PROSPECTIVE OBSERVATIONAL STUDY FOR THE EVALUATION OF CLINICAL AND RADIOLOGICAL CORRELATES IN PATIENTS UNDERGOING SURGERY FOR VESTIBULAR SCHWANNOMA

Dissertation submitted for the partial fulfilment for the requirement of the degree of

M.Ch Neurosurgery

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DECLARATION

This thesis titled **PROSPECTIVE OBSERVATIONAL STUDY FOR THE EVALUATION OF CLINICAL AND RADIOLOGICAL CORRELATES IN PATIENTS UNDERGOING SURGERY FOR VESTIBULAR SCHWANNOMA** is a consolidated report based on a bonafide study of the period from December 2017 to July 2019, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfilment of rules and regulations of MCh Neurosurgery examination.

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06 Aug 2019

CERTIFICATE

This is to certify that the thesis entitled - **Prospective Observational Study for the evaluation of clinical and radiological correlates in patients undergoing surgery for vestibular schwannomas** is a bonafide work of Dr Arunkumar Karthikayan and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram (SCTIMST) under my guidance and supervision.

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CONTENTS

INTRODUCTION

Cerebellopontine angle (CPA) tumours comprise 5 to 10 percent of all intracranial tumours. Around 90 % of all CPA tumours are vestibular schwannomas, which are benign tumours of the vestibular portion of the vestibulocochlear nerve, arising from the Schwann cells. They first originate in the intracanalicular part of the nerve and grow slowly out into the cisterns. They present with unilateral sensorineural hearing loss with poor speech discrimination (77 to 95 %), unilateral non pulsatile tinnitus (53 to 70%), vestibular dysfunction, trigeminal nerve symptoms, cerebellar dysfunction, headache, facial nerve dysfunction, raised intracranial pressure and lower cranial palsy. Long tract signs are a late finding in patients with vestibular schwannomas and these have become extremely rare in modern series. (1,2)

Long tract involvement may present with hyperactivity of ipsilateral deep tendon reflexes, increased tone of the musculature and Babinski sign - extensor plantar response. Rarely extremity weakness and ipsilateral sensory symptoms are found in a small subset of patients. (1 - 10)

Diffusion tensor imaging of the brainstem allows delineation of the white matter tracts of the brainstem. It allows subjective quantification of the directional diffusion of the water in the white matter tracts. Lui et al found that in circumscribed posterior fossa primary lesions there was a correlation between clinical weakness and higher mean diffusivity, lower fractional anisotropy and lower transverse eigenvalue values. (55)

This study can assess the subset of the patients with vestibular schwannomas who present with long tract signs and their correlation with tractography findings preoperatively. The intraoperative nature of the tumour and the histopathological characteristics will be noted and the postoperative outcome with repeat imaging will be assessed. Through this study, we objectively hope to define the less commonly studied manifestation of vestibular schwannomas, the long tract signs - the size of the tumour beyond which they tend to occur - both clinically and radiologically. There is scarcity of research correlating clinical data with DTI imaging findings and the post operative follow up data, showing outcome after resection. This study hopes to assess the utility of diffusion tensor imaging to objectively quantify the involvement of long tracts in vestibular schwannomas and its usefulness in predicting post operative outcome. The Principal Investigator of this study regularly operates on vestibular schwannomas and we hope that this data will add on to the understanding of the long tract involvement in vestibular schwannomas.

AIMS OF THE STUDY

We hope to define the size beyond which subclinical long tract involvement which occur in vestibular schwannomas could be picked up. Diffusion tensor imaging is used to objectively correlate the involvement of long tracts. This will give a better understanding of the behaviour of vestibular schwannomas and their response to surgery.

To add on to the understanding of evolution in the natural history of vestibular schwannomas. To look for correlation between volume of the tumour and the change in DTI metrics.

REVIEW OF LITERATURE

VESTIBULAR SCHWANNOMAS

Vestibular schwannomas, previously referred to as acoustic neurinomas or neuromas, are one of the commonest lesions in the cerebello pontine angle (CPA), constituting around 6 to 8 % of all brain tumours. They are some of the most demanding among the skull base tumours in terms of skill and technical expertise. Even though they have benign histological picture, the critical location of this subset of tumours lead to compression of spinal nerves, and eventually brainstem compression. (1- 5)

Better understanding of the disease itself, advent of microneurosurgical techniques, intraoperative neuromonitoring, and newer modalities of treatment including stereotactic radiosurgery, fractionated radiotherapy and multimodal therapy have gone a long way in providing much better results for the patients.

HISTORICAL VIEW

The previous understanding of the disease itself was flawed as could be evidently seen in the nomenclature. The lesions were thought to arise from the cochlear nerve and were called neuromas by Virchow. The term acoustic neuromas stuck on for a very long time. It was only later in the previous century, that Schwann cells were found to be the origin of these tumours and anatomically they were found to arise from the vestibular division of the eighth cranial nerve. The consensus meeting in 1992 put an end to this confusion;

the terms acoustic neurinoma and acoustic neuroma were no longer recommended and vestibular schwannoma was the preferred term. (1 - 3)

The initial documentation was provided by Sandifort in 1777, as a “small body adherent to the right auditory nerve” which was incidentally discovered in the autopsy of a patient who had developed progressive hearing deficit. In 1830, British physician Charles Bell gave an accurate and detailed description of these lesions. Leading physicians of the 19th century, Jackson and Babinski provided us accurate descriptions of the various clinical presentations and signs to localise these lesions. (5, 7)

The first surgery for vestibular schwannoma, in 1890s by Von Bergmann was a failure with patient dying during the surgery. Four years later, Balance did the first successful removal of the tumor in London. In 1903, Woosley described the unilateral sub occipital craniectomy, the predecessor to the modern retrosigmoid craniotomy. The translabyrinthine approach was also described during that same time period, but was quickly abandoned because of two reasons - operating microscopes hadn’t come into use until 1960s; with poor illumination and no magnification, it was like operating on a deep narrow and dark tunnel. The second reason was the unacceptable high incidence of CSF leak. In fact, Harvey Cushing in 1917, advocated against the use of the translabyrinthine approach (5- 10). Cushing advocated a bilateral suboccipital craniectomy for all cases. He was justified by the fact that it reduced cortical herniation and medullary compression, both of which were common and caused significant mortality and morbidity during those ages. And also during the pre imaging era, bilateral craniectomy gave the liberty of exploring the opposite side if needed. Not long after that, Dandy, the legendary student of

Harvey Cushing, reported the removal of vestibular schwannoma through a small unilateral sub occipital craniotomy.

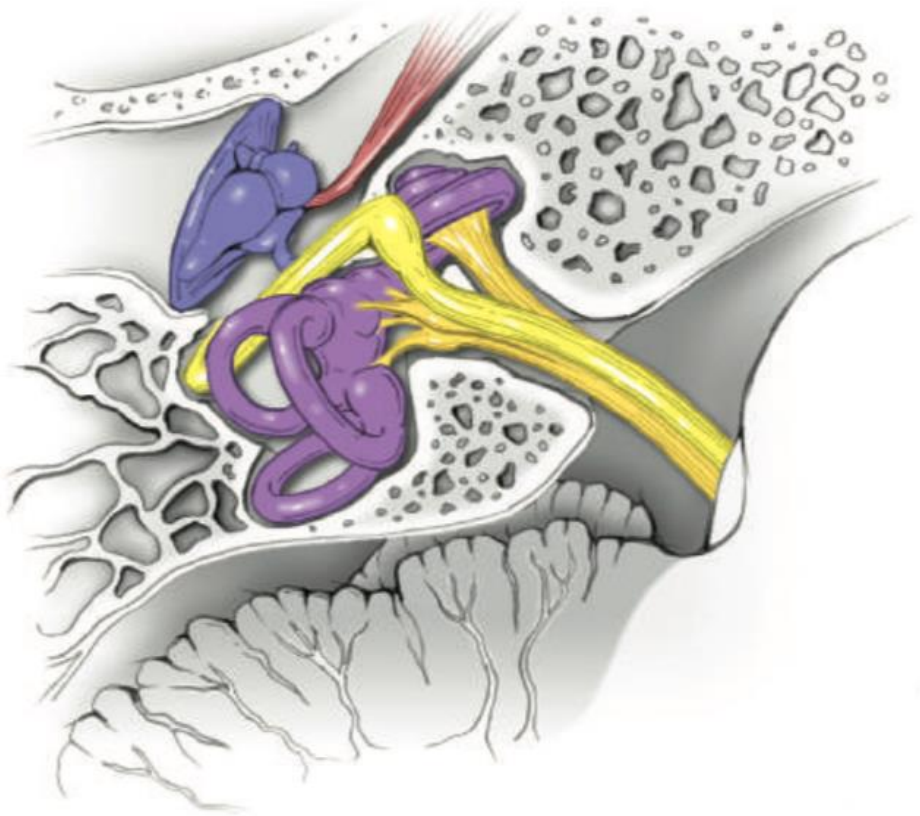


FIGURE - Petrous temporal bone anatomy

In the 1960s, the introduction of the surgical microscopes provided the much needed breakthrough and revolutionised the management of these tumours. It was first used by William House and later by Yasargil and Fox. The operating microscope gave the neurosurgeon, brilliant illumination and the freedom to operate in deep corridors with sufficient magnification and also with difficult trajectories and approaches. It was a proud entry to the neurosurgeon's armamentarium. The critical relations of the structures in the CPA could be well appreciated and radical tumor excision and facial nerve sparing

surgery became a possibility. House also popularised the labyrinthine and middle fossa approaches due to this shift in strategy. (15 - 19)

The history and evolution of the surgery could be glaringly seen when we take a look at the surgical outcomes and mortality. In the early 20 th century, the high mortality of around 86% was reduced to 20 % by the Father of Neurosurgery. Armed with microsurgical techniques, House was able to reduce it to less than 10 %. Intra op death rates in modern series vary between 0.8 to 5 %.

In 1969, Bjorn Myerson and Lars Leksell performed the first gamma knife radiosurgical procedure for vestibular schwannoma.

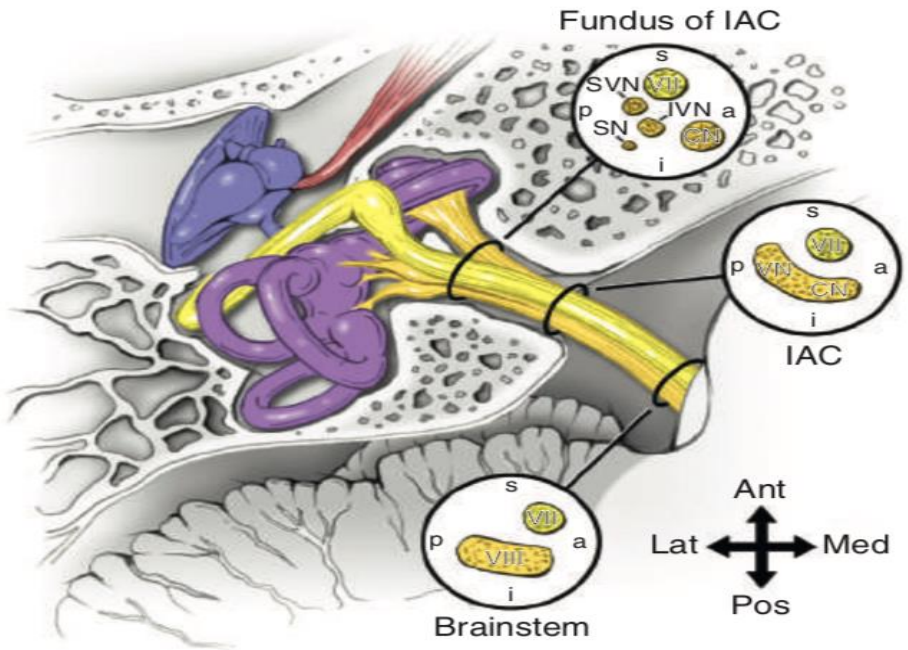


FIGURE - The facial and vestibulocochlear nerves have a complex relationship which is illustrated here

NATURAL HISTORY

Denmark has a very good source of epidemiological data wherein all cases have been entered into a national database. Availability of advanced imaging modalities, improved quality of life and increased life span of the population caused the statistical incidence to increase until 2004 when it plateaued out. The annual incidence has been found to be around 23 cases per million population. In the United States, the incidence is around 16 new cases per million population per year. Mean age at diagnosis is 58 years and there is no major sex predilection.

The mean tumor size in the above mentioned data set at diagnosis was found to be 10 to 15 mm, which also had a decreasing trend over the ages. Though there are no extensive similar data sets pertaining to the Indian population, there is still a huge proportion of patients who present with large and giant vestibular schwannomas. (1, 2, 4, 7, 12)

High dose ionising radiation is the only known risk factor for vestibular schwannomas and the controversial mobile phone usage has not shown any scientific association.

In the natural history of these tumours, there are three growth patterns, tumours that grow continuously, tumours that plateau off and stagnate and a very small subset of tumours that shrink on follow up. Sughrue et al evaluated 982 patients with a mean initial tumor size of 11.3 mm and noted a growth rate of around 2.9 mm per year. Strangerup et al followed up purely intrameatal tumours at diagnosis and found out that only 17 % grew to extrameatal proportions over years. And among the extrameatal tumours, 70 % were unchanged, increase in size was found in 29 % and 1% showed shrinkage. The most useful observation was that beyond 5 years, there was no growth of the tumours. This has

an implication in the follow up of incidentally detected patients, wherein it is recommended to follow up tumours less than 15 mm of size and which doesn't show any increase on serial imaging. This doesn't apply to the cystic vestibular schwannomas which have been known to show acute and dramatic growth patterns. Yet another observation from the above database is that patients presenting with tinnitus have greater chance of tumour growth pattern. (1, 2 , 16, 18 - 20)

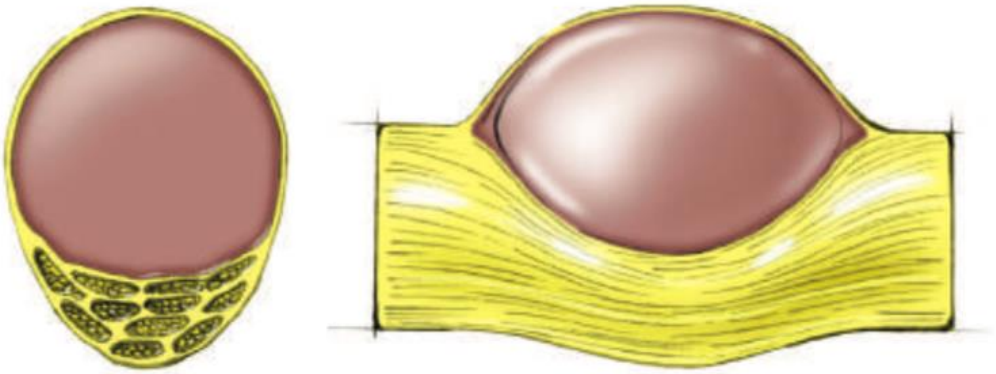


Figure - Vestibular schwannoma and its relation with normal nerve fascicles, which are displaced and flattened along the capsule.

NEUROFIBROMATOSIS TYPE 2

Reported in 1822, by Wishart, with bilateral vestibular schwannomas and other cranial and spinal disease which progress rapidly. Patients present at an younger age and tumour growth is faster.

