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ORIGINAL ARTICLE **CME**

Predictive Factors of Pseudoprogression in Vestibular Schwannoma Treated with Fractionated Stereotactic Radiotherapy

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ABSTRACT

Objective: *Fractionated stereotactic radiotherapy (FSRT) is a well-established treatment for vestibular schwannoma (VS). Tumour pseudoprogression may lead to worsening symptoms leading to the necessity of urgent salvage surgery. This study aimed to assess the predictive factors of pseudoprogression and treatment related toxicities in VS treated with FSRT.*

Methods: *This retrospective cohort study included all patients with VS treated with FSRT between 1999 and 2015. Risk factors assessed included sex, age, previous surgical resection, tumour diameter, gross tumour volume, planning target volume, overall treatment time, equivalent dose in 2-Gy fractions, and the presence of brainstem or cerebellar compression prior to radiotherapy. Fisher's exact test and two-sample* t *test were used for statistical analysis.*

Results: *Eighteen patients were included. The median follow-up time was 80.3 months. The overall disease control rate after FSRT was 94.4%. Of the 18 patients, one (5.6%) developed local tumour progression, seven (38.9%) underwent tumour pseudoprogression; and 10 (55.6%) had stable disease. Median time to tumour pseudoprogression was 8.63 months (range, 4.5-13.1 months). Tumours with pseudoprogression and those with at least stable disease had a mean diameter of 2.7 cm and 2.1 cm, respectively (p = 0.18). The mean treatment planning target volume in the pseudoprogression group was larger than that in the non-progression group with volume measured (22.2 cc vs. 10.0 cc; p = 0.04). Patients with brainstem or cerebellar compression observed on magnetic resonance imaging before radiotherapy were associated with a higher risk of pseudoprogression (p = 0.0498). The overall salvage surgery rate was 17.7%.*

Conclusion: *Upfront surgery may be more desirable than FSRT for those surgically fit patients with considerable treatment volume and evidence of mass effect. Large prospective studies are needed to confirm our findings and to identify further predictive factors for pseudoprogression.*

Key Words: *Neuroma, acoustic; Radiotherapy; Risk factors*

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Contributors: AWSL, SFN, WHM, and CSW designed the study. AWSL, SFN, and WHM were responsible for acquisition of data. AWSL and JJH analysed the data. AWSL wrote the article. AWSL, SFN, and KMK made critical revisions of the intellectual content of this article. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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中文摘要

分次立體定向放療前庭神經鞘瘤假性進展的預測因素

盧穎嬋、饒仕鋒、梅永豪、黃嘉杰、甘冠明、黃志成

目的：分次立體定向放療（FSRT）是前庭神經鞘瘤（VS）的成熟治療方法。腫瘤假性進展可導致症狀惡化，而接受緊急搶救手術。本研究旨在評估FSRT治療VS假性進展的預測因素和與治療相關毒性反應。

方法：本回顧性隊列研究納入1999年至2015年期間接受FSRT治療的所有VS患者。評估的危險因素包括性別、年齡、手術切除史、腫瘤直徑、腫瘤總體積、計劃靶體積、總體治療時間、2 Gy分次的等效劑量，以及放療前腦幹或小腦是否受壓。使用Fisher精確檢驗和雙樣本*t*檢驗作統計分析。

結果：納入18名患者。中位隨訪時間為80.3個月。FSRT後的總體疾病控制率為94.4%。18名患者中，1例（5.6%）出現局部腫瘤進展惡化，7例（38.9%）出現腫瘤假性進展；10例（55.6%）病情穩定。腫瘤假性進展的中位時間為8.63個月（4.5至13.1個月）。具有假性進展的腫瘤和至少疾病穩定的腫瘤平均直徑分別為2.7 cm和2.1 cm（$p = 0.18$）。假性進展組的平均治療計劃靶體積大於非進展組的體積（22.2 cc比10.0 cc；$p = 0.04$）。在放療前通過磁共振成像觀察到腦幹或小腦受壓的患者與假性進展的風險較高相關（$p = 0.0498$）。整個搶救手術率為17.7%。

