Bilateral Vestibular Schwannoma: An Institutional Experience

Submitted for MCh Neurosurgery

By

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CERTIFICATE

This is to certify that the thesis entitled “Bilateral Vestibular Schwannoma: An Institutional Experience” is a bonafide work of **Dr. Shivashankar Marajakke** and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram (SCTIMST), under my guidance and supervision.

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DECLARATION

This thesis titled “Bilateral Vestibular Schwannoma: An Institutional Experience” is a consolidated report based on a bonafide study of the period from Jan 1998 to Sept 2012, 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 fulfillment of rules and regulations of MCh Neurosurgery examination.

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Dr. Shivashankar Marajakke

ABBREVIATIONS

ABI	–	Auditory brain stem implant
BAER	-	Brain stem evoked response
CPA	-	Cerebellopontine angle
CT	-	Computed tomography
CNS	-	Central nervous system
CSF	-	Cerebrospinal fluid
DVT	-	Deep venous thrombosis
ETV	-	Endoscopic third ventriculostomy
EVD	-	External ventricular drain
Eg	-	Example
F/U	-	Fallow up
FLAIR	-	Fluid attenuated inversion recovery.
FSE	-	Fast spin echo
GKS	-	Gamma knife surgery
HB	-	House Brackman
IAM	-	Internal acoustic meatus
IAC	-	Internal acoustic canal
LCN	-	Lower cranial nerve
LINAC	-	Linear accelerator
MCF	-	Middle cranial fossa

MRI	-	Magnetic resonance imaging
NF	-	Neurofibromatosis
NIH	-	National institute of health
NNFF	-	National neurofibromatosis foundation
PTA	-	Pure tone audiometry
SRS	-	Streriotactic radiosurgery
SNHL	-	Sensorineural hearing loss
SDS	-	Speech discrimination score
SRT	-	Speech reception threshold
SD	-	Standard deviation
VS	-	Vestibular schwannoma.
VP	-	Vetriculoperitoneal
WHO	-	World health organization.

INDEX

INTRODUCTION

1. INTRODUCTION

Acoustic neuroma is a benign tumor arising from the vestibular division of vestibulocochlear nerve that is found in the cerebellopontine cistern and internal auditory canal. The earliest description of this term is found in Walter Dandy's description in Surgery of the Brain, 1945. In the cerebellopontine angle, vestibular schwannoma is the most common lesion. Bilateral vestibular schwannomas (VS) are rare. Among CNS tumors, bilateral VS is the hallmark of NF2 and is associated with considerable morbidity. How to manage and when to treat bilateral VS represent crucial issues. Many patients die from complications of the disease or become severely handicapped. The cornerstone of modern bilateral VS management is conservation of function and the maintenance of quality of life. Only through a multimodal treatment plan that addresses the genetic, life-style, and surgical considerations of NF2 can optimal management be provided. This study discusses about the surgical experience with 19 patients of bilateral vestibular schwannomas and discuss the management issues involved.

REVIEW OF LITERATURE

2. REVIEW OF LITERATURE

Historical aspects of Vestibular schwannoma

Eduard Sandifort, Leweque Lasource and Charles Bell are widely credited with the first autopsy description, first clinicopathological correlation and first clinical description of vestibular schwannoma respectively [2]. Wishart [3] reported the first known case of bilateral acoustic neuromas in 1822. On autopsy he found several tumours, including 2 attached to the "seventh cranial nerve pair," each "the size of a small nut, and very hard [4.] In 1900, Sternberg was the first to describe the histopathology of VS. Leading physicians such as Oppenheim, von Monakow, Jackson, Gowers, Babinski, and Starr refined their knowledge of functional brain anatomy, facilitating an earlier diagnosis of VS-while the patient was still alive and set the stage for surgical intervention [4.]

