially fibrotic and friable, with several necrotic and haemorrhagic areas.

Microscopically, most fragments were composed of usual schwannoma with prominent Antoni A areas and some fibrotic areas. Intermingled with this tissue, a malignant peripheral nerve sheath tumour (MPNST) was evident exhibiting prominent cellularity and extensive geographic-type necrosis. The borders between schwannomatous and malignant components were mostly sharp without transition features (Fig. 2).

Malignant cells ranged from spindle to epithelioid-oval shape, with very scanty cytoplasm, frequent apoptotic cells, and many mitoses. Nuclei were small and hyperchromatic, with well-evident nucleoli. Most malignant cells were immunoreactive for S-100 protein and P53, the staining being of variable intensity. Furthermore, focal areas were immunoreactive for smooth muscle actin, EMA, neurofilament, NSE, PGP

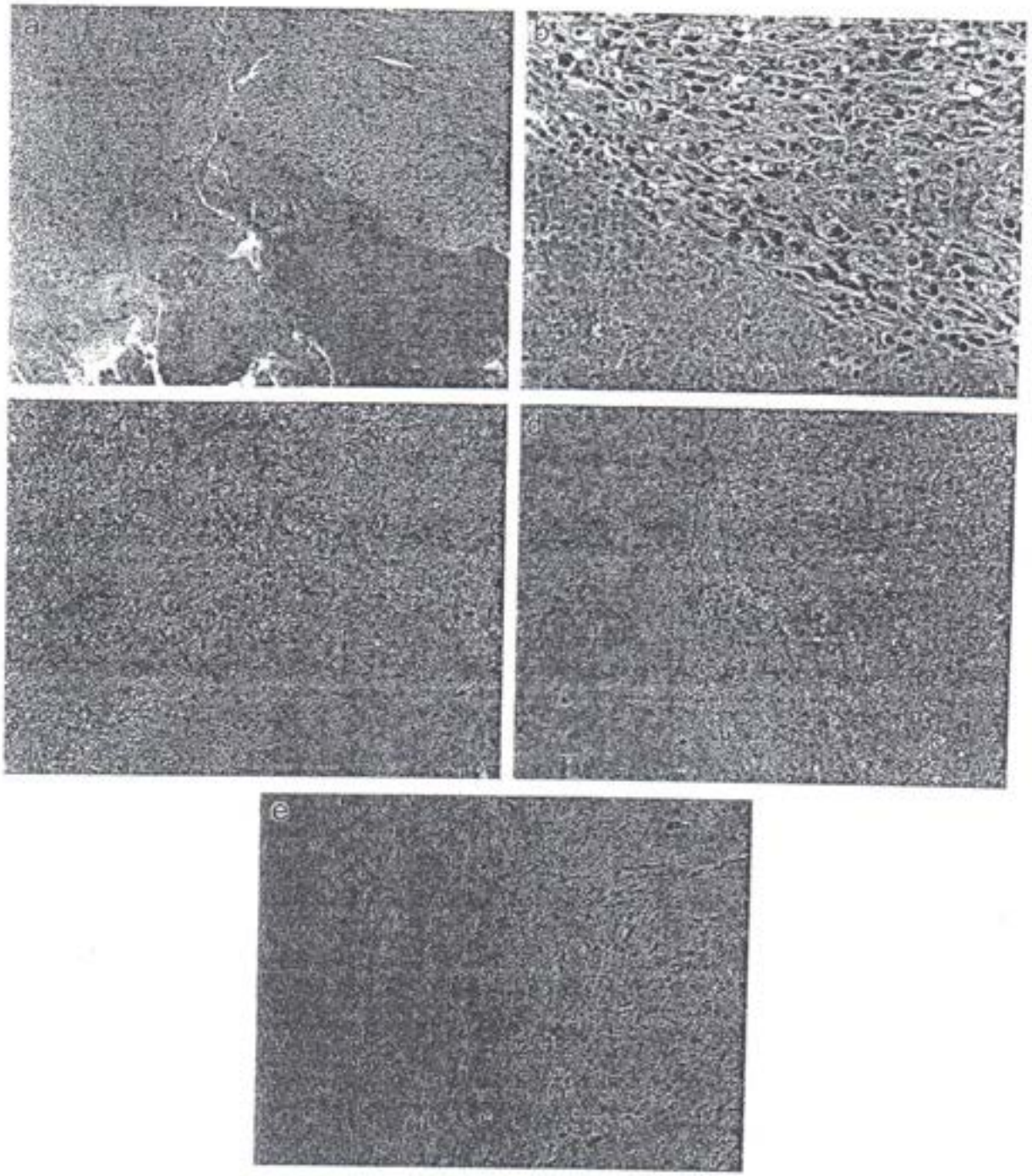

Fig. 2. (a) Photomicrograph showing histological appearance of the malignant peripheral nerve sheath tumor (MPNST) with extensive geographic type necrosis, hematoxylin and eosin (H&E,40× total magnification). (b) Higher magnification showing the oval and epithelioid cells. (H&E, 400× total magnification). (c) MPNST (top of the figure) and benign schwannoma with nuclear palizading (arrows) (H&E, 100× total magnification). (d) Sharp border between schwannomatous and malignant component (H&E, 100× total magnification). (e) The same field immunostained for protein S-100 (100× total magnification).

9.5, and CD99. The proliferative index as evaluated by the proliferative antigen Ki-67 was around 60%, and there were no evident heterologous components, such as osseous metaplasia or rhabdomyoblastic differentiation.

DISCUSSION

In 1902, Frieben[3] suggested the relation between malignancy and radiation exposure when he reported a case of squamous cell carcinoma in the hand of an X-ray technician.