National Neurofibromatosis Foundation had given the criteria for the diagnosis of NF 2

PROBABLE NF 2

- Unilateral VS and age less than 30 years *plus* one of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities, or cortical cataract

- Two or more meningiomas *plus* Unilateral VS and age less than 30 years *or* One of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities, or cortical cataract

DEFINITE NF 2

- Bilateral VS or

- First degree relative with confirmed NF2 plus

- Unilateral VS at age less than 30 years or

- Any two of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities, or cortical cataract

HISTOPATHOLOGY

VS are classified as WHO Grade I tumours. The transition between the central glial cells and the peripheral Schwann cells, namely the Obersteiner-Redlich zone, which usually occurs in and around the Porus acousticus, is the origin of these tumours.

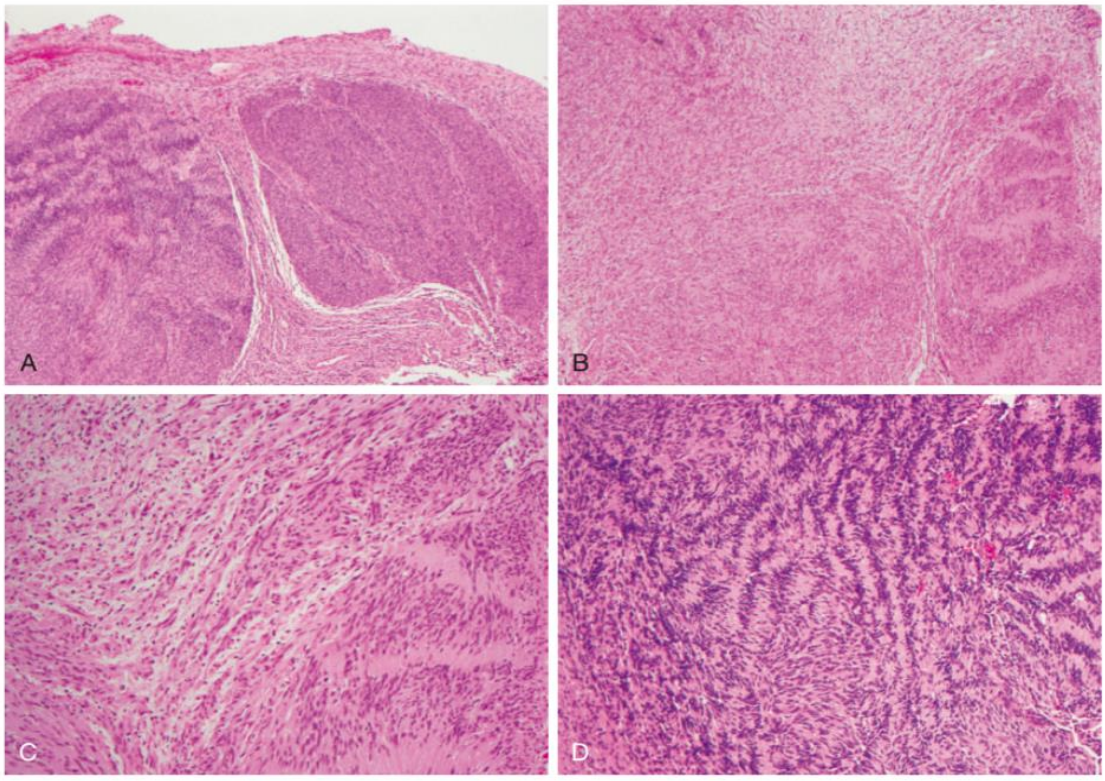


FIGURE A - shows thick collagenous capsule, B and C show juxtaposition of both Antoni A and B areas.D shows Verocay body rich schwannomas.

The inferior division of the vestibular nerve is the origin in 90 % of the cases. The qualities of the VS that they are well circumscribed and that they splay the nerve fibres rather than invade them differentiate them from neuromas. In gross appearance, they are firm, rubbery tumours, greyish yellow with foci of microhemorrhage and cyst formation. Under the microscope, the neoplastic Schwann cells arrange themselves in two discrete patterns - cells with compact spindle cells with elongated nuclei and pink cytoplasm,

Antoni A tissue. Verocay bodies which consist of palisading nuclei and cell bodies arranged alternatively occur in the above tissue. Antoni B tissue on the other hand consist of loosely arranged cells which are prone to micro cyst formation. Immunohistochemistry shows positive nuclear staining for Vimentin and S 100. (1, 18)

The extremely small subset of malignant VS exist only as sporadic case reports.

CLINICAL PRESENTATION

The vestibular division of the VIII cranial nerve gives rise to VS. They appear initially within the IAC - Internal Auditory Canal. Slow growing nature leads to IAC enlargement and then erosion of the posterior lip of the Porus acousticus.

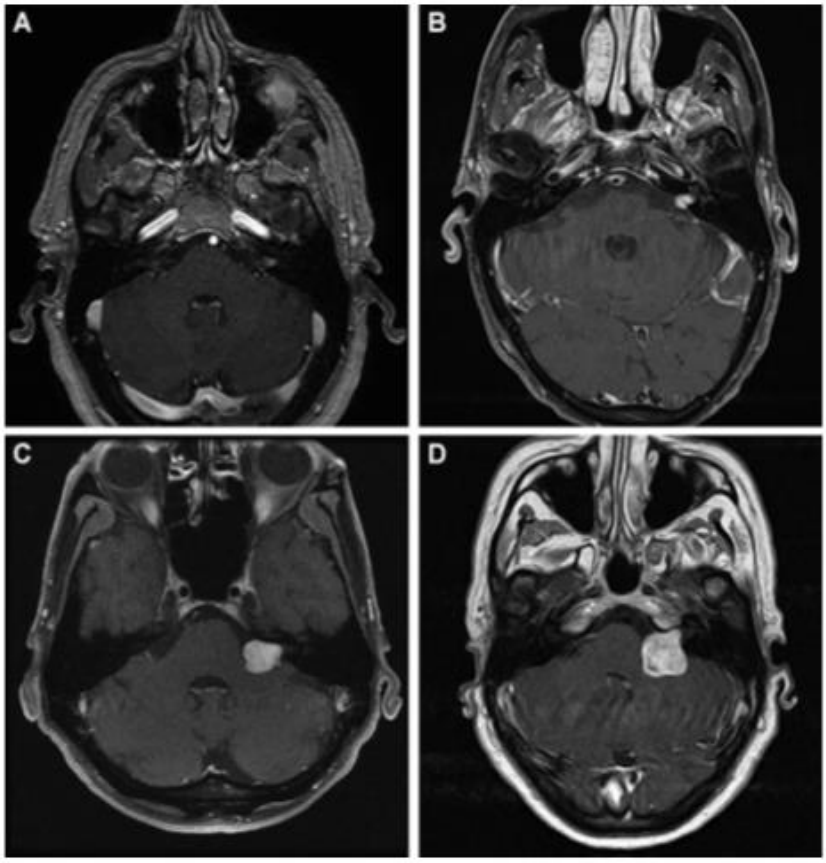
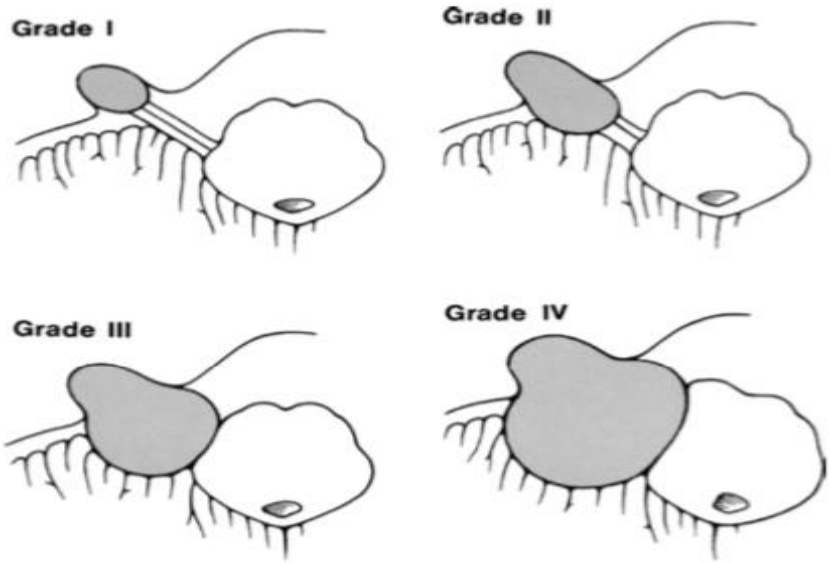


FIGURE - Koos Grade I (A), II(B) , III (C) and IV (D**)**



KOOS GRADE	DESCRIPTION
I	Small intracanalicular tumour
II	Small tumour with protrusion into the CPA, no contact with brainstem
III	Tumour occupying the cerebellopontine cistern with no brains displacement
IV	Large tumour with brainstem and cranial nerve displacement

FIGURE - KOOS GRADING SYSTEM Wolfgang T Koos et al described this classification system for VS based on radiological features. Though simple, it has the advantages of having decreased interrater variability. A study in 2013 found that with each increase in Koos grade, the volume of the tumour doubled or tripled and also within each Koos Grade, volumes varied widely.

Other grading systems include Hannover grading system (1,2, 24)

HANNOVER GRADE	DESCRIPTION
T 1	Purely intrameatal
T 2	Intra extrameatal
T 3 a	Filling the cerebellopontine cistern
T3 b	Reaching the Brainstem
T 4 a	Compressing the Brainstem
T 4 b	Severely dislocating the brainstem and compressing fourth ventricle

TABLE - clinical presentation of vestibular schwannomas

SYMPTOM	INCIDENCE in %
Hearing Loss	90
Tinnitus	70
Dysequilibrium	20
Trigeminal Nerve Dysfunction	33 - 71
Facial Nerve Dysfunction	10
Hydrocephalus	4
Headache	43

The commonest and the earliest symptom for which the patient seeks medical care is hearing loss. The irritation of the vestibular and cochlear divisions initially lead to episodic symptoms.

The gradual progression, episodic nature of the symptoms in the initial stages and poor health seeking behaviour of the Indian population leads to late presentation being very common in this part of the world.

The incidence of long tract signs in Vestibular schwannoma in older series is around 10 % due to the increased proportion of giant vestibular schwannomas at diagnosis. The reported incidence in western series is nearly negligible because of the initial size at diagnosis of the tumours. (2 - 4)

Gardner-Robertson Modified Hearing Classification

Grade	Pure-Tone Average (dB)	Speech Discrimination (%)
I: Good-excellent	0-30	70-100
II: Serviceable	31-50	50-69
III: Nonserviceable	51-90	5-49
IV: Poor	91-maximum	1-4
V: None	Not testable	0

American Academy of Otolaryngology–Head and Neck Surgery Hearing Classification

Class	Pure-Tone Average (dB)	Speech Discrimination (%)
A: Useful	≤30 and	≥70
B: Useful	>30 and ≥50 and	≥50
C: Capable of aid	>50 and	≥50
D: Nonfunctional	Any level	<50

FIGURE - HEARING LOSS GRADING

RADIOLOGICAL FEATURES

Computed Tomography (CT) shows most often widening and sometimes erosion of the IAM. Solid areas are usually isodense and calcifications are usually not seen. On MRI - mostly T 1 hypo intense or sometimes T 1 isointense lesions. T 2 is heterogeneously hyperintense with interspersed cystic areas if present. Post contrast imaging shows avid contrast enhancement. Most VS have an intracanalicular component - with resulting Trumpeted Internal Acoustic Meatus IAM sign; ice cream cone appearance. Larger tumours most often have cystic degeneration.

Differential diagnosis include other CPA lesions like meningiomas and epidermoid cysts. Meningiomas have calcification, dural tailing and hyperostosis of the underlying bone. Epidermoid cysts are usually iso intense lesions and not contrast enhancing. Schwannomas of the other adjacent cranial nerves, vascular lesions like aneurysms, vertebrobasilar dolichoectasia and metastasis are other common differential diagnosis.

MANAGEMENT OF VESTIBULAR SCHWANNOMAS

Over the last 20 years, oncologic control and quality of life were the most important goals, until recently where preservation of hearing and facial nerve function have assumed more importance. Apure-tone average of 50 dB or less and a speech discrimination score of 50% or more is the definition of Serviceable hearing (referred to as the 50/50 rule). (25 - 28)

In patients with an incidentally found VS, Hoa and associates after extensive review of literature put forth an evidence- based guideline (level III evidence):

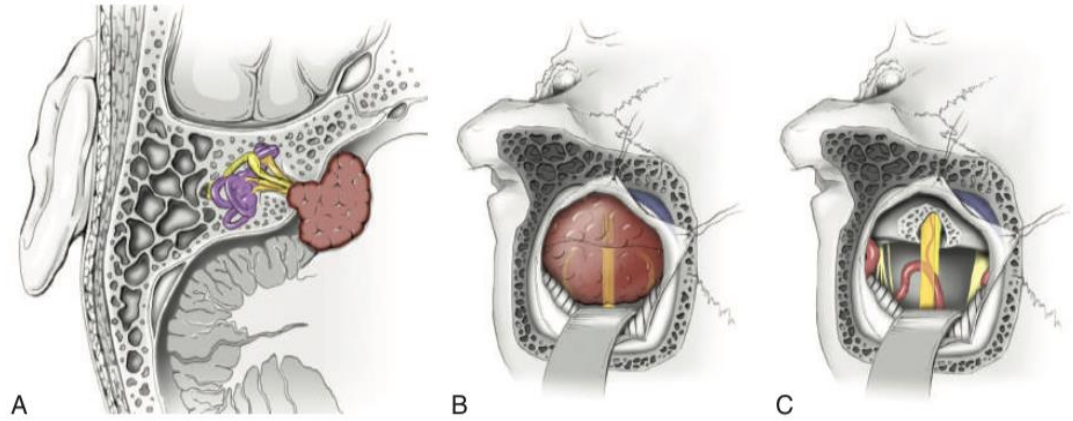
- Around two thirds of tumors do not grow during a 5-year observation period. Using a volume-doubling time model, Varughese and colleagues demonstrated prospectively that a 5-year cutoff is adequate to distinguish growing from nongrowing tumors.
- Growth within the first year may warrant early intervention.
- Approximately 50% of patients maintain "good" hearing at 5 years' observation.
- "Good" hearing is defined as a speech discrimination score of 70% or greater.
- Larger initial tumor size may predict future tumor growth.
- Large tumor size is defined as larger than 1.5 to 2.0 cm.
- Initial hearing loss may predict a greater chance of loss of good hearing over time.
- Poor prognostic signs for hearing preservation include the following:

  • Abnormal auditory brainstem response latency • Inferior vestibular nerve origin

  • Fundus opacification by tumor

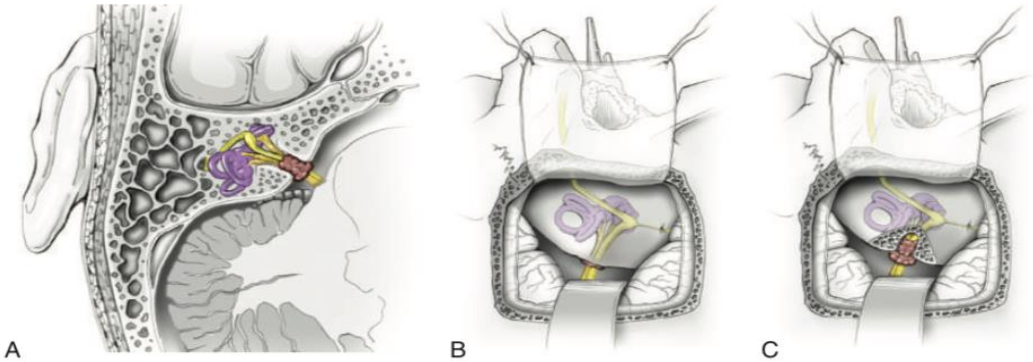
SURGICAL APPROACHES

The tumour size, extent of the cisternal involvement and the base line hearing function are the most important factors that help in deciding an ideal approach for the patient.