Surgery for Vestibular schwannoma

Historically, surgery in the cerebellopontine angle was one of the extreme challenges. This was due to lack of microsurgical techniques, limited space in the posterior fossa, the vicinity of brainstem and cranial nerves; safe resection was considered a daunting task. Although Ballance of London is commonly credited with the first successful surgery of VS in 1892, Cushing credits Annadale of Edinburgh with the first successful surgery in 1895[5]. Cushing, the pioneer in achieving a significant successful operative series of VS, and Dandy, whose approach to total excision achieved outstanding results, were instrumental in stimulating many neurosurgeons to venture into what Cushing named “the bloody angle, the gloomy corner of neurological surgery”[5,6]. Noteworthy contributions in refining microsurgical excision of VS have been made by House, Malis, Yasargil, and Samii over the years[2.]

In 1905, Horsley achieved total removal of an acoustic neuroma and the patient survived, but became severely disabled due to brainstem ischemia[7]. In 1905 Borchardt performed the first transsigmoidal approach for resection of an acoustic neuroma [7]. In 1903, Garre was the first to attempt surgery for bilateral

VS [8,9.] De Martel, introduced the sitting position for posterior fossa surgery; in contrast to the lateral or prone positions. In 1916, Henschen discovered that acoustic neuromas originate in the vestibular portion of the acusticus [8].

Cushing in 1917 in his famous monograph Tumours of the Nervus Acusticus and the Syndrome of the Cerebellopontine Angle, advocated bilateral suboccipital craniectomy in 30 cases of acoustic neuromas where intracapsular tumour removal rather than separating the tumour from the brainstem and the cranial nerves reduced fatalities to a range of 10 to 15% [5]. Cushing's method of partial resection for VS was associated with a higher tumour recurrence rate; the 5-year mortality rate was 54%.

Dandy advocated unilateral suboccipital approach in 46 cases and showed that acoustic neuromas could be resected in their totality, with a mortality rate of 10.87% if capsular dissection was performed with meticulous techniques rather than a simple intracapsular removal [10] . In 1931, Cairns became the first surgeon to perform total removal of VS while preserving the function of the facial nerve [11]. In 1939, Olivecrona demonstrated that the facial nerve could be preserved in 65% of patients in surgical treatment of acoustic neuromas [12].

Epidemiology

Intracranial schwannomas are common neoplasms, accounting for 8-10 % of all primary intracranial neoplasms [13,14]. Cerebellopontine angle tumours account for 5-10% of all intracranial tumours [15]. In the cerebellopontine angle, vestibular schwannoma is the most common lesion: 80% of all tumours [16,17,14], some others estimating it to be 85-92% [15].

Neurofibromatosis type 2 (NF2) is a disorder of autosomal dominant inheritance. There have only been two epidemiological studies of NF2 one in North West England[18,19] and one in Finland[20]. A recent update suggests incidence may be as high as 1:25,000. Disease prevalence has now risen to around 1 in 60000 due to earlier diagnosis and better survival due to improved

treatment. A lower incidence of 1 in 87,410 was reported in a 1.7 million population in Finland[20]. It is suspected that approximately one-half of cases are inherited, and one half are the result of new, de novo mutations [20].

Anatomy

VS most commonly arise from the vestibular nerve (80%) with origin from cochlear nerve in only 5-7% [21]. Koos et al found the inferior vestibular nerve involved in 70%, superior vestibular nerve in 20% and cochlear nerve in 10% [22].

The eight nerve is derived from the lateral margin of the rhombencephalon from a group of cells known as acousticofacial ganglion which lies medial and ventral to auditory vesicle. The cells of vestibular ganglia are the first to extend fibres towards the auditory vesicle after which there is an outgrowth from cochlear ganglia. This egress of fibres is accompanied by Schwann cells, however the fibres grow rapidly and glia are drawn from rhombencephalon into the proximal segment of nerve.

The adult human vestibular nerve is 18 mm in length; its proximal 8-12 mm is endowed with neuroglia, distal portion by Schwann cells. This interface of neuroglia and Schwann cells is located more distally in vestibular than cochlear division and the transition zone in former is marked by greater degree of intermingling of the two cell types and regional overproduction of Schwann cells. Origin of the tumour is from the junctional Obersteiner Redlich zone where the central and peripheral myelin meet. This zone is situated at the region of the lAM or canal.