TABLE I.
Cases of Malignant Brain Tumor Occurring Following Stereotactic Radiotherapy for Vestibular Schwannoma Treatment

Author	Age/Gender	S	NF 2	FP	Preoperative Size	Peripheral Dose (Gy)	Pathology of Secondary Tumor	Years to Secondary Tumor	Survival Rate
Comey 1998	50/M	R	N	Y	3.4 cm	14.4	Triton	5	12 m
Noren 1998	18/F	R	Y	N	4 cm	20	Triton	8	N/A
Thomson 2000	19/F	R	Y	N	4 cm	12	Sarcoma	6	24 m
Baser 2000	N/A	N/A	Y	N/A	N/A	N/A	MPNST	N/A	N/A
Baser 2000	N/A	N/A	Y	N/A	N/A	N/A	MPNST	N/A	N/A
Baser 2000	N/A	N/A	Y	N/A	N/A	N/A	MPNST	N/A	N/A
Baser 2000	N/A	N/A	Y	N/A	N/A	N/A	Malignant ependymoma (de novo)	N/A	N/A
Baser 2000	N/A	N/A	Y	N/A	N/A	N/A	Malignant Meningioma (de novo)	N/A	N/A
Shamisa 2001	57/F	R	N	N/A	N/A	11	GBM (de novo)	7.5	N/A
Hanabusa 2001	51/F	R	N	Y	2.5 cm	a-15b-14	Sarcoma	6 m	13 m
Ho 2002	14/F	L	Y	N/A	3.5	18	Rapid growth	7	2 weeks
McEvoy 2003	22/M	R	Y	N/A	N/A	15	Rapid growth	2	3 m
Barl 2002	28/F	L	Y	Y	3.1 cm	15	MPNST	4	3 m
Shin 2002	26/F	R	N	N	3.5 cm	17	MPNST	6	10 m
Kubo 2004	51/M	L	N	N/A	N/A	14	MPNST	8 m	N/A
Wilkinson 2004	53/M	R	N	N/A	N/A	N/A	MPNST	4	N/A
Muracciole 2004	61/F	L	N	N	2.5 cm	a-10b-12	Triton	6	N/A
Maire 2006	N/A	N/A	N	N/A	N/A	FRT	MPNST	19	N/A
Balasubramaniam 2007	64/F	R	N	N	N/A	50 (FRT)	GBM (de novo)	5	4 m
Chen 2008	51/F	R	N	N/A	9 cm	N/A	MPNST (de novo)	8 m	N/A
Rowe 2008	F	N/A	Y	N/A	N/A	N/A	GBM (de novo)	3	6 m
Van Rompaey (2009)	53/F	R	N	N	4 cm	12	MPNST	8	Autopsy
Carlson 2010	25/F	R	Y	Y	2.5 cm	52 (FRT)	Sarcoma (de novo)	10	3 m
Yang 2010	74/M	L	N	Y	2.5 cm	12.5	Sarcoma	6	2 m
Demetriades 2010	37/M	L	N	Y	3 cm	15	MPNST with further dedifferentiation to anaplastic sarcoma	10	6 m
Our case 2010	20/M	L	Y	Y	3 cm	13.5	MPNST	5	3 m

F = female; L = left; m = month; M = male; N = No.; R = right; S = side; Y = yes; GBM = glioblastoma multiforum; FP = facial paralysis; FRT = fractionated radiotherapy; MPNST = malignant peripheral nerve sheath tumor; N/A = not available; NF 2 = neurofibromatosis type 2.