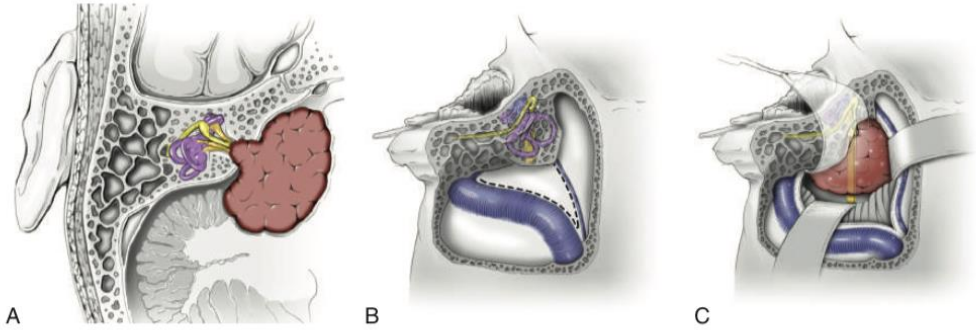


Retrosigmoid (RS) approach. A, The RS approach is used primarily for medium to large tumors with a predominantly cisternal component. Often the most familiar approach to neurosurgeons, the RS approach affords an excellent view of the posterior cranial fossa contents, including the interface between the tumor and cerebellum/brainstem. **B,** A suboccipital craniotomy is performed medial to the sigmoid sinus, including exposure of the sigmoid and transverse sinuses and their junction. **C,** The posterior wall of the porus can be drilled to expose the internal auditory canal. *(Copyright Michael Gallagher, Department of Neurological Surgery, Northwestern Memorial Hospital, Chicago, IL.)*

The most common and routinely performed approach is the retrosigmoid approach. It provides good exposure of the tumour and the adjacent cranial nerves which help in safe and complete resection in most cases.



Middle cranial fossa (MCF) approach. A, The MCF approach is typically employed for small tumors with a primarily canalicular component in the setting of preserved hearing. Because the MCF approach limits the exposure of the posterior cranial fossa and requires temporal lobe retraction, it is not well suited for tumors with a large cisternal component. After the temporal craniotomy has been performed (**B**), the MCF approach allows for exposure of the internal auditory canal from the porus to the fundus through the superior aspect of the petrous temporal bone (**C**). *(Copyright Michael Gallagher, Department of Neurological Surgery, Northwestern Memorial Hospital, Chicago, IL.)*



Translabyrinthine (TL) approach. A, The TL approach is best suited for large tumors with significant cisternal and canalicular components in the setting of absent hearing. The TL approach allows access to the internal auditory canal and the cerebellopontine angle without cerebellar retraction, at the expense of sacrificing the labyrinth and hearing. **B,** The TL approach is performed by exposing Trautmann's triangle (between the bony labyrinth laterally, the sigmoid sinus medially, and the dura covering the superior petrosal sinus superiorly). **C,** The exposure is further expanded by drilling the bony labyrinth and gently retracting the sigmoid sinus medially. *(Copyright Michael Gallagher, Department of Neurological Surgery, Northwestern Memorial Hospital, Chicago, IL.)*

DIFFUSION TENSOR IMAGING

The introduction of MRI into clinical use in the 1980's revolutionised the field of imaging in medicine. Neurosurgery, a previously a harsh and difficult terrain became little amenable when we could glance what is inside our heads and it was never the same again. Through the last three and half decades, the better understanding, maturation and subsequent evolution of MRI lead to developments of new sequences. When we realised that unique and clinically relevant information pertaining to the architecture and microstructural organisation of the brain could be obtained non invasively without any need of external contrast agents, merely by measurement of the diffusion properties of the neural tissue, the field of MR diffusion imaging blossomed into existence. (55- 58)

Water is ubiquitous and forms of most of what we call as ourselves. Invasive tracers exogenously administered used the Fick's law of diffusion to determine the diffusion of metabolites in the brain.

Brownian motion on the other hand is a probabilistic model for the prediction of aggregate behaviour of molecules. The displacement and distribution and the probability of finding a molecule with respect to a previous time and place is analysed and in this case water molecules.

The distinction of Brownian motion versus the Fickian principle carries importance because the former makes it possible to study molecular diffusion coefficients without the exogenous use of tracers. This forms the basis for the understanding of Nuclear Magnetic resonance and Diffusion MRI. Erwin Hahn described the interaction of molecular diffusion and NMR signals. The possibility of the precise measurement of self diffusion co efficient of solvents, namely water was the key in making this possible. The next step in the evolution of this method was the use of pulsed field gradient methodology. (60)

Tanner proposed the concept of apparent diffusion coefficient (ADC) to replace self diffusivity to describe the interaction in complex media.

Lauterbur conceived this concept in 1973 but only in 1985, it came into clinical use. (54-60)

To sum up, the blending of diffusion gradient pulses within the so called “conventional” MRI sequence gave birth to Diffusion Weighted Images (DWI). It is basically a one dimensional technique and is a cumulative measure of the projection of the displacement of molecules. In isotropic tissue like the grey matter of the brain, it is orientation independent. But in anisotropic tissue like muscle and more importantly the white matter of the brain, the apparent diffusion tensor of water characterises the orientation; its

measurement and analysis within each voxel of information is called Diffusion Tensor Imaging (DTI).

A diffusion ellipsoid is formed by the root- mean - squared values of displacement. In isotropic media, its shape is spherical; whereas in anisotropic media, it is either prolate or oblate and we get the Eigen vectors namely λ_1 , λ_2 and λ_3 in the three principal directions.

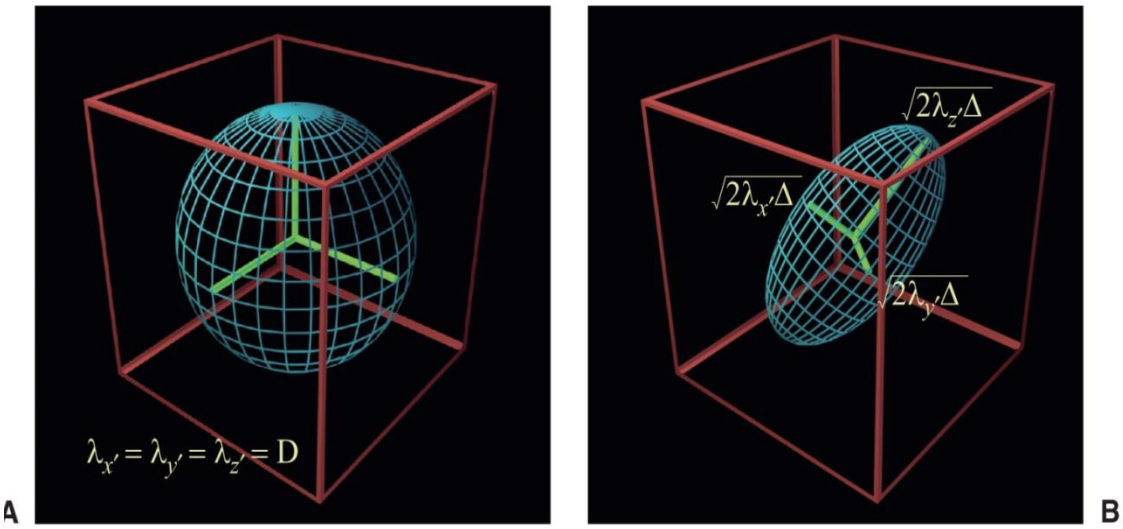


FIGURE - A - The root mean squared displacement of the diffusion ellipsoid is spherical B - In anisotropic media, the diffusion ellipsoid is either prolate or oblate, its three principal directions are coincidental with the eigenvectors of Diffusion Tensor D.

Depending on the size, shape, orientation and distribution of patterns within the imaging volume, new quantitative scalar parameters are provided - the above mentioned eigenvectors.

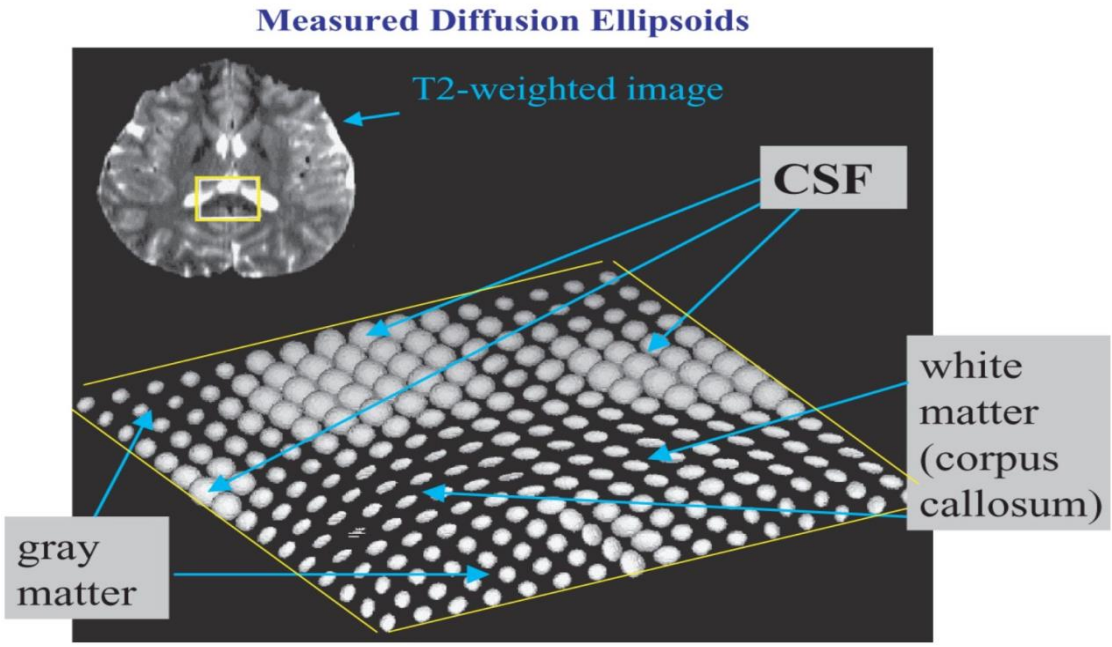


FIGURE - T 2 weighted axial image - region of interest (ROI) encompassing the posterior corpus callosum and the lateral ventricles. A diffusion ellipsoid image constructed from each voxel within the ROI shows the size, shape and orientation of the diffusion ellipsoid. CSF is clearly depicted by large spherical ellipsoids in which diffusion is free and isotropic. Grey matter is depicted by smaller ellipsoids, indicating its isotropic nature but lower mean diffusivity than the CSF. White matter is indicated by prolate diffusion ellipsoids whole polar axis is aligned with the purported white matter fibre direction in the corpus callosum.

The quantitative scalar parameters, the previously described eigenvalues - λ_1 , λ_2 and λ_3 are useful in defining the size and shape of the diffusion ellipsoid.

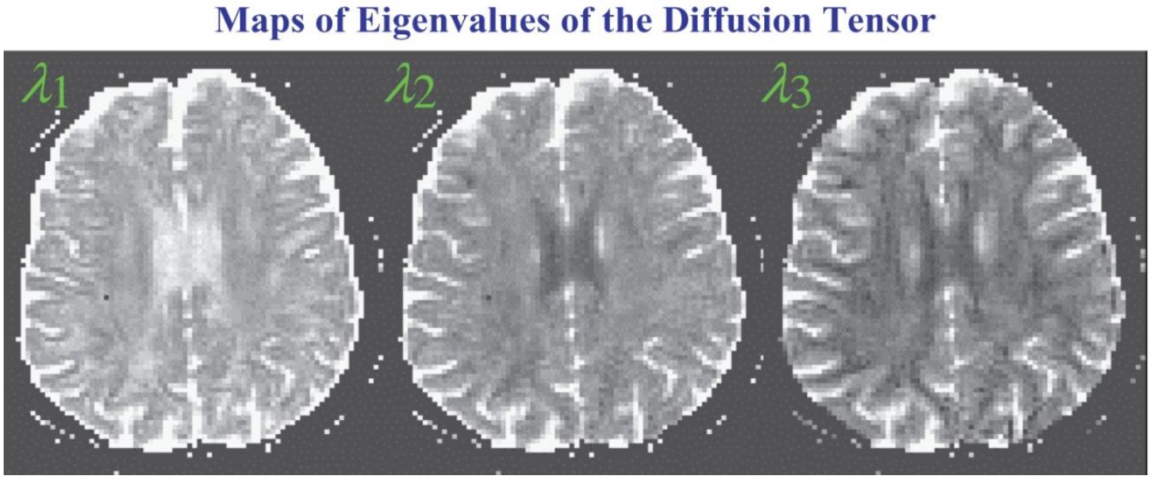


FIGURE - Images or maps of three sorted Eigenvalues - λ_1 , λ_2 and λ_3. Different regions of the brain can be distinguished by examining these images. CSF - cerebrospinal fluid is uniformly bright in all these three images, indicating that diffusion is isotropic and high there. Gray matter regions are nearly uniform in brightness, whereas white matter regions, like the corpus callous at the centre, is bright in the λ_1, but dark in the λ_2 and λ_3 images, indicating significant diffusion anisotropy there.

In order to characterise the orientation of the diffusion ellipsoids and their directional pattern, Direction encoded colour mapping (DEC) mapping, in which the local fibre tract direction is indicated by colour coding given to each voxel within.

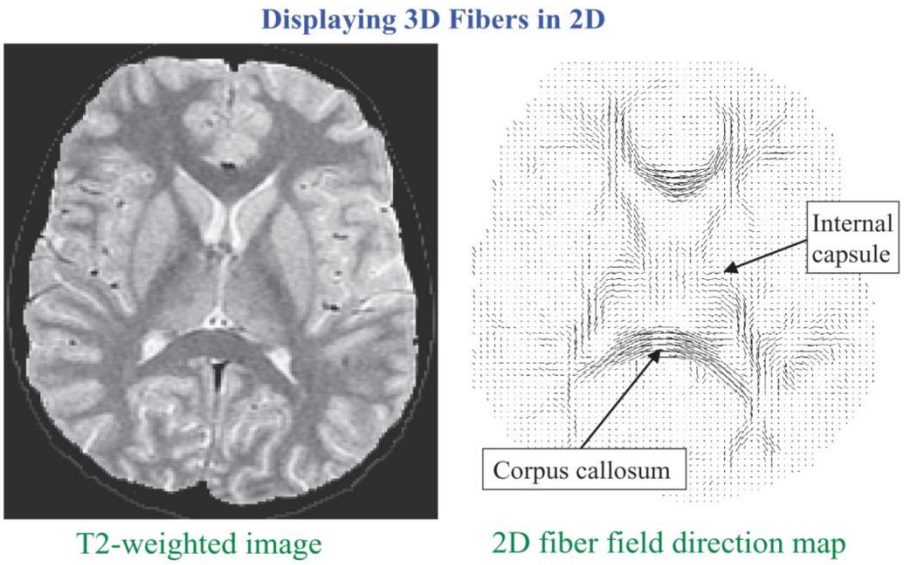


FIGURE - Fibres lying in the plane of the image such as corpus callous are well depicted, whereas fibres running perpendicular to the image such as internal capsule are difficult to discern.