結論：對於具有相當大治療靶體積和出現佔位效應的手術適合患者，優先手術可能比FSRT更為理想。需要進行大型前瞻性研究以確認本研究結果並進一步確定假性進展的預測因素。

INTRODUCTION

Vestibular schwannoma (VS), also known as acoustic neuroma, is a benign tumour that accounts for approximately 80% to 90% of cerebellopontine angle tumours. Symptoms at diagnosis often include sensorineural hearing loss, tinnitus, dizziness, change in facial sensation, and headache. In some patients, presentation is delayed until the tumour is much larger causing symptoms related to mass effect. These include cerebellar and brainstem symptoms or hydrocephalus due to the effacement of the fourth ventricle. Typically, VS is diagnosed by magnetic resonance imaging (MRI), presenting as a contrast enhanced solid nodular mass with an intracanalicular component causing widening of the porus acusticus. Cystic degeneration can be observed in larger lesions. Calcification is not typically seen. Treatment approach often depends on patients' symptoms, tumour size, and location. Small, slow growing, or asymptomatic lesions can be managed conservatively with clinical and radiological monitoring.

Surgery, stereotactic radiosurgery (SRS), and fractionated stereotactic radiotherapy (FSRT) are well-established treatment modalities. In addition to having a similar tumour control rate to that of surgery, SRS has the advantages of being non-invasive, having better hearing preservation, and having a shorter immediate recovery time.[1] A recent meta-analysis comparing SRS with microsurgery for tumours <3 cm showed a similar tumour control rate (96.2% vs. 98.7%) and better hearing function (70.2% vs. 50.3%).[2] Typically, FSRT is offered for tumours with larger volume or irregular shape in order to better spare organs at risk and to enable a higher treatment dose to be delivered. A standard dosage of >45 Gy given in a fractionation of 1.8 to 2 Gy per day has been shown to achieve local control in VS.[1] Different dosage regimens have been used worldwide. Two large European studies adopting 52.2 Gy in 25 fractions and 50.4 Gy in 25 fractions demonstrated local tumour control rates at 5-year follow-up of 93% and 97.5%, respectively.[3,4] A study from Thomas Jefferson University showed that further reduction of dose to 46.8 Gy in 1.8 Gy daily fraction led to comparable tumour control rate but improved preservation of functional hearing status.[5]

Tumour pseudoprogression is observed after radiotherapy treatment as a transient tumour expansion mimicking

progressive disease. Pseudoprogression may lead to increase in severity of neurological symptoms or mass effect rendering the necessity of urgent salvage surgery. Recent studies have reported pseudoprogression rates after SRS as 14% to 74%.[6-13] However, the underlying physiopathology is poorly understood, and there is limited understanding on pseudoprogression rate and its predictive factors after FSRT.

Therefore, the primary objective of our study is to report the pseudoprogression rate and assess the predictive factors in patients with VS treated with FSRT. The secondary objective is to assess the treatment related toxicities.

METHODS

Patients

From 1999 to 2015, 22 patients were diagnosed with VS and treated with FSRT at Tuen Mun Hospital, Hong Kong. Eligible patients were adults with at least 18 months of follow-up examinations with serial gadolinium-enhanced MRI. Patients who passed away due to unrelated causes within 18 months of treatment were excluded. Patients were followed up at least every six months in the first three years after radiotherapy until disease was stable. Patients' clinical data were reviewed to define the pretreatment characteristics; and to assess for deterioration of hearing and facial weakness. All pretreatment MRI scans (if images were available) were reviewed to assess for tumour size and presence of mass effect (brainstem or cerebellar compression). Small changes in size were sometimes difficult to detect on MRI images taken at 5-mm intervals. Tumour sizes, determined as the maximal tumour diameter on contrast-enhanced MRI, were taken from the MRI reports made at the time of the scan. The risk factors assessed were sex, age, previous surgical resection, tumour diameter, gross tumour volume (GTV), planning target volume (PTV), equivalent dose in 2-Gy fractions (EQD2), overall treatment time and the presence of brainstem or cerebellar compression.