VS most commonly arise from the vestibular nerve (80%) with origin from cochlear nerve in only 5-7% (90). Koos et al found the inferior vestibular nerve involved in 70%, superior vestibular nerve in 20% and cochlear nerve in 10% [22].

Though vestibular schwannoma arises from vestibular division which traverses the porus acousticus or lAM, the earliest symptom do not express

this localisation but rather compression of cochlear nerve results in sensineural hearing loss.

Neoplasm expands the porus acousticus and spills over in the cerebellopontine angle, grows symmetrically centered over the porus acousticus. It remains closely applied to petrous pyramid; ventral surface acquires the mosaic irregularities of the bony ridge. Vertex of mass encounters the soft tissue of cerebellum and pons and is dome shaped. The tumour stretches the facial nerve which being motor nerve is highly relisant to stretch. The fifth nerve is compressed as it exits from pons. Caudal extension of the tumour brings it in contact with ninth and tenth cranial nerves, thrusts the cerebellar tonsils inferiorly resulting in tonsillar herniation while medial extension causes distortion of brainstem and fourth ventricle with obstruction to CSF outflow from foramen of Lushka and Magendie resulting in obstructive hydrocephalus. Since the tumour arises outside the CSF space, it pushes the lateral layer of arachnoid inwards till it comes in contact with more medial layer. The double layer thus formed contains important blood vessels and nerves of the cerebellopontine angle and is an important aid in dissection. There is often loculation of CSF which presents as arachnoid cyst dorsolateral to the tumour.

Pathology

According to 2007 World Health Organization classification, schwannomas are encapsulated benign nerve sheath tumors composed of differentiated Schwann cells which correspond to WHO grade I.

Macroscopic appearance

Schwannomas are variegated in color, with areas of gray, red, and yellow corresponding to areas of dense cellularity, increased vascularity, and xanthomatous degeneration. Typically no necrosis is evident. They usually are encapsulated.

Microscopic appearance

Histologically, the tumors are formed of interweaving bundles of spindle-shaped cells with cigar-shaped nuclei. Distinct areas designated as Antoni A and B are seen. Antoni A areas are densely cellular and interwoven, whereas Antoni B areas are less cellular, less structured, and often contain areas of microcyst formation and hemorrhage. Occasional cells with large pleomorphic nuclei are common but are not indicative of anaplasia, which is rare or nonexistent in these tumors (Vogel 1985; Mrak et al 1994). Eighth cranial nerve schwannomas are known for their infrequent presence of Verocay bodies, predominance of Antoni B tissue and clusters of lipid-laden cells .Reticulin stains or electron microscopy reveal a distinct basement membrane external to the plasma membrane, which distinguishes acoustic schwannoma from meningiomas with a similar appearance. Although the tumor surface is covered with connective tissue, this "capsule" is often no thicker than 3 to 5 µm in most areas .A nodular architecture has been reported to occur in 40% of NF2-associated tumors, but is rare in sporadic cases [23].