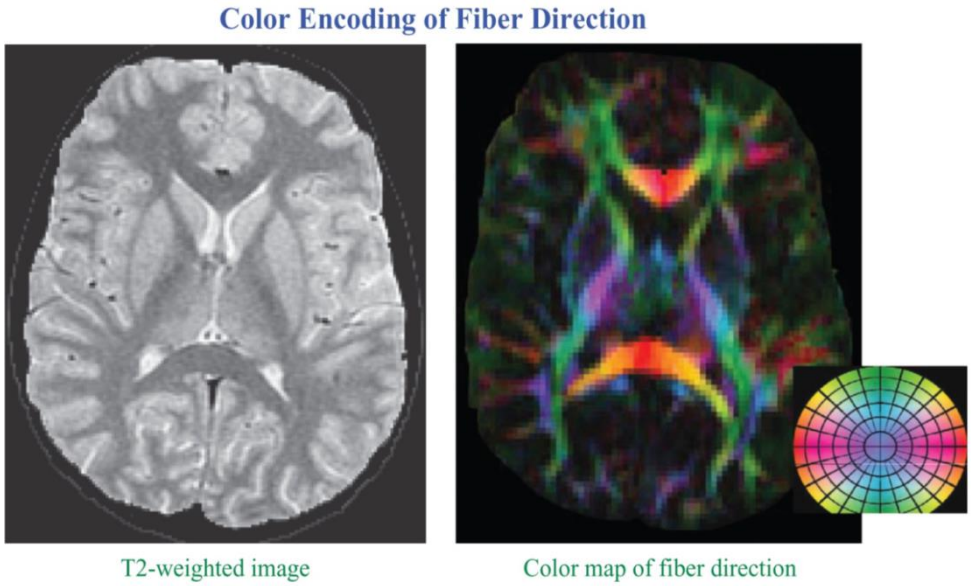


FIGURE - Direction encoded colour map of the same slice as the previous image. Orientation of the fibres is shown in the colour wheel in the legend.

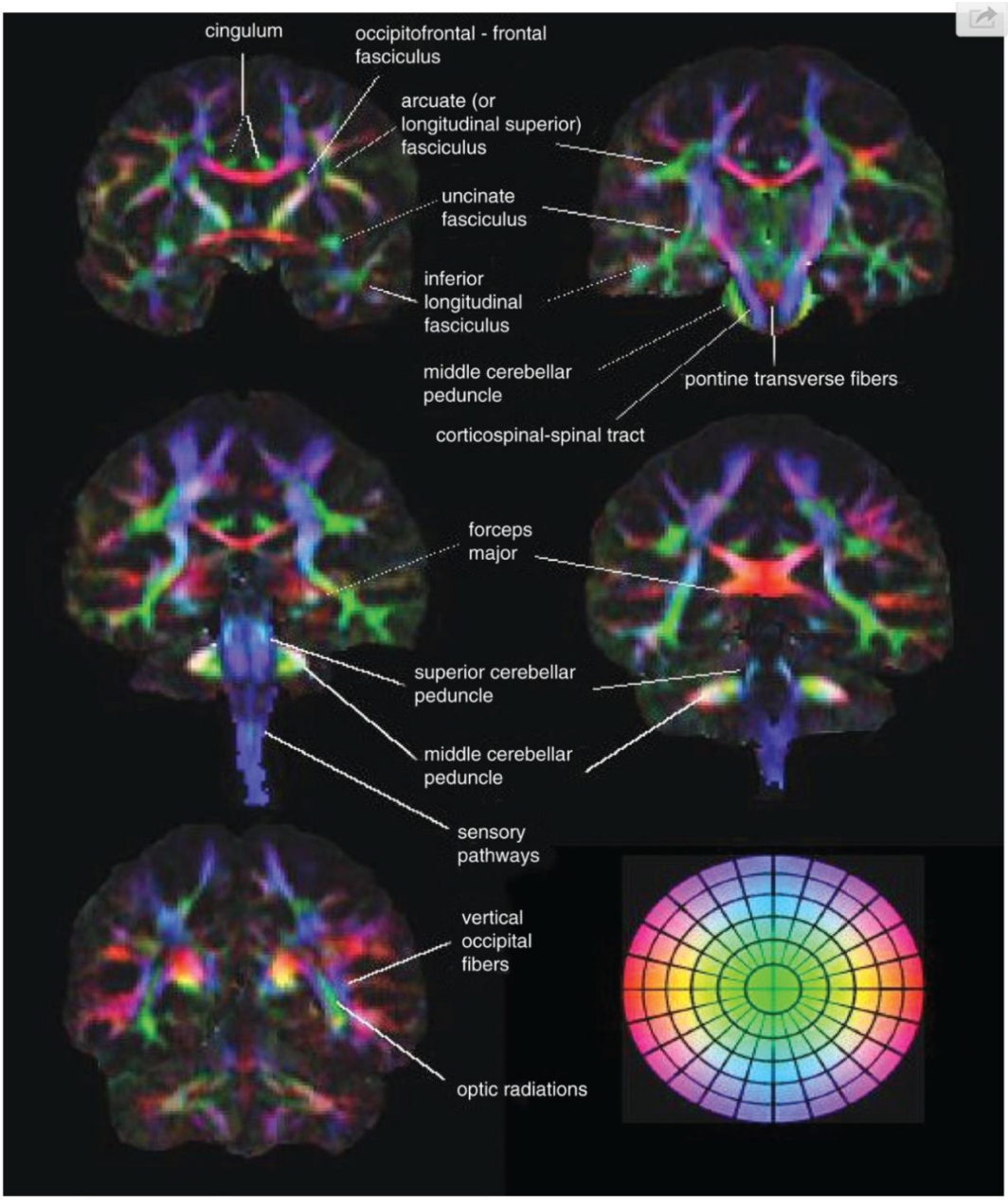


FIGURE - This direction encoded colour map allows us to identify major association, commissural and projection pathways in the brain

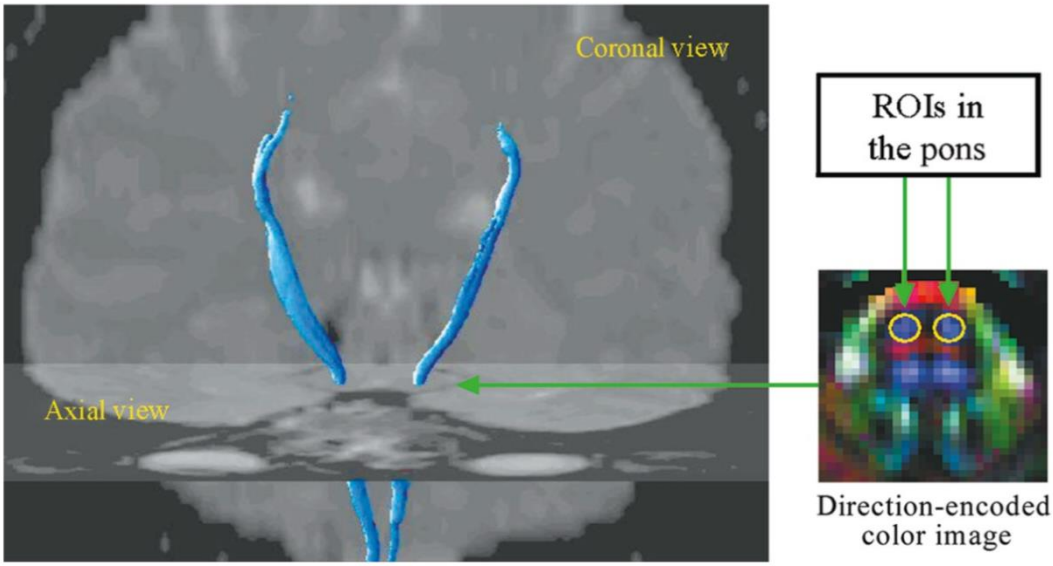


FIGURE - The ROIs are chosen in the pons and the pyramidal tracts are reconstructed by launching trajectories in both directions.

DWI ARTEFACTS

The quality of the DWI image and hence the subsequent analysis could be compromised by means of artefacts. Subject motion artefacts during image acquisition in the MR scanner leads to artifactual distortion and redistribution of the signal intensities. Rigid body motion artefacts such as translation or rotation are easier to correct for whereas non rigid body motion artefacts namely rapid eye movements, CSF pulsations… are more difficult to rectify. Some of these artefacts could be reduced by using echo - planar DWI sequences and cardiac gating.

During the diffusion sequence, the gradient coils produce large and rapidly switching magnetic field. This induced Eddy currents in the electrically conductive structures of the scanner which in turn produces a slow decaying magnetic field. This has to be accounted for during the analysis of the data image set.

DTI IN VESTIBULAR SCHWANNOMAS

In a study comparing the objective DTI parameters of posterior fossa tumours and their association motor weakness and outcome, Lui et al concluded that well circumscribed Intra axial primary posterior fossa tumours, higher mean diffusivity and lower Fractional Anisotropy in the adjacent Corticospinal tract are associated with contralateral motor deficits. But the study included only the primary intra axial tumours of the posterior fossa.

When it comes to extra axial tumours like vestibular schwannomas, Koos Grade IV tumours cause brainstem compression and hence mass effect on the long tracts especially the Corticospinal Tract. But the incidence of Long tract signs namely Increased tone, spasticity of the limbs, Upper motor neurone type weakness, loss of posterior column sensations like fine touch, vibration, proprioception and joint position sense, have not been routinely touched upon by the western literature. This is partly due to the early detection leading to smaller mean size at diagnosis. This is still not the case in many Indian neurosurgery institutions, where patients tend to present late due to various factors.

MATERIALS AND METHODS

AIM

We hope to define the size beyond which subclinical long tract involvement which occur in vestibular schwannomas could be picked up. Diffusion tensor imaging is used to objectively correlate the involvement of long tracts. This will give a better understanding of the behaviour of vestibular schwannomas and their response to surgery.

To add on to the understanding of evolution in the natural history of vestibular schwannomas. To look for correlation between volume of the tumour and the change in DTI metrics.

DESIGN:

Prospective Hospital based observational study of newly diagnosed patients with vestibular schwannomas, in the Neurorsurgery Department of Sree Chitra Institute of Medical Sciences and Technology (SCTIMST). A formal clearance was obtained after the evaluation of the study by the Institute Ethics Committee (IEC).

DURATION OF THE STUDY: 1.5 years

FUNDING: There were neither external sources of funding nor conflicts of interest in the current study

ETHICAL COMMITTEE CLEARANCE - The stud protocol was presented to the SCTIMST ethical committee and scrutinised at various angles regarding the aim of the study and the safety of the patients involved in it. The study was started after the formal clearance from the IEC.

SUBJECT /PARTICIPANT SELECTION:

All patients diagnosed with vestibular schwannoma and worked up for surgery by the PI and through this approach and consenting for the study will be included in the study.

NUMBER:

After analysing the routine previous statistics of the Neurorsurgery Department of Sree Chitra Institute of Medical Sciences and Technology (SCTIMST), an arbitrary sample size number of 30 consecutive patients was fixed. This being a descriptive and observational study, the maximum number of samples that could be taken within the stipulated study duration of 1.5 years were included.

ELIGIBILITY:

Inclusion criteria: All patients aged more than 18 years of age, newly diagnosed with vestibular schwannoma in electively operated for vestibular schwannoma. Since the study involved analysing long tract signs which occur due to compression of the brainstem by the tumour, only Koos Grade IV tumours were included in the study. It may not be relevant to analyse smaller tumours due to obvious reasons.

Exclusion criteria:

1. Patients undergoing a Redo surgery
2. Patients who did not consent for the study
3. Less than 18 years of age

INFORMED CONSENT - After fulfilling the inclusion criteria, the patients were fully informed about the study and consent was taken in their own language. The decision to participate in the study was purely voluntary. It was clearly explained to the patients that the treatment options would not undergo any change. The patient's decision whether to participate or not participate in the current study will in no way affect the management of the disease, which was also made very clear to the subjects. Written consent was taken either in English or the local language Malayalam.

MATERIALS AND METHODS

Consecutive patients electively operated by the PI through this approach and consenting will be subjected to this study. Patients will be evaluated and imaged via MRI sequences as per standard protocol.

Available CT imaging shall be reconstructed for the study for assessment of tumour volume. Detailed pro forma that is included as Annexure I will be filled and this includes preoperative clinical evaluation, audiometry, and imaging analysis.

Proforma Annexure II shall include observations during surgery such as involvement of lower cranial nerves, structures visualised, initially recorded through a dictaphone immediately during/ after the procedure and later written down.

This MRI imaging shall be processed with already available software, especially with respect to diffusion tensor imaging, for the study and objective values namely fractional anisotropy, mean diffusivity and transverse Eigen values (radial diffusivity) will be measured for the corticospinal tracts.

Proforma Annexure III will be filled during the immediate postoperative period prior to discharge from hospital which will include immediate complications and deficits.

There will be no additional imaging or cost burden to the patient. All reconstructions shall be done using in-house proprietary software and analysed by consultant neuroradiologist.

MRI ANALYSIS - The routine MRI images taken for preoperative planning were analysed. CISS 3D images or cube Flair images whichever is available were taken along with the 64 direction DTI data image set. Myriam software was used to import the data from the hospital PACS system for MRI analysis.

Nordic Brain Ex software which specialises in tractography and DTI parameters was used for the analysis. Ciss 3 D images were used as the structural frame work.