Treatment

The FSRT was delivered using 6-MV photons by volumetric modulated arc therapy or intensity modulated radiotherapy. Patients were immobilised with a thermoplastic cast. The GTVs were delineated with 2-mm computed tomography images co-registered with T1-weighted gadolinium-enhanced MRI images. A 2-mm margin was added to the GTV to create the PTV. Treatment was verified with ExacTrac®. All radiotherapy treatment records were reviewed. The treatment dose and calculated EQD2 were recorded.

Tumour Assessment and Treatment Outcome

Maximal tumour diameter was assessed on consecutive follow-up MRIs. Pseudoprogression was defined as maximum diameter increase of at least 2 mm with subsequent stabilisation or regression of tumour size. The definition was adapted from the largest retrospective study to date concerning this topic involving 208 patients by Pollock in 2006.[6] Disease progression was defined as progressive increase in tumour size recorded on at least two follow-up MRI examinations. Time to pseudoprogression was defined as time from date of radiotherapy commencement to date of MRI scan showing tumour pseudoprogression. Time to disease stabilisation was defined as time from date of pseudoprogression to date of MRI showing tumour stabilisation or regression on at least two serial MRI scans. Tumour control rate was the percentage of tumour achieving stable disease or tumour regression.

Statistical Analysis

Patients were divided into pseudoprogression group and non-progression group (which included stable and regression tumour post radiotherapy). Independent sample *t* test was used for comparison of GTV diameter, GTV, and PTV between these two groups. Fisher's exact test was used for comparison of radiation dose (EQD2 dose <48 Gy and ≥48 Gy) and the presence or absence of brainstem or cerebellar compression between these two groups. Mann Whitney *U* test was used to compare the difference in median radiotherapy dosage given in the two groups in terms of EQD2. A two-sided P value of ≤0.05 was considered statistically significant. Data were analysed with SPSS Statistics (Windows version 23.0; IBM Corp., Armonk [NY], United States).

Ethics Approval

Approval for this study was granted by the local cluster clinical research ethics committee.

RESULTS

A total of 18 patients were included in our study (Figure 1). Patient characteristics are summarised in Table 1. The mean age at treatment was 54 years (range, 30-73 years). There were 7 men and 11 women. The overall median follow-up time was 80.3 months (range, 21.6-212.8 months). The median follow-up time in the pseudoprogression group and the non-progression group

was 2.7 years and 10.7 years, respectively (p = 0.02, Mann-Whitney *U* test). The mean pretreatment tumour diameter was 25.2 mm (range, 4-41 mm). The mean pretreatment GTV was 11.4 cc (range, 0.4-51.3 cc). The prescribed doses were between 33 and 54 Gy (EQD2 40.7 to 55.6 Gy, α/β = 2.33) [Table 2]. The median time to first MRI was 9.8 months and 10.6 months in pseudoprogression group and non-progression group, respectively (p = 0.56, Mann-Whitney *U* test).

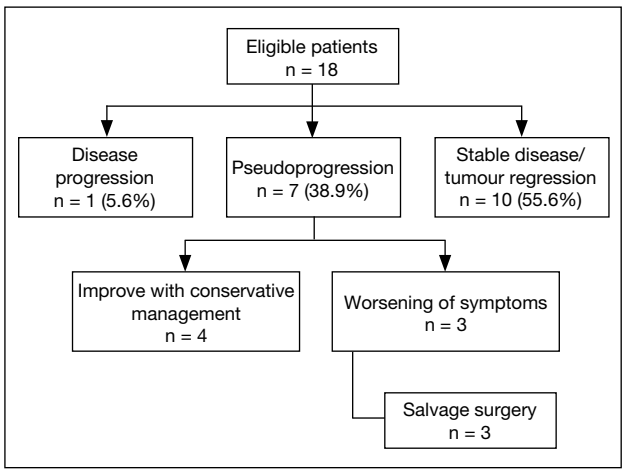

Figure 1. Summary of patient inclusion and tumour response.