In 1969, the first stereotactic radiation therapy for the treatment of VS was performed, and in 1997, at the International Stereotactic Radiosurgery Society meeting in Madrid, Kurita and Shin[4] reported in a poster the first case of malignant transformation of a VS following stereotactic radiotherapy.

Since then, several cases of intracranial radiation-induced tumor have been reported in the literature, but there is no single complete review of all these cases.

We performed a detailed search in Pubmed and Medline database with a complete review of all the literature published using the following key words: malignant schwannoma, malignant peripheral nerve sheath tumor, NF2, neurosarcoma, triton, radiosurgery, vestibular schwannoma, radiation therapy, Gamma knife, and malignant transformation.

We found 26 cases of malignant brain tumor following radiotherapy of VS, including our case (Table I).[4–7]

De novo secondary tumors induced by stereotactic radiotherapy for brain tumors other than VS were excluded in this study.[7,8] De novo secondary tumor refers to the new tumor that appeared in the field of irradiation of VS.

There were 17 cases of malignant transformation of VS: de novo secondary malignant tumors were encountered in 7 cases, and in 2 patients the tumor had grown rapidly several years after radiotherapy, then the patient passed away within few months.

Male-to-female ratio was 1:2, the right side was more involved than the left, and none of the patients had a tumor size less than 2.5 cm. In 13 cases the tumor occurred in context of NF2 (Table II).

NF2 is a rare (1:60,000) autosomal dominant disorder caused by mutations and loss of an important tumor suppressor gene (NF2 gene) on the long arm of chromosome 22. This gene produces the protein Merlin, responsible of Schwann cell regulation. As in retinoblastoma, such mutation might be considered as a "first hit" and the radiation therapy could provide the "second hit" of a two-hit process oncogenesis that might induce a second tumor or malignant transformation.[9]

In a survey done on 1,348 NF2 cases, Baser et al.[5] found that NF2 patients who have received radiotherapy

TABLE II.
Summary of the Literature Review

Patients	Radiation Response					
	Malignant Transformation			De Novo Secondary Malignant Tumor	Rapid Growth	
	MPNST	Triton	Sarcoma			
NF 2	5	1	1	4	2	13
Sporadic	6	2	2	3	0	13
M/F: 1/2 L/R: 1/2 Age range (14–74) y Median of age: 40 y Mean latency to malignant tumor development: 5.8 y	11	3	3	7	2	26

F = female; L = left; M = male; N = No.; R = right; MPNST = malignant peripheral nerve sheath tumor; NF 2 = neurofibromatosis type 2; y = year.

had a 14-fold increased risk of developing malignant brain tumors. (The incidence was 10% in irradiated patients compared to 0.7% in non irradiated patients).

Primary malignant VS is a rare entity. To our knowledge, it has never been described in NF2 patients, whereas malignant transformation of VS has been found in seven irradiated NF2 patients.[5,7]

These findings raise the suspicion whether VS in NF2 patients are prone to malignant transformation after stereotactic radiotherapy.

Radiation might cause chromosomal injury and induce atypical proliferation in Schwann cells. A relation between conventional radiotherapy and the development of malignant schwannomas and intracranial tumors have been proved in several reports.[10–12]

Warren et al.[13] found that VSs removed from NF2 patients previously irradiated have more chromosomal anomalies than nonirradiated ones.

After radiation therapy, most of the irradiated cells usually undergo cytoplasmic vacuolization and subsequent cell death. Rarely, some of the surviving cells might acquire genetic mutations, which are responsible of the malignant transformation of VS.[4]

One of the important genetic alterations is TP 53 mutation, which was found in our case and was expressed as intranuclear deposits of P53 protein, which are highly correlated with malignant tumors. Other mutations are K-ras mutations, p16 deletions, and epidermal growth factor receptor amplification.[7,12]

In 1948, Cahan et al.[2] outlined the criteria of a radiation-induced tumor:

1. a second tumor occurs within the radiation field and it was not present at the time of irradiation
2. a latency period is required between radiotherapy and tumor development (several years)
3. a histological difference must exist between the primary and the new tumor
4. The patient should not have any genetic predisposition for cancer development.