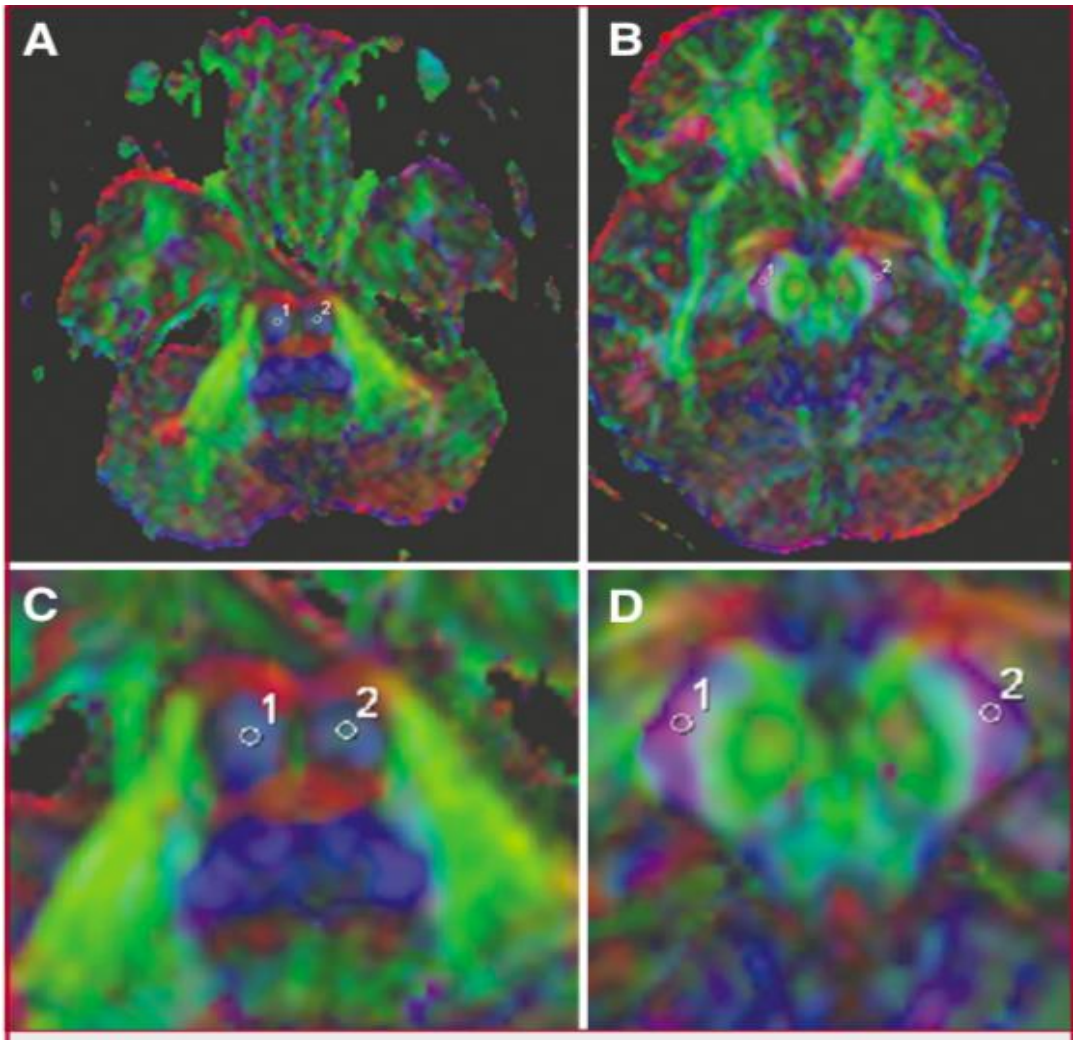


FIGURE 1. *FA color maps at two brainstem levels.* **A** *and* **B**, *nonmagnified views showing the pons (***A***) and midbrain (***B***) with regions of interest placed approximating the right (1) and left (2) corticospinal tracts at these levels.* **C** *and* **D**, *corresponding magnified views.*

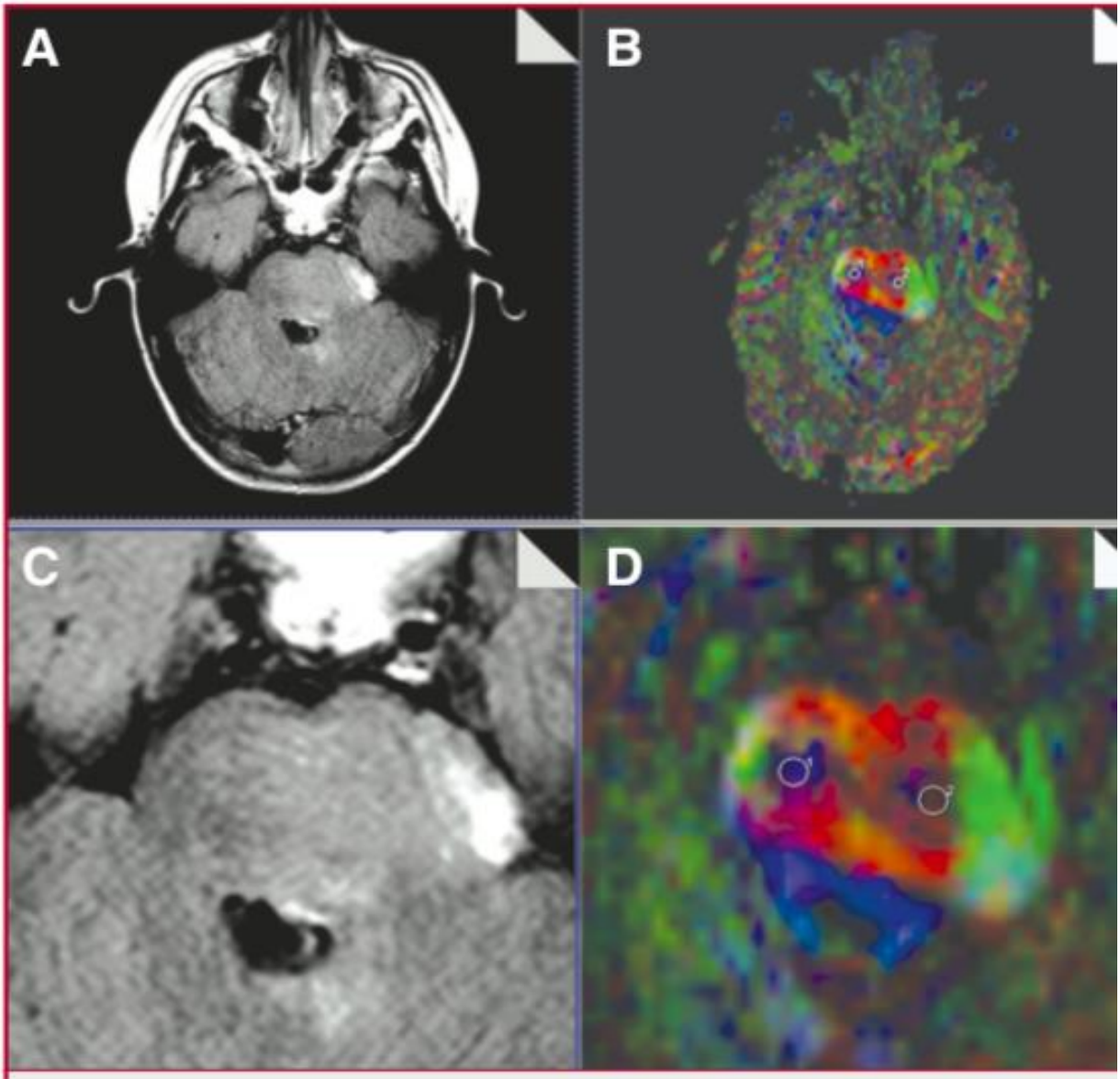


FIGURE 2. *Demonstration showing RO! placement in a patient with tumoral involvement of the region of the corticospinal tracts as seen in fluid attenuation inversion recovery (**A**) and FA color map (**B**) images. **C** and **D**, corresponding magnified views.*

DATA ANALYSIS:

There will be no mention of the patient's personal details with the names removed and the hospital number coded. Patient data will be comprehensively evaluated by Clinical parameters. Operative notes will be reviewed for types of lesions and subsequent approaches. The routine post operative MRI brain will be analysed with the in house proprietary software for dimensions. Clinical outcome with respect to any complications will be assessed from hospital data when the patient was indoor. PI and Co PI will assess the data. Standard Statistical analysis will be done from the data obtained from the Pro forma. Data will not be analysed to understand gender, caste, ethnicity and race differentials. This study will not involve any genetic analysis.

The statistical analysis were done with Software R - version 3.5.2.

Non parametric tests were used for analysis. Due to the small sample size, Spear man correlation was used to compare the volume of the tumor and the various DTI parameters.

Wilcoxon signed rank test was used to compare the difference between ipsilateral and contralateral tracts.

RESULTS

The study group consists of 20 patients, who have been diagnosed with vestibular schwannomas and planned for surgery. The mean age was around 49 years, with a minimum of 20 years and maximum of 67 years. There were 12 males and 8 females in the group. All the 20 patients had tumour size - extrameatal - more than 3 cm. Eight patients out of the above had giant vestibular schwannomas. Three of the 20 patients had Neurofibromatosis type 2, but the opposite side tumour was mostly cisternal and did not cause any compression on the brainstem. Three patients had signs of corticospinal tract involvement. The mean volume of the tumour was 19 ± 9.82 ml.

The volume of the tumour was plotted against the occurrence of corticospinal tract involvement which was present preoperatively and worsened post operatively. There was no evidence of any correlation.

The tumour volume was compared with various DTI metrics - namely - Eigen vector values - Lambda 1, 2 and 3, Fractional Anisotropy (FA), Mean Diffusivity (MD), Apparent Diffusion Coefficient (ADC), volumetric ratio (VR) , number of fibers and radial diffusivity (RD).

Usually the correlation coefficient of > 0.6 or < -0.6 is taken as significant. Since no significance definite correlation could be established in this data set; we had defined > 0.3 and < - 0.3 as a weak correlation.

POSITIVE	**NEGATIVE**
L 1 OF IPS MB	MD OF C/L PONS
L1 OF IPS PONS	ADC OF C/L PONS
L2 - 3 IPS PONS	MD OF C/L MB
L 2 - 3 C/L MB	ADC OF C/L MB

The DTI values of ipsilateral and contralateral pons and medulla were compared. No statistical correlation could be established.

RESULTS - Tables

Table 1: Age distribution of patients studied

Age in years	No. of patients	%
20-30	2	10.0
31-40	3	15.0
41-50	4	20.0
51-60	6	30.0
61-70	5	25.0
Total	20	100.0

Mean ± SD: 49.00±14.12

Table 2: Gender distribution of patients studied

Gender	No. of patients	%
Female	8	40.0
Male	12	60.0
Total	20	100.0

Table 3: Side

Side	No. of patients	%
Left	12	60.0
Right	8	40.0
Total	20	100.0

Table 4: R MB CST

R MB CST	Right side		Total	P value
	Ipsilateral	Contralateral		
FA	0.53±0.07	0.56±0.05	0.55±0.06	0.322
VR	641.63±405.04	562.50±388.52	594.15±386.54	0.666
ADC	88.63±12.02	82.33±11.57	84.85±11.86	0.256
ƛ 1	145.00±9.18	139.92±14.59	141.95±12.68	0.394
ƛ 2	70.13±14.64	63.00±10.95	65.85±12.70	0.228
ƛ 3	50.88±14.02	43.92±11.48	46.70±12.69	0.239
FIBRES	161.5±125.04	182.17±158.73	173.90±143.02	0.761
MD	88.67±12.01	82.28±11.48	84.83±11.82	0.247

Table 5: R MB CST

R MB CST	Right side		Total	P value
	Ipsilateral	Contralateral		
λ1 - λ3	94.13±8.97	96.00±8.49	95.25±8.50	0.642
λ1 - λ2	74.88±10.11	76.92±11.02	76.10±10.44	0.680
λ2 - λ3	19.25±2.43	19.08±3.70	19.15±3.18	0.912
RD	60.50±14.29	53.46±11.06	56.28±12.59	0.230

Table 6: R P CST

R P CST	Right Side		Total	P value
	Ipsilateral	Contralateral		
FA	0.54±0.06	0.58±0.04	0.56±0.05	0.100
VR	618.25±380.82	548.67±373.42	576.5±367.95	0.690
ADC	87.75±10.32	82.75±7.92	84.75±9.05	0.236
λ 1	144.38±10.89	143.08±10.67	143.60±10.49	0.795
λ 2	69.00±12.08	62.17±7.86	64.90±10.07	0.141
λ 3	49.25±11.00	42.58±7.84	45.25±9.56	0.130
FIBRES	262.88±217.65	138.92±139.50	188.50±180.56	0.136
MD	87.54±10.25	82.61±7.78	84.59±8.94	0.236

Table 7: R P CST

R P CST	Right Side		Total	P value
	Ipsilateral	Contralateral		
ƛ1 - ƛ3	95.13±9.40	100.50±7.42	98.35±8.47	0.170
ƛ1 - ƛ2	75.38±10.86	80.92±9.76	78.70±10.31	0.249
ƛ2 - ƛ3	19.75±2.38	19.58±4.08	19.65±3.42	0.918
RD	59.13±11.49	52.38±7.58	55.08±9.67	0.129

Table 8: L MB CST

L MB CST	Left side		Total	P value
	Contralateral	Ipsilateral		
FA	0.57±0.02	0.58±0.05	0.58±0.04	0.608
VR	669.13±434.74	585.25±398.91	618.80±404.39	0.662
ADC	78.00±4.11	81.25±5.80	79.95±5.33	0.188
ƛ 1	136.00±5.78	142.67±9.52	140.00±8.72	0.094+
ƛ 2	59.00±3.21	60.42±7.25	59.85±5.90	0.612
ƛ 3	39.38±4.44	40.58±6.13	40.10±5.42	0.638
FIBRES	250.13±159.51	190.42±133.07	214.30±143.27	0.375
MD	78.13±3.95	81.22±5.78	79.98±5.25	0.204

Table 9: L MB CST

L MB CST	Left side		Total	P value
	Contralateral	Ipsilateral		
ƛ1 - ƛ3	96.63±2.67	102.08±10.15	99.90±8.35	0.157
ƛ1 - ƛ2	77.00±5.40	82.25±11.02	80.15±9.38	0.230
ƛ2 - ƛ3	19.63±3.66	19.83±4.09	19.75±3.82	0.909
RD	49.19±3.41	50.50±6.40	49.98±5.33	0.603

Table 10: L P CST

L P CST	Left side		Total	P value
	Contralateral	Ipsilateral		
FA	0.54±0.06	0.58±0.05	0.56±0.05	0.101
VR	649.50±403.33	557.08±369	594.05±375.40	0.603
ADC	85.63±11.89	82.42±5.52	83.70±8.50	0.423
ƛ 1	140.75±9.53	143.17±8.84	142.20±8.95	0.568
ƛ 2	67.63±14.79	62.00±6.45	64.25±10.62	0.256
ƛ 3	48.63±12.99	41.75±6.03	44.50±9.76	0.126
FIBRES	165.25±97.87	175.58±116.58	171.45±106.89	0.839
MD	85.67±12.03	82.31±5.35	83.65±8.53	0.402

Table 11: L P CST

L P CST	Left side		Total	P value
	Contralateral	Ipsilateral		
λ1 - λ3	92.13±7.47	101.42±9.8	97.70±9.90	0.036*
λ1 - λ2	73.13±8.54	81.17±9.91	77.95±10.00	0.077+
λ2 - λ3	19.00±2.14	20.25±4.03	19.75±3.39	0.433
RD	58.13±13.88	51.88±5.91	54.38±10.05	0.180