Table 1. Patient characteristics (n = 18).

Patient characteristics	Value
Sex	
Men	7
Women	11
Age, mean (range), years	54 (30-73)
Follow-up time, median (range), months	80.3 (21.6-212.8)
Pretreatment tumour diameter, mean (range), mm	25.2 (4-41)
Pretreatment gross tumour volume, mean (range), cc	11.4 (0.4-51.3)
Previous surgical resection	12 (67%)

Table 2. Fractionated stereotactic radiotherapy regimen (patient with disease progression was not included).

Dose	Equivalent dose in 2-Gy fractions dose (α/β ratio 2.33)	No. of patients
50.4 Gy in 28 fractions	48 Gy	6
54 Gy in 27 fractions	54 Gy	2
54 Gy in 30 fractions	51.4 Gy	1
50 Gy in 25 fractions	50 Gy	2
50 Gy in 20 fractions	55.6 Gy	1
48.6 Gy in 27 fractions	46.3 Gy	1
45 Gy in 25 fractions	42.9 Gy	1
44 Gy in 22 fractions	44 Gy	1
36 Gy in 9 fractions	52.9 Gy	1
33 Gy in 11 fractions	40.7 Gy	1

The overall tumour control rate after FSRT was 94.4%. Of the 18 patients, one (5.6%) developed local tumour progression, seven (38.9%) underwent tumour pseudoprogression; and 10 (55.6%) had stable disease or tumour regression. Time to tumour progression was 4.4 years (from the date of radiotherapy completion). Median time to tumour pseudoprogression was 8.63 months (range, 4.5-13.1 months).

In order to assess the predictive factors of pseudoprogression, patients with disease progression were not included for statistical analysis. Patients were divided into pseudoprogression group and non-progression group (which included patients with stable disease and tumour regression). Tumours with and without pseudoprogression had mean diameters of 2.7 cm and 2.1 cm, respectively (p = 0.18). The mean PTV in the pseudoprogression group was significantly larger than that in the non-progression disease group with volume measured 22.2 cc versus 10.0 cc (p = 0.04). Pretreatment MRI showed evidence of brainstem or cerebellar compression in 30% of the non-progression group and 86% of the pseudoprogression group (p = 0.0498). This suggested that patients with mass effect on MRI before radiotherapy were associated with a significantly higher risk of pseudoprogression (Table 3).

Table 3. Factors associated with pseudoprogression rate.

Risk factors	Pseudo-progression group	Non-progression group	p Value
Age, mean, years	59.4	50	0.13*
Sex			0.62†
Men	5	5	
Women	2	5	
Previous surgical resection	50%	86%	0.30†
GTV diameter, mean, cm	2.7	2.1	0.18*
GTV, mean, cc	12.6	6.5	0.17*
PTV, mean, cc	22.2	10.0	0.04*
Pretreatment mass effect	86%	30%	0.05†
Overall treatment time (days)	33.9	32.8	0.86*
RT dose EQD2, median, Gy	48	50.7	0.05‡

Abbreviations: EQD2 = equivalent dose in 2-Gy fractions; GTV = gross tumour volume; PTV = planning target volume; RT = radiotherapy.
* Two-sample *t* test.
† Fisher's exact test.
‡ Mann-Whitney *U* test.

Of the seven patients with pseudoprogression, three developed significant symptoms (increased dizziness, facial spasm and unsteadiness) due to worsening of brainstem compression and hydrocephalus. In view of the debilitating symptoms, they subsequently underwent salvage surgery. The remaining four of the seven patients with pseudoprogression were monitored clinically with serial MRIs. The median time for subsequent tumour stabilisation or regression in this group of patients was 11.9 months (range, 9.1-26.3 months). The overall salvage surgery rate was 17.7%.

The pseudoprogression group had a higher incidence of facial weakness (42.9%) compared with non-progression group (10%); however, this was not statistically significant (p = 0.25). There was no significant difference in hearing impairment between the pseudoprogression group compared with the non-progression group, 14.3% and 20% respectively (p = 1.0) [Table 4].