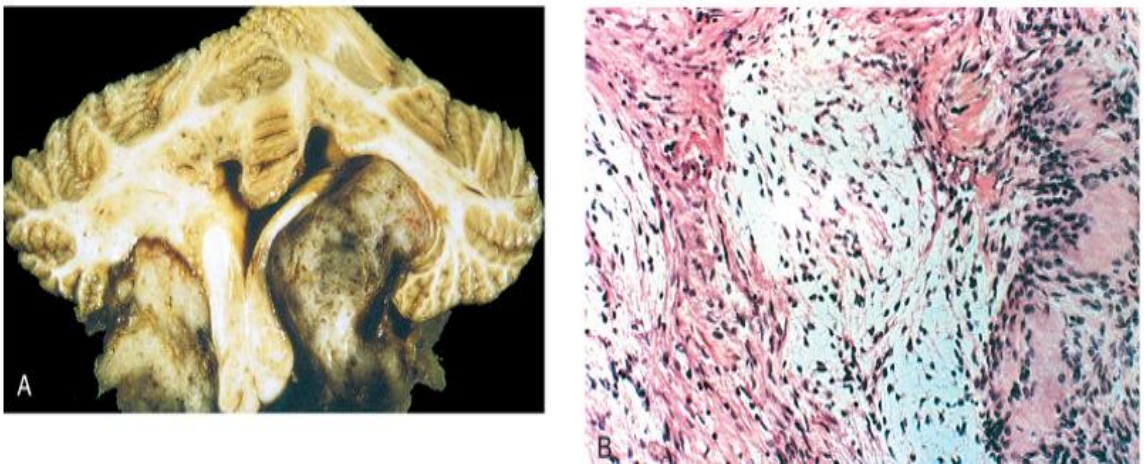


Fig 1. A.Bilateral eight nerve schwannoma gross specimen.

B.Microscopic image showing cellular areas (Antoni A), Verocay boodies

(far right) and Antoni B areas(center).

Types of Schwannomas:

Ancient schwannoma

This is a variant of Schwannoma displaying prominent degenerative changes. The degenerative changes include cyst formation, calcification, hemorrhage and hyalinization.

Macroscopically these are large tumours which are usually deeply located (eg. retroperitoneum).

There is prominent cellular atypia characterized by hyperchromatic nuclei and coarse clumping of chromatin. These changes are purely degenerative. No mitotic figures are identified. These tumours behave as ordinary schwannomas.

Cellular schwannoma: This variant is usually found in the deeper tissues (retroperitoneum or mediastinum). Histologically, there are compact spindle shaped cells arranged in a fascicular or whorled growth pattern, composed predominantly of Antoni A patterns and devoid of well formed.Verocay bodies . The most common location of cellular schwannoma is the pelvis, retroperitoneum and mediastinum. Cranial nerves -fifth and eight may be affected . Clinical presentation of cellular schwannoma is similar to conventional schwannoma, but the histological features of hypercellularity, fascicular growth of cells, nuclear hyperchromasia and atypia and low mitotic activity, may lead to the mistaken diagnosis of malignancy. Cellular schwannomas are benign, do not metastasize or follow a clinically malignant course.

Melanotic schwannoma: This rare variant usually occurs in middle aged adults and commonly arises from the posterior spinal nerve roots. Melanotic schwannomas are well circumscribed, partly encapsulated lesions characterized by polygonal and vesicular cells with grooved nuclei. These cells contain abundant melanin pigment. In psammomatous melanotic schwannoma, varying numbers of psammoma bodies are present. Some of

these cases are associated with Carney's complex (myxoma, spotty pigmentation and endocrinopathy).

Malignant melanotic schwannoma usually arises from the sympathetic chain and is characterized by brisk mitosis and prominent nucleoli. Immunohistochemistry reveals that tumour cells stain positively for S100, HMB45, MART-1, synaptophysin and vimentin.

Plexiform schwannoma: Plexiform schwannoma may demonstrate conventional, cellular, or mixed appearance. Worrying histologic features are increased cellularity and mitoses. These schwannoma grow in a plexiform or multinodular manner. Site:1. Common superficial (dermal and subcutaneous) tumours 2. Deep somatic soft tissue.The tumor is associated with NF-2 but not with NF 1, and has been noted in non -NF2 patients with multiple schwannomas (schwannomatosis).

Malignant Schwannoma: Malignant nerve sheath tumors are uncommon, and occur chiefly in the spinal nerve root, when they often form dumbbell shaped tumor, expanding inward and outward from an intervertebral foramina. Atleast 50% of these are associated with Von Recklinghausen's disease. The microscopic appearance is highly cellular, the tumor being composed of interlacing bundles of spindle cells with sausage- shaped nuclei showing pleomorphism and mitotic figures. Reticulin is widely distributed throughout the tumor. The tumors that occur peripherally can be difficult to distinguish microscopically from other malignant spindle cell tumors of the soft tissue.