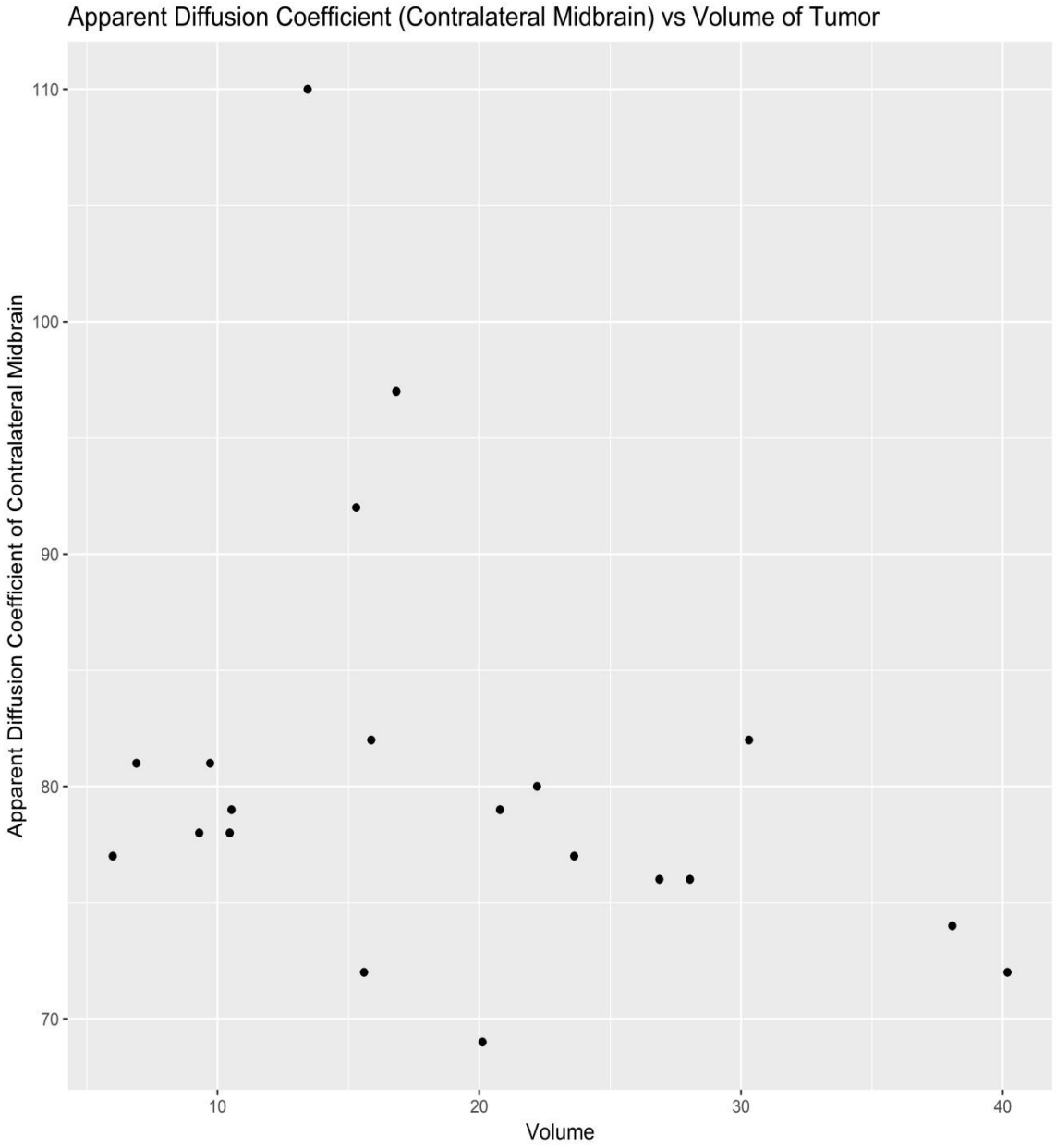
Table 12: Side

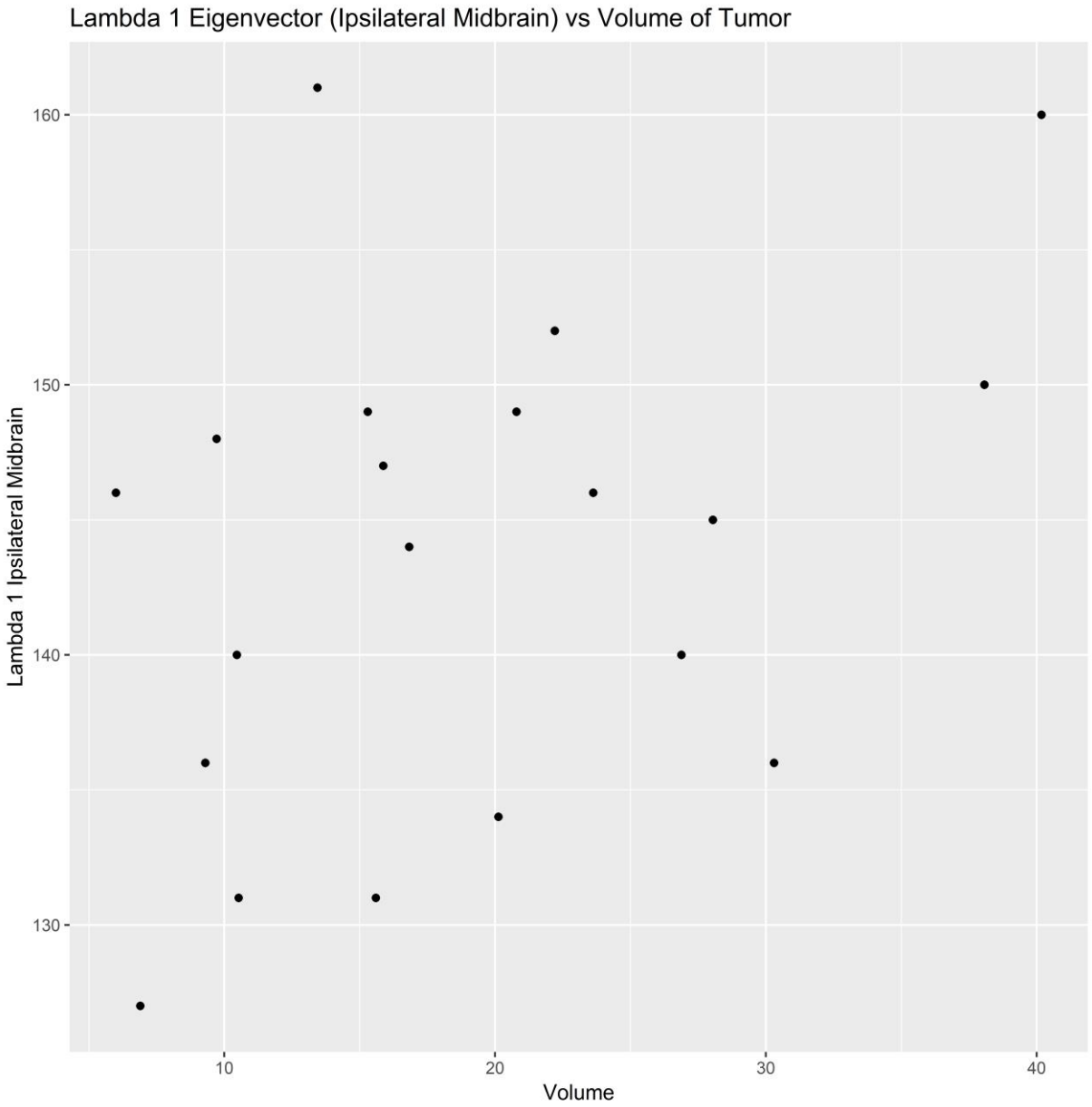
Side	No. of patients	%
Left	12	60.0
Right	8	40.0
Total	20	100.0

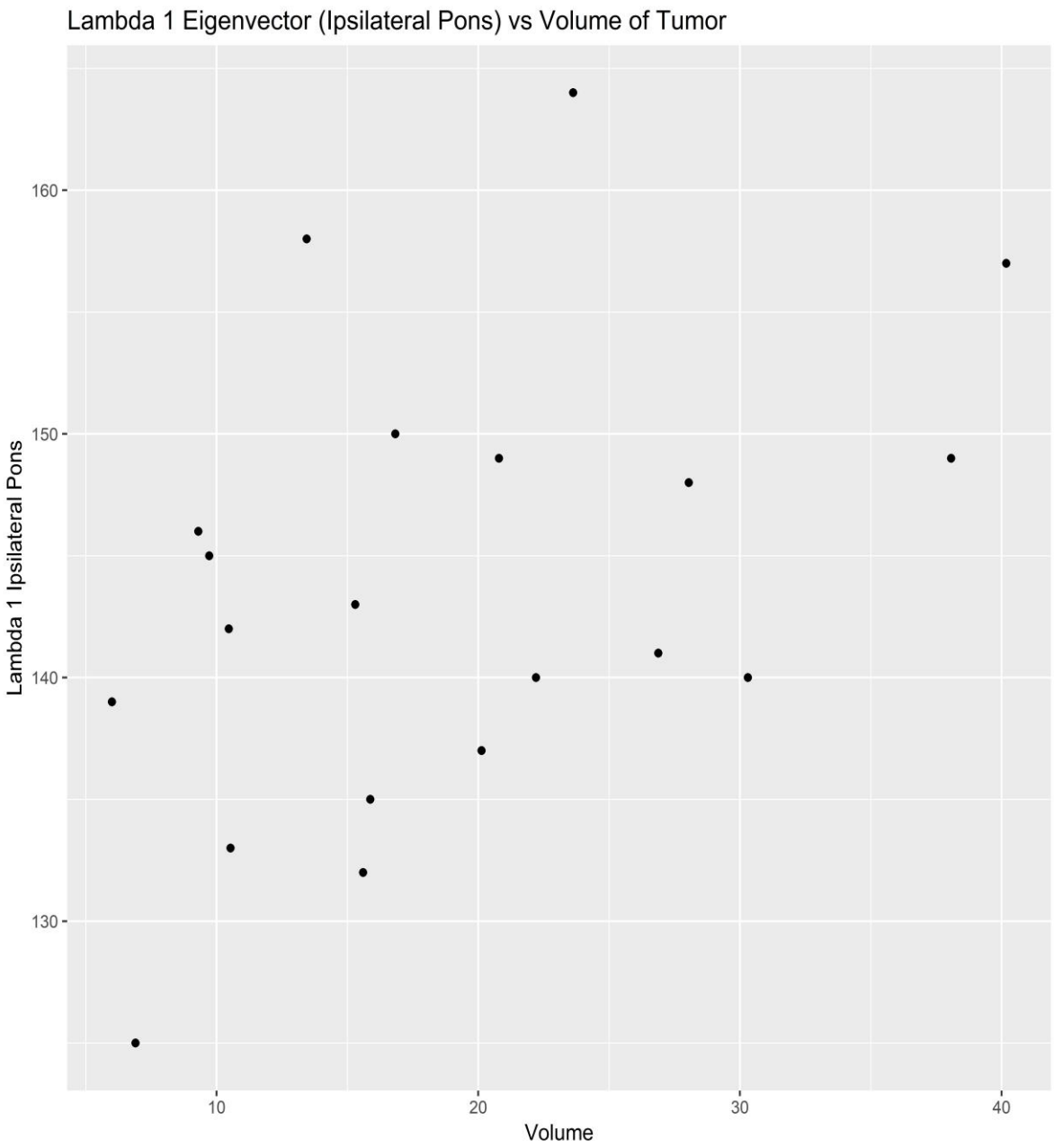
Table 13: Volume

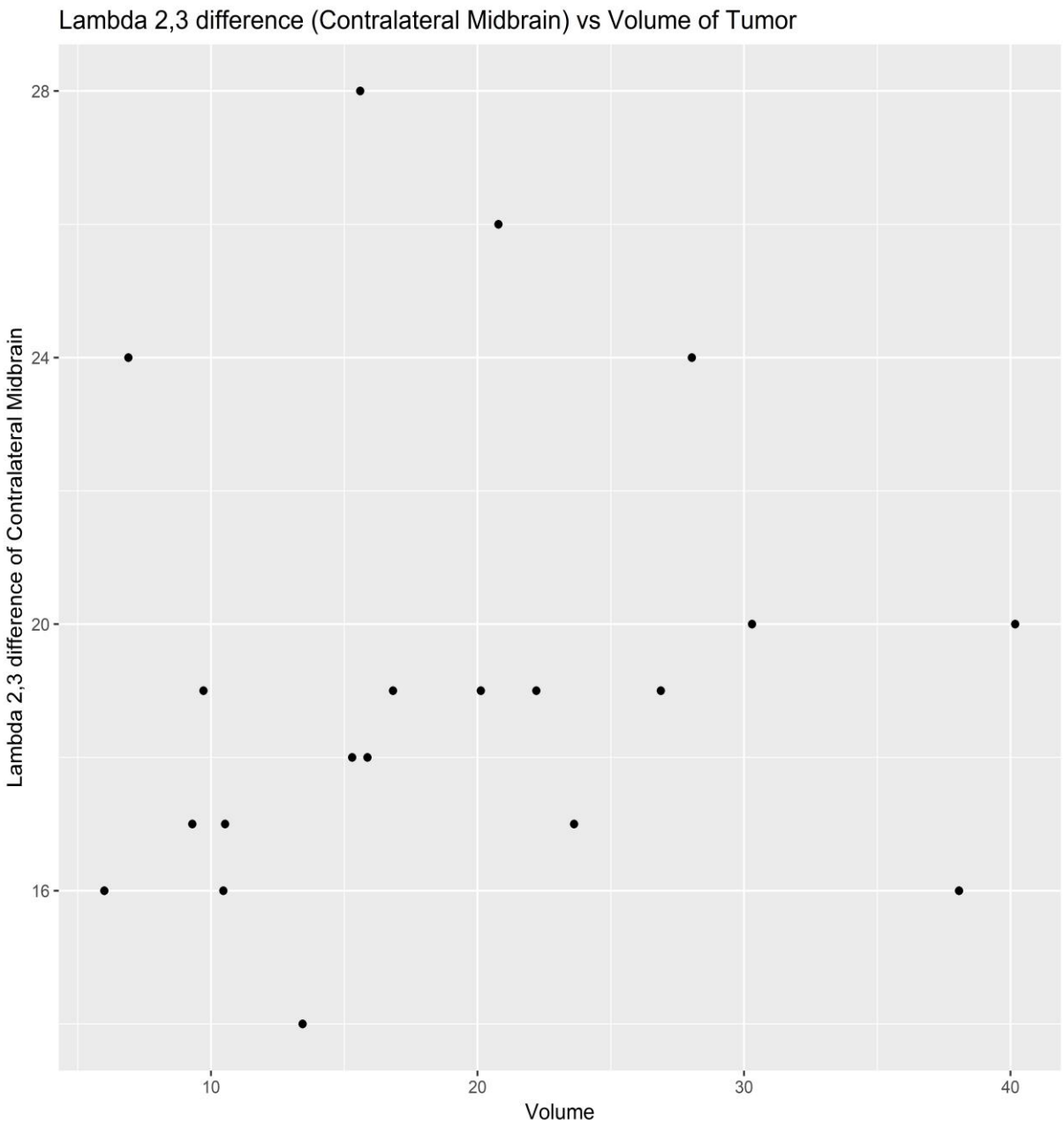
Volume	No. of patients	%
<15	7	35.0
15-30	10	50.0
>30	3	15.0
Total	20	100.0