Age, sex, overall treatment time, tumour diameter, GTV, and previous surgical resection were not associated with increased pseudoprogression rate (Table 3). There were no significant differences in the radiotherapy dosage (in EQD2) between the pseudoprogression group and the non-progression group, 48 Gy and 50.7 Gy, respectively (p = 0.054). In patients treated with EQD2 dose <48 Gy and ≥48 Gy, pseudoprogression rates were 75% and 30.7%, respectively, but this difference was not significant (p = 0.25).

DISCUSSION

It is important to identify pseudoprogression of VS and distinguish it from frank tumour progression in order to avoid unnecessary salvage surgery. In this series, we demonstrated a significant proportion (38.9%) of VS underwent pseudoprogression after FSRT, with onset of tumour expansion at around 9 months. Our finding was comparable to previous studies with reported rate of VS pseudoprogression after FSRT of 18% to 39%.[14-16] The overall median time for tumour stabilisation or regression in the pseudoprogression group was 11.9 months (range, 9.1-26.3 months). Typically, the pseudoprogression rate of VS after FSRT is lower than that of tumours treated with SRS (18%-39%[14-16] vs. 14%-74%[6-13]). Most reported studies have shown that pseudoprogression after SRS occurs at around 6 to 9 months and stabilises within 2 years.[6,7,10,11] Comparably, pseudoprogression after FSRT mostly occurs between 5.5 and 8.5 months,[14] including our findings, but it can occur up to 3 years after FSRT, according to a report from Japan.[16] In our study, the average time for tumour regression or stabilisation was up to 26.3 months. In general, follow-up for 24 months is recommended after SRS to assess overall treatment response. In cases of VS after FSRT, we advocate monitoring tumours with pseudoprogression with serial MRIs for at least 26 months before declaring treatment failure unless clinical deterioration is evident.

Table 4. Treatment toxicity.

Risk factors	Pseudo-progression group	Non-progression group	p Value*
Increased facial weakness	42.9%	10%	0.25
Reduced hearing	14.3%	20%	1.0

* Fisher's exact test.

Pseudoprogression after FSRT was observed frequently in tumour ≥30 mm in diameter in a Japanese study.[16] In our series, we examined the effect of tumour size on the outcome of VS after FSRT and found no significant difference in the rates of pseudoprogression in tumour diameters ≥30 mm compared with <30 mm (p = 0.64). There were also no significant differences in tumour diameters in VS with or without pseudoprogression, 2.7 cm and 2.1 cm, respectively (p = 0.177). Larger PTV was significantly associated with higher incidence of pseudoprogression (p = 0.04). However, although mean GTVs were larger in the pseudoprogression group than the non-progression group (12.6 cc vs. 6.5 cc), this difference was not significant. The exact pathogenesis of post irradiation pseudoprogression is not fully understood. The hypothesis was that radiation injury to tumour cells causes endothelial damage, necrosis and release of thrombosis promoting cytokines. The inflammatory response causes disruption of blood brain barrier, oedema and subsequent transient increase in tumour size.[17,18] The reason why this phenomenon only happens in a subset of radiotherapy treated VS is unclear. A larger PTV causes relatively more normal tissues to be irradiated. Normal tissue radiation injury is well known to cause DNA damage and changes in the microenvironment through chemokines, fibrotic cytokines, inflammatory cytokines, altered cell–cell interactions and influx of inflammatory cells.[19] Whether this dynamic and progressive process causes further local inflammation in tumour with larger PTV is not known. The exact mechanism of how larger PTV leads to higher pseudoprogression risk remains unclear. More studies in this area are needed. With advancing image-guidance and immobilisation techniques, we may

consider reducing the PTV margin in order to reduce the volume of normal tissue being irradiated.