Pathology of vestibular schwannomas in NF2

Unlike the solitary, sporadic tumors that tend to displace the auditory portion of the eighth cranial nerve, tumors associated with NF2 tend to form grapelike clusters that often infiltrate and engulf the cochlear nerve[24].

The vestibular schwannomas in NF2 often show a grapelike lobulated or nodular appearance, and foci of increased cellularity and Verocay bodies are more common than in sporadic schwannomas.

VSs in the context of NF2 demonstrate a higher proliferation index, are more lobular, may have axons trapped within the tumor, and tend to arise earlier in life[24].

Immunohistochemistry

Tumor cells routinely strongly and diffusely express S-1 00 protein, often express Leu-7 and may focally express glial fibrillary acidic protein. All schwannoma cells have basal lamina, so stain for collagen IV and laminin. Low-level p53 protein immunoreactivity may be seen.

Electron microscopy

Elongated cells with continuous basal lamina, thin cytoplasmic processes, aggregates of intracytoplasmic microfibrils, peculiar intracytoplasmic lamellar bodies, extracellular long-spacing collagen .Stromal long spacing collagen (Luse body) is a common finding.

Neurofibromatosis type 2

Neurofibromatosis type 2 (NF2) is a disorder of autosomal dominant inheritance .The hallmark of neurofibromatosis type 2 (NF2) is bilateral schwannomas arising from the vestibular nerves. Actually the designation as NF2, "neurofibromatosis 2," is quite inappropriate because there are no neurofibromas in NF2 and all of the neural tumors are schwannomas.

This condition tends to manifest itself in the second and third decade, often with insidious symptoms[36].

Like NF1, NF2 patients have a predilection for intracranial, ocular, and skin lesions. Skin findings are less characteristic of NF2 than NF1, but clinical investigation has demonstrated a surprisingly high 60% incidence of skin tumors, including schwannomas, neurofibromas, and mixed tumors as well. Café au lait spots, too, are evident in a third of patients[25]. The prototypical and pathognomonic finding in NF2 patients, however, remains the presence of bilateral acoustic schwannomas**.** NF2 was first identified as having a distinct

genetic basis from NF1 when the NF2 gene was mapped to chromosome 22, where it encodes a cytoskeletal protein dubbed merlin or schwannomin. The disease NF2 has the highest spontaneous mutation rate of any human genetic disorder (50%)[35].

Central nervous system tumours are multiple and occur in an unpredictable fashion. Any handicap from dysfunction of the facial, vestibulocochlear and the lower cranial nerves caused by cerebellopontine angle tumours has the added potential of being bilateral. Furthermore, in these patients, spinal tumours have the capacity to produce further handicap by spinal cord compression[37].

Genetics

Although most schwannomas are sporadic tumors, multiple schwannomas occur in two inherited syndromes. Bilateral vestibular schwannomas are pathognomonic of NF 2. Multiple peripheral schwannomas in the absence of other NF 2 features is characteristic of schwannomatosis. Psammomatous melanotic schwannoma is a component of Carney complex. NF 2 gene is a tumor suppressor gene integral to the ,formation of sporadic schwannomas. Inactivating mutations of NF 2 gene have been detected in 60% of schwannomas. These genetic events are predominantly small frame shift mutations that would be predicted to result in truncated protein products. Mutations occur throughout the coding sequence of the gene, although they have not been described in exons 16 and 17. In most cases they are accompanied by loss of the wild-type allele on chromosome 22q.Still other cases demonstrate loss of chromosome 22q in the absence of detectable NF 2 mutation. Nonetheless, loss of merlin expression, demonstrated by immunohistochemistry, is universal finding in schwannomas, regardless of their mutation or allelic status. This suggests that abrogation of merlin function is an essential step in schwannoma tumorigenesis. Loss of chromosome 22 has also been noted in cellular schwannona. Interestingly, the type of mutation in the NF2 gene appears to dictate disease severity, with single

codon/single amino acid missense alterations, somatic mosaicism, splice site mutations, or large deletions (leading to no protein product) resulting in mild phenotypes. Protein-truncating mutations and frames shift mutations result in a severe phenotype[25].