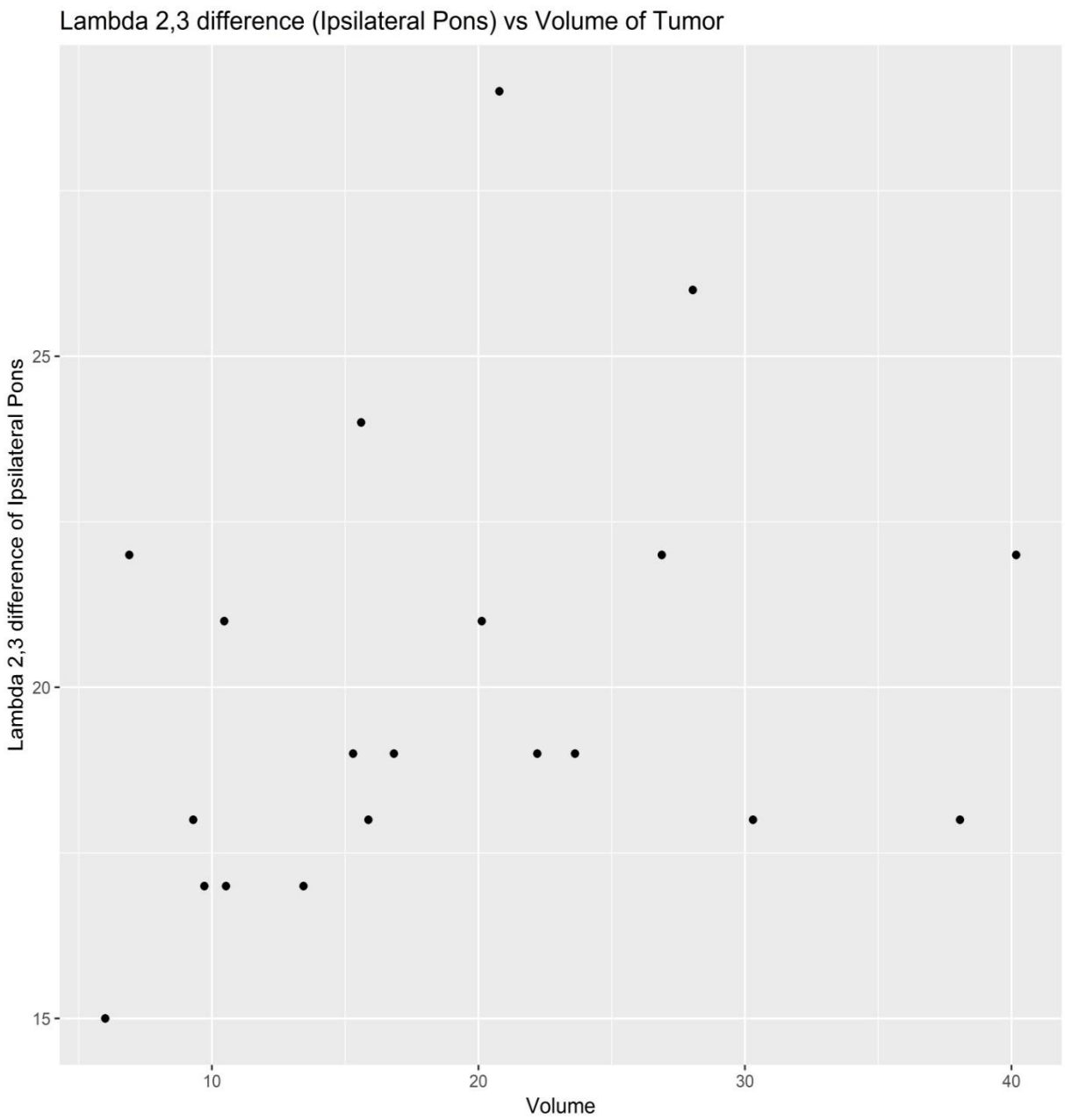
SCATTER PLOT DIAGRAMS

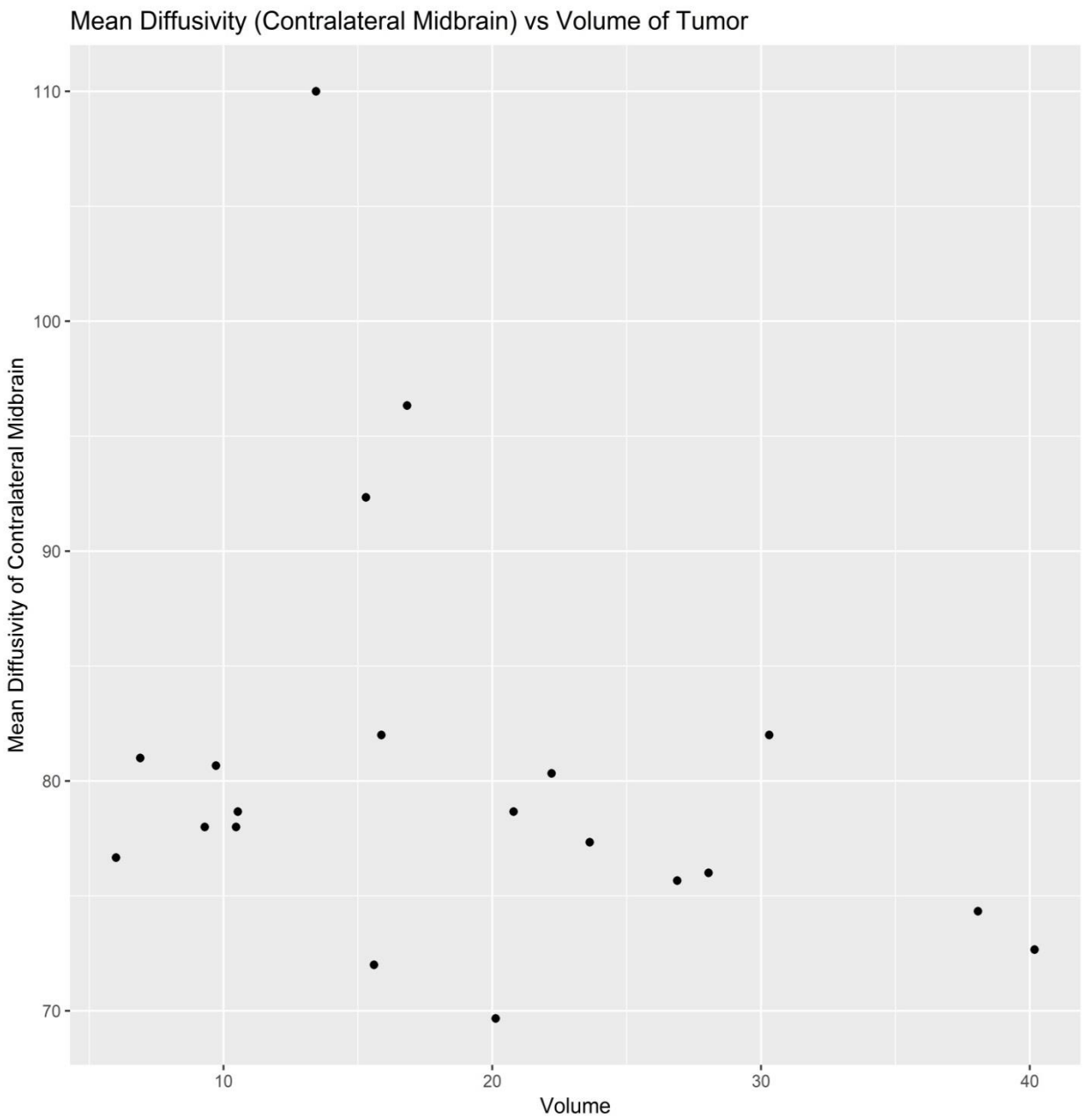


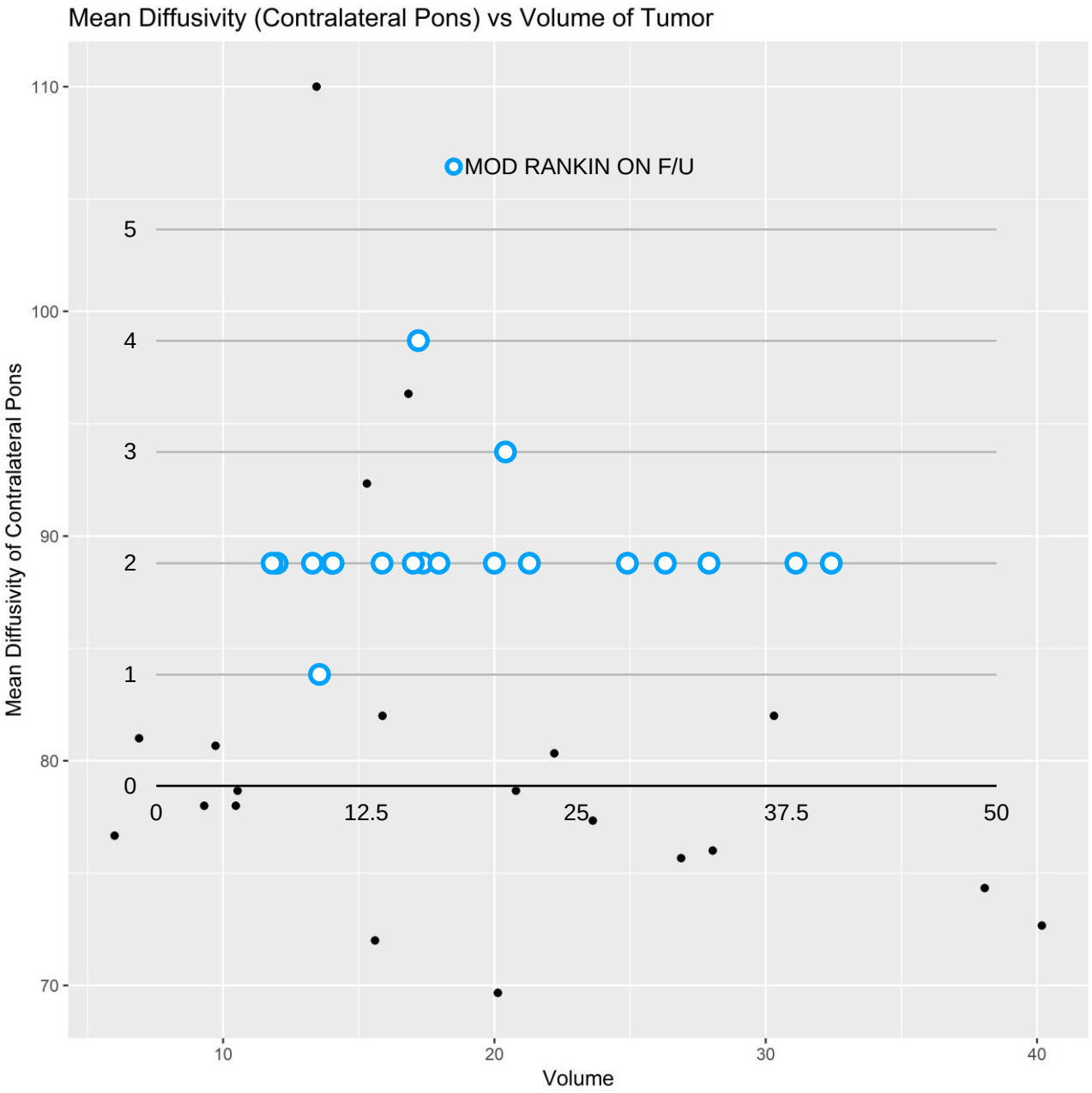

Lambda 1 Eigenvector (Ipsilateral Midbrain) vs Volume of Tumor
Lambda 1 Ipsilateral Midbrain
160
150
140
130
10
20
30
40
Volume

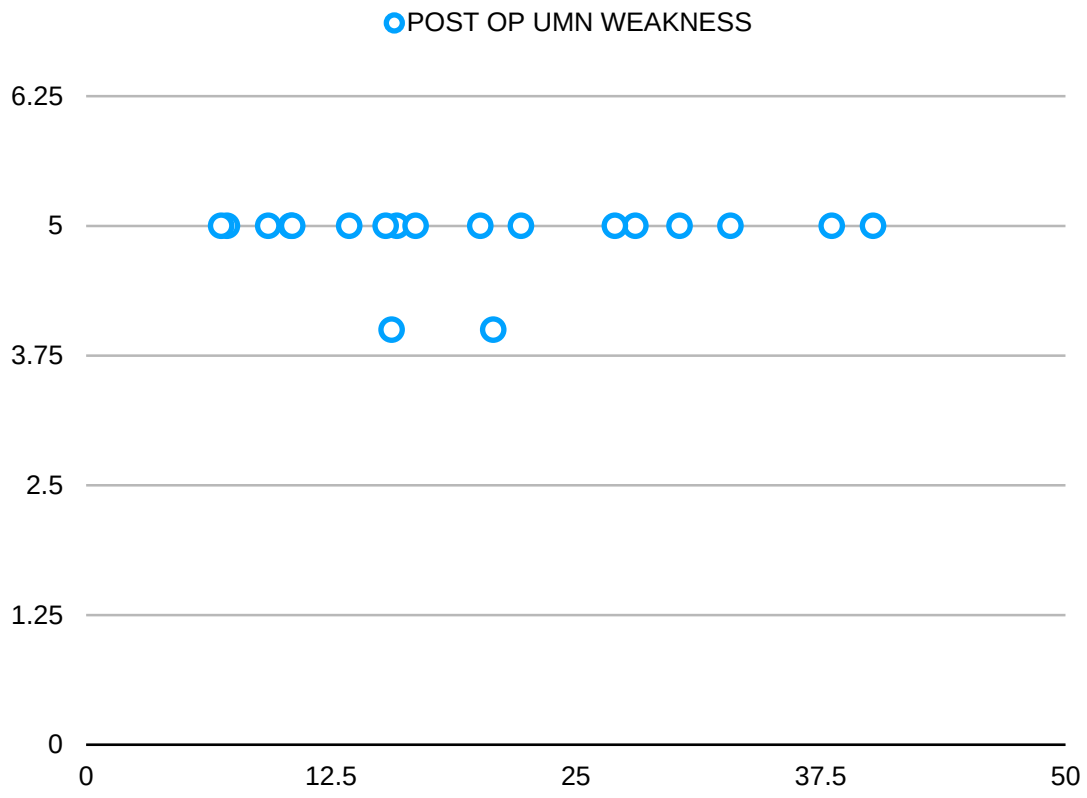

Lambda 1 Eigenvector (Ipsilateral Pons) vs Volume of Tumor
Lambda 1 Ipsilateral Pons
160
150
140
130
10
20
30
40
Volume

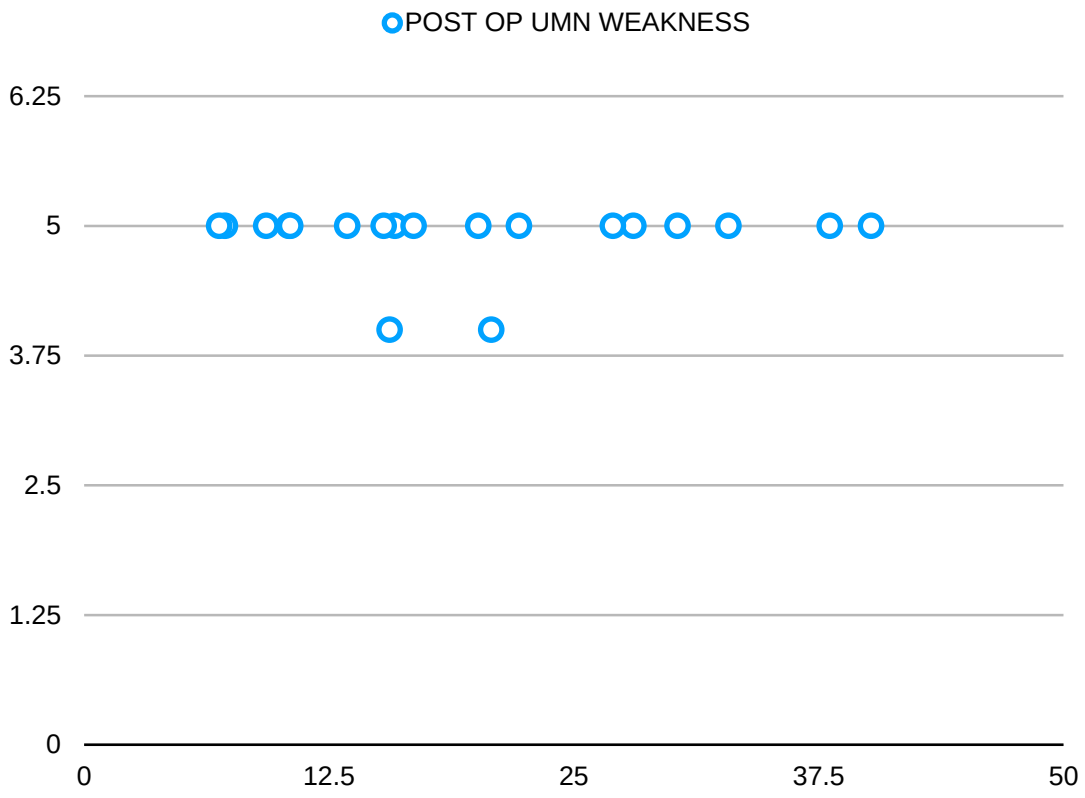

Lambda 2,3 difference (Contralateral Midbrain) vs Volume of Tumor
Lambda 2,3 difference of Contralateral Midbrain
28
24
20
16
10
20
30
40
Volume