Our study identified that the presence of brainstem or cerebellar compression on pretreatment MRI was associated with a higher risk of pseudoprogression. The presence of brainstem or cerebellar compression was 86% in the pseudoprogression group and 30% in the non-progression group ($p = 0.0498$). We postulate that the post-irradiation inflammatory response and cytokine release may be more profound in tumours with pre-existing mass effect, leading to oedema of the tumour and surrounding tissue. Moreover, the cystic transformation after radiotherapy may further increase tumour volume and subsequent mass effect. In our series, three of the seven patients with tumour pseudoprogression subsequently required salvage surgery due to increase in compression symptoms after FSRT. A recent report suggested surgery after radiotherapy in brain tumour is technically more difficult.[20] Intraoperative findings of VS after failed radiation treatment demonstrated fibrous change of tumour mass, new cyst formation and brownish discoloration of the tumour capsule.[20] Severe fibrous adhesions between tumour capsule and cranial nerves, vessels, and the brainstem were seen. Moreover, the facial nerve was more fragile after radiotherapy leading to a higher risk of injury with surgical manipulation. Gross total tumour resection was only possible in a third of the cases.[20] Post-irradiation new cystic formation in VS was seen in our pseudoprogression group (Figures 2 to 4). In summary, salvage surgeries for tumours failing radiotherapy were deemed technically more

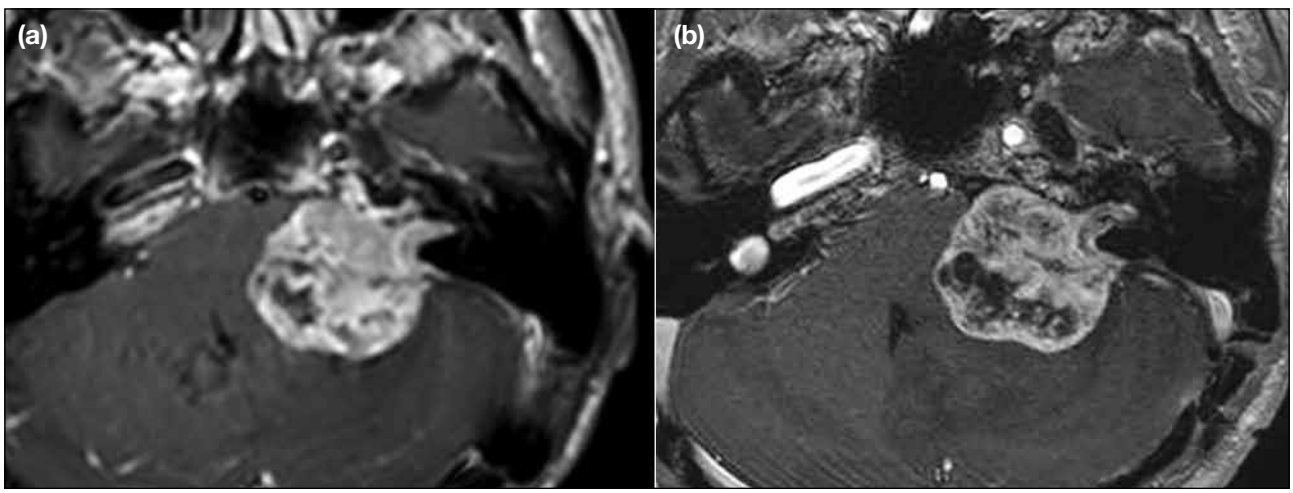

Figure 2. (a) Pre– and (b) post–fractionated stereotactic radiotherapy magnetic resonance images in a 57-year-old man with vestibular schwannoma.