Although our case does not fulfill all these criteria because it lacks a histologic evidence of the previous pathology, and is considered as malignant conversion of the primary benign tumor, we highly suspect that radiation therapy might have had a major role in the pathogenesis of this malignancy.

It is hard to believe that the tumor was malignant before the radiation therapy, because of the long time elapsed between radiotherapy and surgical resection of the tumor.

A malignant brain tumor could not remain stable with no sign of growth or progression for 5 years. Our review showed that malignant VS is an aggressive tumor, and most of the patients passed away within few months after the surgery (Table I).

Besides, the coexistence of benign schwannomatous cells and the malignant component might confirm the hypothesis of malignant transformation.

This concept is applicable for the other reviewed cases where the malignancy has been reported from 6 months to 19 years after radiation therapy with a mean latency period of 5.9 years for the "malignant transformation of VS" and 5.2 years for the "de novo secondary malignant tumor" formation.

This latency period is shorter than the time required for the development of a secondary benign tumor following conventional radiotherapy as described by Ron et al.[10] (15 years for schwannomas, 14 years for gliomas, and 21 years for meningiomas).

Furthermore, Brada et al.[14] reported that malignant tumors developed earlier than benign tumors following fractionated radiotherapy of pituitary tumor.

The potential risk of malignant degeneration has not been properly addressed in the literature by those who practice the stereotactic radiotherapy. They argued that the carcinogenic risk of stereotactic radiotherapy is low and much less than the conventional method; with the new technique the irradiated peritumoral normal tissues receive low-dose of radiation, and the targeted lesions receive a high cytotoxic radiation dose that will lead to the death of cells and not mutation. The Pittsburgh experience showed no radiation induced tumor or atypical changes after stereotactic radiotherapy for VS after a median follow up of 53 months.[15]

On the other hand, Ron and Sadetzki[10,11] found that brain tissue exposure to radiation doses as low as 1 Gy is sufficient for the development of a secondary tumor.

Radiation-induced tumor might be underestimated in the literature due to the fact that the reported cases

of de novo secondary benign tumor are not taken into consideration specially in NF2 patients in whom the new appearance of brain meningioma or schwannoma in the radiation field is attributed to the NF2 condition.[13]

In addition, there are some cases in whom the tumor grew after radiotherapy and the patient died without postmortem examination.[6,7]

Therefore, although GK treatment is considered as an attractive conservative treatment modality in NF2 with a high rate of hearing preservation, the above-mentioned suspicions should be considered in the counseling and the decision-making process for the treatment of such patients. Stereotactic radiation therapy might be approved for those patients who refused surgery only if tumor growth is demonstrated on imaging; otherwise, "wait and scan" should be the option.

Furthermore, it is important to note that excision of the tumor is more difficult after radiotherapy, with a poor facial nerve outcome and nearly impossible hearing preservation.[9]

Our analysis of published series showed that 50% of the patients presented with facial paralysis and 50% of those who were investigated with spinal MRI were found to have spinal metastasis.[4] Thus, once the diagnosis of malignancy is confirmed, a spinal MRI is mandatory.

Our review showed also that four patients have received postoperative fractionated radiation therapy with a mean survival of 13.3 months, whereas in another group of eight patients who did not receive postoperative radiotherapy the mean survival was 4.4 months.

The prognosis of these patients is poor. The majority of those who underwent surgical resection died from local recurrence within months, but those who received postoperative fractionated radiation therapy had a slightly higher survival rate.

CONCLUSION

Patients who receive stereotactic radiation therapy for the treatment of VS should be made aware of the rare, yet possible risk of radiation-induced malignancy, especially in NF2 cases.

Long-term follow-up including MRI of the brain of all patients who underwent GK treatment is mandatory because the mean latency period between the radiotherapy and malignant tumor development is 5.8 years.

The prevalence of radiation-induced tumor might be underestimated in VS treatment, so we strongly recommend publication of any encountered cases in the future.

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