Lambda 2,3 difference (Ipsilateral Pons) vs Volume of Tumor
Lambda 2,3 difference of Ipsilateral Pons
25
20
15
10
20
30
40
Volume


Mean Diffusivity (Contralateral Midbrain) vs Volume of Tumor
Mean Diffusivity of Contralateral Midbrain
110
100
90
80
70
10
20
30
40
Volume


Mean Diffusivity (Contralateral Pons) vs Volume of Tumor
MOD RANKIN ON F/U
5
4
3
2
1
0
Mean Diffusivity of Contralateral Pons
110
100
90
80
70
0
12.5
25
37.5
50
10
20
30
40
Volume


POST OP UMN WEAKNESS
6.25
5
3.75
2.5
1.25
0
0
12.5
25
37.5
50


POST OP UMN WEAKNESS
6.25
5
3.75
2.5
1.25
0
0
12.5
25
37.5
50

DTI PARAMETERS	MID BRAIN VALUES	P value
FA	107.5	0.940
VR	118	0.641
ADC	121	0.127
L1	155.5	0.062
L2	95.5	0.381
L3	130	0.359
Fibres	78	0.322
MD	135	0.112
L1_3	139	0.210
L1_2	144	0.150
L2_3	64	0.485
RD	130.5	0.350

TABLE showing modified Ranking score at follow up of the patient versus tumour volume in the x axis

DTI PARAMETERS	PONS VALUES	P value
FA	100.5	0.881
VR	86.5	0.501
ADC	134.5	0.116
L1	125	0.089
L2	128	0.190
L3	135	0.270
Fibres	99	0.837
MD	146	0.130
L1_3	119	0.344
L1_2	123	0.513
L2_3	96.5	0.141
RD	126	0.219

TABLE showing post operative UMN weakness - power of the contralateral limbs plotted against the tumour value in the x axis

DISCUSSION

The clinical occurrence of long tract signs by itself in a group of vestibular schwannoma patients by itself is relatively rare occurrence. The long tracts especially the corticospinal involvement is more common with intra axial lesions and more so with ill defined lesions, than the well circumscribed counterparts.

The incidence of long tract signs in vestibular schwannoma patients, in olden literature is around 10 % ; but this value might be biased taking into account the mean size at diagnosis three to four decades back was much larger than the current value. Large and giant vestibular schwannomas formed a sizeable proportion in olden days. But the relatively increased availability of imaging facilities with the better health seeking behaviour of patients, especially in the western world has lead to drastic decrease in the mean size at diagnosis.

Samii et al had compared a series of 50 patients with giant vestibular schwannomas (> 4 cm), versus 167 patients with VS < 3.9 cm size. The mean size of the former group in the series was 4.4 cm as against 2.3 cm in the latter group. The incidence of long tract signs in the giant vestibular schwannomas group was 14 % compared to 1.8 % in the latter group.

In the current study, only 20 patients qualified for the inclusion criteria and imaging analysis. All the patients had tumours more than 3 cm in largest dimension. Three (15 %) patients had clinical signs of long tract involvement due to brainstem compression. Even though the sample size is very small to statistically correlate, the incidence of long tract signs roughly correlates with that of Samii et al.

Two patients had post operative weakness, hemiparesis, which persisted beyond two weeks duration. As opposed to the vestibular schwannomas series by Samii et al wherein 10 patients develop hemiparesis in a a total of 1000 operated cases, roughy around 1 %. The increased frequency in the current study might be due to the fact that all the patients have tumour size > 3 cm - with 11 giant vestibular schwannomas.

We could not establish any linear trend or correlation between the tumour volume and incidence of long tract involvement in this study. This might suggest factors other than tumour volume alone which might interplay to cause Upper Motor Neuron (UMN) weakness namely location of the cystic components of the tumour, maintenance of the arachnoid plane with the brainstem.

The other aim of the study was to identify objective and quantitative DTI metrics which could help identify pyramidal tract involvement before it becomes evident clinically.

Only a weak correlation could be identified between the DTI metrics and volume of the tumour.

Positive correlation might exist with Eigenvector values - Lambda - 1 of ipsilateral midbrain and ipsilateral pons and also with the Lambda 2 - 3 difference of ipsilateral pons and contralateral medulla.

Negative correlation could possibly be present with the mean diffusivity and apparent diffusion coefficient of both contralateral pons and contralateral medulla.

In a study by Lui et al on posterior fossa neoplasms, mean diffusivity and fractional anisotropy could predict motor deficits in patients before they are observed

Even though, in the current study, strong correlation between DTI metrics and the size of the tumour might not be feasible to demonstrate, the results might indicate a possible association.

The importance of DTI metric data is that objective quantification and stratification of the patients who are in the subclinical stage of long tract involvement could be identified well ahead of time. This might help in formulating a clinical and radiologic score for predicting long tract involvement. The patients and their relatives can be counselled regarding the increased possibility of persisting weakness after surgery and also regarding the various modalities of treatment. From the surgeons point of view, it might help to create a surgical strategy preoperatively - patients with possible objective evidence of radiological long tract involvement might benefit from a hybrid approach - where near total or even subtotal resection is planned, due to the possibility of poor planes with the brainstem. These patients could then be subjected to stereotactic radio surgery later on during follow up, thus increasing the quality of life of the patients.

Further studies with larger sample size and elaborate methodology might throw light in this perspective

CONCLUSION

The extra meatal size and volume of vestibular schwannomas roughly correlate with the onset and chronology of symptoms in the natural history of this condition.

There may not be direct linear correlation between size and volume of the tumour with clinical long tract signs. The same applies to the post operative outcome of the patient.

We have to take into consideration the various factors that come into play in deciding the final outcome namely surgical expertise. Meticulous surgical dissection techniques, respecting the arachnoid plane causing minimal pial breach have more impact on the outcome. Preserving important vasculature during the excision of the tumour is crucial. The importance of the utmost proficient and delicate dissection of the tumour from the brainstem can be emphasised as the pivotal step to triumph in the microsurgery of vestibular schwannomas.

The preoperative long tract compression and the post operative neurological outcome in terms of limb weakness might have a varying association. The brain stem is one of the most important structure in the nervous system with its vital centres and high density white fibre tracts and it is possible that the inherent plasticity of the this tissue itself might contribute to the above mentioned fact.

The weak correlation which might exist between Objective DTI parameters and subclinical corticospinal tract compression is a thing to delve into in the future to tap its further potential implications. Larger studies with adequate sample size, with more proportion of giant vestibular schwannomas and power to statistically prove an association and a cut off will pave way for assorting vestibular schwannoma patients in

an unbiased way and to predict the prognosis and the clinical course. A meaningful and objective correlation of DTI parameters could possibly become a part of the preoperative assessment in the future.

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QUESTIONNAIRE

"PROSPECTIVE OBSERVATIONAL STUDY FOR THE EVALUATION OF CLINICAL AND RADIOLOGICAL CORRELATES IN PATIENTS UNDERGOING SURGERY FOR VESTIBULAR SCHWANNOMAS"

CODE NO: _____

ANNEXURE I

GENERAL INFORMATION

Serial Number	
Age	
Sex	M/ F
Date of admission	
Date of discharge/ death	

CLINICAL DETAILS

Mode of Presentation	**Duration**
Headache	
Vomiting	
Diplopia	
Gait difficulty	
Seizure	
Tremors	
Hearing loss	
Long tract symptoms	
Other cranial nerve deficit	
Others	

Co-morbid conditions: Hypertension/ Diabetes/ Heart disease/ CVA

AUDIOMETRY (DD/MM/20YY)

PTA L	
PTA R	
Speech Discrimination score	

EXAMINATION FINDINGS (DD/MM/20YY)

GCS		
Fundus		
Eye Movements		
Pupil Size		
Pupil Reaction		
Corneal Reflex		
Schirmer's test		
Corneal haziness		
Masseter bulk		
Facial Sensations		
Jaw opening		
Facial Deviation		
Weber's test		
Any other cranial nerve deficits		
Tone		
Weakness		
DTR		
Plantar response		
Sensory Loss - fine touch vibration, proprioception		

MR IMAGING (DD/MM/20YY)

Site	
Side	Right/ Left
Preop Imaging Diagnosis	
Extend	
Extension below IAC	Yes/ No
Volume	
Maximal Dimension	
Hydrocephalus	Yes/ No
Edema (grade)	
5th nerve compression	Yes/ No
6th nerve compresssion	Yes/ No
7th nerve compression	Yes/ No
8th nerve compression	Yes/ No
Relation to brainstem	Intra-axial/ Extra-axial/ Compression
Vascular involvement	Yes/ No
Long tracts involvement	

TRACTOGRAPHY VALUES	**CORTICOSPINAL TRACT**

ANNEXURE II

SURGERY

Date of surgery	**(DD/MM/20YY)**
Intraoperative Impression of lesion	
CSF drainage	No/ EVD/ Lumbar Drain
Skin Flap	
Type of craniotomy	
Sinus Opened	Yes/ No
Intra operative events if any	
Injury/ Sacrifice of petrosal sinus	Yes/ No
Injury to VIth Nerve	Yes/ No
Extend of lesionectomy	
Use of hemostats – descriptive	
Nerve monitoring	Yes/ No
Dural closure	
EVD/ lumbar drainage	NA/ removed/ intemittent/ continuous
VII nerve status	
VIII nerve status	
IAC drilling	
Brainstem compression	
Nature of the tumor - cystic components	
Plane with the brainstem	

ANNEXURE III

CLINICAL DETAILS

Complaints	**Duration**
Diplopia	
Gait difficulty	
Seizure	
Tremors	
Hearing loss	
Long tract symptoms	
Other cranial nerve deficit	
Others	
CSF leak	No/ Wound/ Otorrhea/ Rhinorrhea
Days of post op stay.	
Days of intensive care unit stay	
Days of ventilator	
Tracheostomy	Yes/ No
GOS at discharge	
Wound at discharge	
Antiepileptics	
Tarsorrhaphy	

EXAMINATION FINDINGS (DD/MM/20YY)

GCS		
Eye Movements		
Pupil Size		
Pupil Reaction		
Corneal Reflex	Present/ Absent	Present/ Absent
Schirmer's test		
Corneal haziness	Yes/ No	Yes/ No
Facial Sensations		
Jaw opening		

Facial Deviation		
House-Brackmann score		
Weber's test		
Any other cranial nerve deficits		
Weakness		

CT IMAGING (DD/MM/20YY)

Hydrocephalus	
Edema (grade)	
Arterial infarcts	Yes/ No
Tumour removal	Total/ Near (90%)/ Partial (70%)/ < 50%
Volume of tumor residue	
Venous infarcts	Yes/ No
Haematoma	Yes/ No

ANNEXURE IV

CLINICAL DETAILS

Mode of Presentation	**Duration**
Headache	Yes/ No
Vomiting	Yes/ No
Diplopia	Yes/ No
Gait difficulty	Yes/ No
Seizure	Yes/ No
Tremors	Yes/ No
Hearing loss	Yes/ No
Long tract symptoms	Yes/ No
Other cranial nerve deficit	
Others	
CSF leak	No/ Wound/ Otorrhea/ Rhinorrhea
Visual disturbance	Yes/ No
mRS	
Tracheostomy	NA/ Present/ Absent
Pathological diagnosis	
Adjuvant treatment	
Need for Shunt	
KPS	
GOS	
Antiepileptics	
Tarsorrhaphy	

EXAMINATION FINDINGS (DD/MM/20YY)

GCS		
Eye Movements		
Pupil Size		
Pupil Reaction		
Corneal Reflex	Present/ Absent	Present/ Absent
Schirmer's test		

Corneal haziness	Yes/ No	Yes/ No
Facial Sensations		
Jaw opening		
Facial Deviation		
House-Brackmann score		
Weber's test		
Any other cranial nerve deficits		
Sensory Loss		
Weakness		
Wound scar		

AUDIOMETRY (DD/MM/20YY)

PTA L	
PTA R	
Speech Discrimination score	

MR IMAGING (DD/MM/20YY)

Residuum extent	
Edema (grade)	
Volume of tumor residue	
Tumour removal	Total/ Near (90%)/ Partial (70%)/ < 50%
Maximal Dimension	
Venous infarcts	Yes/ No
Haematoma	Yes/ No
Arterial infarcts	Yes/ No
Long tracts involvement	

TRACTOGRAPHY VALUES	**CORTICOSPINAL TRACT**

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
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Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/1168/FEBRUARY-2018

06.04.2018

Dr. Mathew Abraham
Professor
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Mathew Abraham,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "PROSPECTIVE OBSERVATIONAL STUDY FOR THE EVALUATION OF CLINICO RADIOLOGICAL FEATURES IN PATIENTS UNDERGOING SURGERY FOR VESTIBULAR SCHWANNOMAS (IEC/1168)" on 17th February, 2018.

The following documents were reviewed:

Original submission

1. *Covering Letter addressed to the Chairperson, IEC, SCTIMST dated 19.01.2018 with checklist*
2. *TAC Approval Letter*
3. *Forwarding Letter from the HOD*
4. *IEC Application Form*
5. *Project Proposal*
6. *Questionnaires*
7. *Proforma*
8. *Patient Information Sheet and Consent Form in English and Malayalam*
9. *CV of Principal Investigator and Co-Principal Investigators*

Revised submission

1. *Covering Letter addressed to the Chairperson, IEC, SCTIMST dated 20.03.2018 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Questionnaire*
6. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
7. *CV of Principal Investigator and Co-Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 17th February, 2018 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
5.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
6.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
7.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
8.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	Medical Technology	Yes
9.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
10.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
11.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
12.	Dr.Lekha Pandit	MD.DM Neurology, PhD (Bioscience)	Female	Clinician	No
13.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
14.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

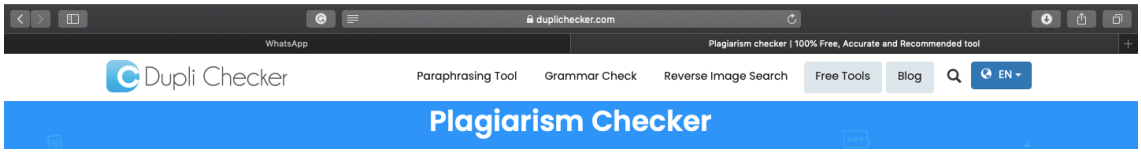
The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC



The long tracts especially the corticospinal involvement is more common with intra axial lesions and more so with ill-defined lesions, than the well circumscribed counterparts.

The incidence of long tract signs in vestibular schwannoma patients, in olden literature is around 10 % ; but this value might be biased taking into account the mean size

at diagnosis three to four decades back was much larger than the current value.

Large and giant vestibular schwannomas formed a sizeable proportion in olden days.

But the relatively increased availability of imaging facilities with the better health seeking behaviour of patients, especially in the western world has lead to drastic decrease in the mean

Samii et al had compared a series of 50 patients with giant vestibular schwannomas (> 4 cm), versus 167 patients with VS < 3.9 cm size.

The mean size of the former group in the series was 4.4 cm as against 2.3 cm in the latter group.

The incidence of long tract signs in the giant vestibular schwannomas

Results

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