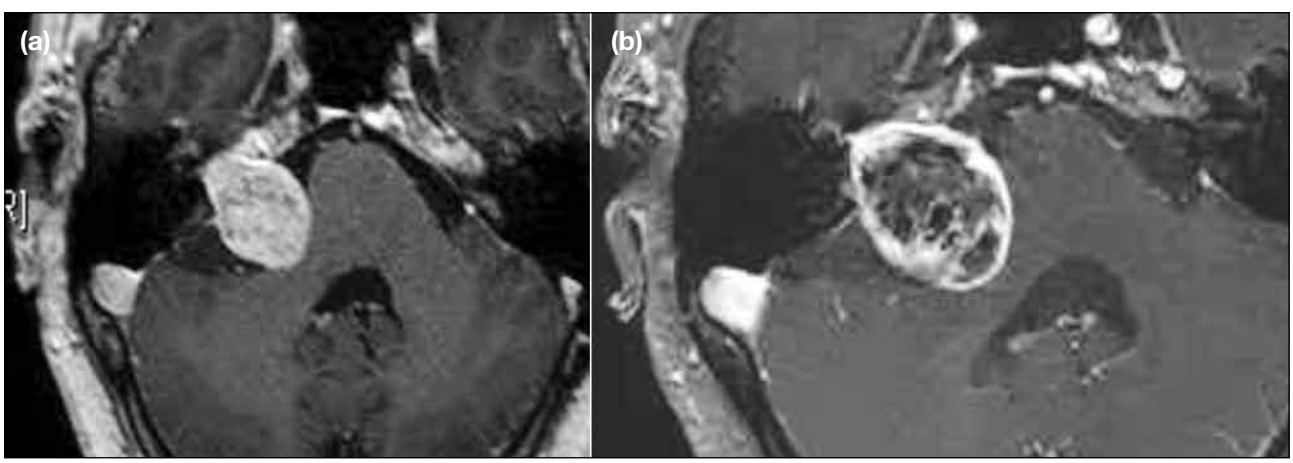

Figure 3. (a) Pre– and (b) post–fractionated stereotactic radiotherapy magnetic resonance images in a 51-year-old woman with vestibular schwannoma undergoing pseudoprogression.

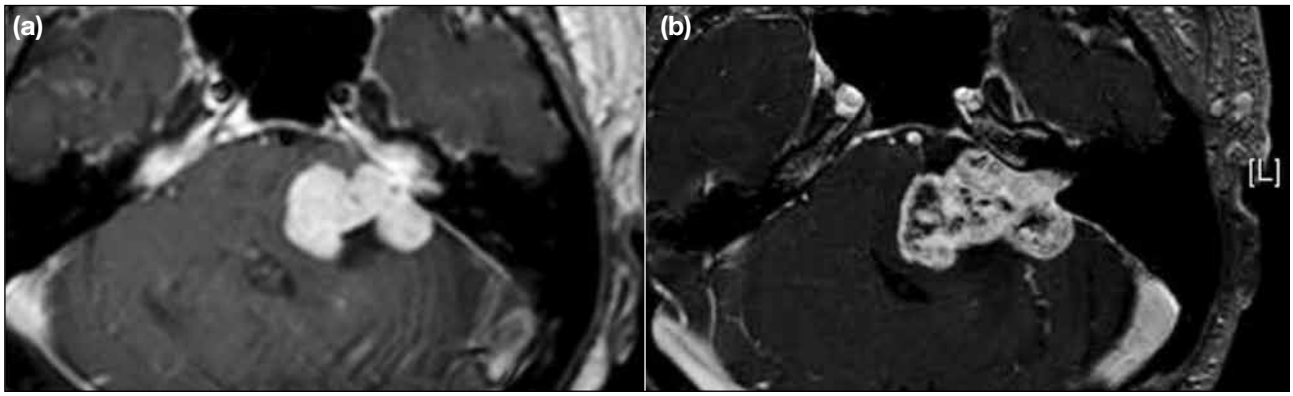

Figure 4. (a) Pre– and (b) post–fractionated stereotactic radiotherapy magnetic resonance images in a 57-year-old woman with vestibular schwannoma.

difficult. We recommend that patients with pre-existing brainstem or cerebellar compression should be treated with upfront surgery. For asymptomatic patients with pseudoprogression, it is reasonable to manage conservatively as all tumours were stabilised by 26.3 months. Salvage surgery should only be considered for patients with rapid clinical deterioration.

A recent report showed that prior surgical resection was significantly associated with transient tumour volume increase.[14] It was speculated that the transient tumour progression was due to vascular injury. However, no significant difference in pseudoprogression rate was demonstrated in VS patients with or without previous surgical resection in our study ($p = 0.30$). Age, sex, treatment duration and tumour diameter were not found to predict pseudoprogression rate in this current series (Table 3).

Little is known about the relationship between radiotherapy dosage and pseudoprogression. The commonly used radiotherapy dosages are 50.4 Gy in 28 fractions (EQD2 48 Gy), 52.5 Gy in 25 fraction (EQD2 54 Gy) and 46.8 Gy in 26 fractions (EQD2 44 Gy). The radiotherapy dosage for treatment of VS at our oncology centre ranges from 33 Gy to 54 Gy. The reported pseudoprogression rates from previous studies were from patients who were treated with 50 Gy given in 25 fractions (EQD2 50 Gy). By reducing the dosage, we may assume that there is less pseudoprogression due to less radiation injury. In our series, radiation dose EQD2 <48 Gy however did not appear to reduce the risk of pseudoprogression compared with EQD2 ≥48 Gy. There were also no statistically significant differences in the radiotherapy dosage (in EQD2) between the pseudoprogression group and the non-progression group, 48 Gy and 50.7 Gy respectively. It remains unclear whether the radiotherapy dosage affects pseudoprogression risk; a prospective trial with a larger number of patients may help to clarify this relationship.

Regarding toxicities, Hathout et al[14] reported an association between transient tumour volume increase and increased facial and trigeminal nerve dysfunction after FSRT. In our study, 42.9% and 10% of patients in the pseudoprogression group and the non-progression group, respectively, were observed to have increased in facial weakness after FSRT. Although pseudoprogression appeared to associate with increased in facial neuropathy, it did not reach statistical significance likely due to our small sample size. Additionally, 14% of patients in pseudoprogression group and 20% in stable group had worsening of hearing impairment after radiotherapy. Pseudoprogression was not found to be significantly associated with reduced in hearing.

The indications of FSRT to the pseudoprogression group patients were reviewed retrospectively. Four patients (57%) had RT due to worsening of symptoms while the remaining asymptomatic three were given RT as an adjuvant treatment after subtotal resection. In view of the benign and slow growing nature of VS, we would recommend observation for the group of patients with residual tumour after surgery and reserving radiotherapy as a salvage treatment.

There is currently a lack of established consensus in the literature as to the definition of pseudoprogression of VS after radiotherapy. Flickinger et al[21] defined pseudoprogression as temporary tumour diameter growth

of 1 mm in any two directions or 2 mm growth in one direction. Similarly, Pollock defined pseudoprogression as an increase in tumour diameter of at least 2 mm.[6] The advantage of this measurement is relatively easier to follow but prone to human error. More recently, Mohammed et al quoted an increase in 10% of volume as pseudoprogression.[15] Comparison between studies in this field with different pre-defined pseudoprogression is therefore difficult. A global consensus on the definition of pseudoprogression is needed. Moreover, the follow-up MRI intervals vary from 3 months to 12 months which may subsequently affect the accurate detection of disease progression and pseudoprogression. In view of the retrospective nature of the present study, the toxicities (facial neuropathy and hearing impairment) were reported as 'improved', 'static' or 'worsened'; a more detailed analysis with grading was impossible.

The main limitation of this study is the small number of patients included. A larger multicentre prospective study with a well-structured follow-up schedule would provide more data and greater statistical power for better assessment of predictive factors of pseudoprogression and treatment toxicities.

CONCLUSION

Tumour pseudoprogression is a common phenomenon and should not be regarded as treatment failure. Tumours with larger PTV or evidence of brainstem or cerebellar compression on pretreatment MRI have been shown to be associated with a higher risk of pseudoprogression. Upfront surgery may be more desirable than radiotherapy for those surgically fit patients with considerable treatment volume and evidence of brainstem compression. Unless clinical deterioration is evident, it is reasonable to monitor VS with pseudoprogression after FSRT with serial MRI examinations for at least 26 months before considering any surgical intervention. Further large prospective studies are needed to confirm our findings and to identify further predictive factors for pseudoprogression.

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