Bilateral VS in NF2 may manifest as three distinct phenotypes.

1. The Wishart type has an early onset and a rapid course with coexisting multiple other tumors in addition to bilateral VS[26].

2. The Gardener type on the other hand has a late onset, a more benign clinical course and usually has bilateral VS and no other tumors[27].

3. The Lee Abbott type has a variable age of presentation and is characterized by the association of multiple generalized meningiomatosis[28].

The NF2 gene

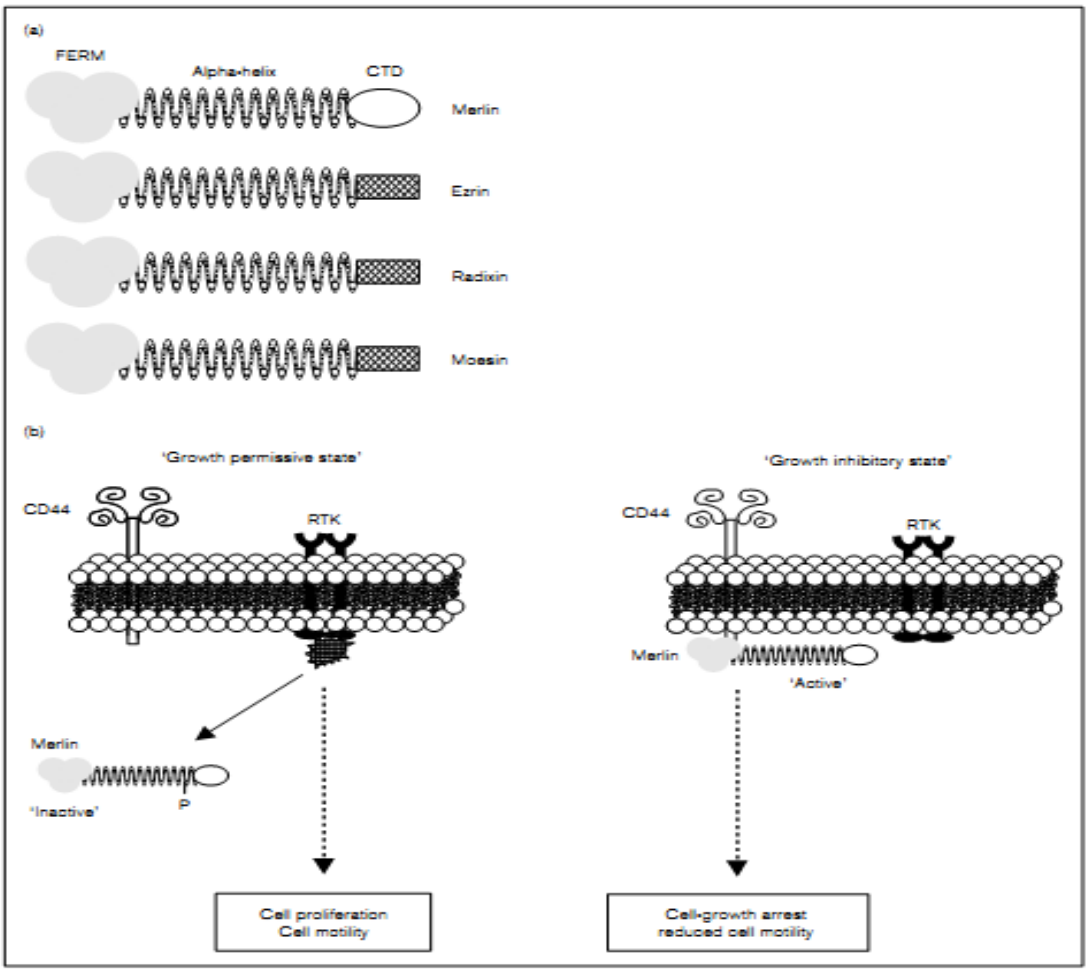
The NF2 gene on chromosome 22q codes for merlin, a 595-amino-acid protein that contains three predicted structural domains .[29,30].Structurally, merlin is most closely related to a family of proteins that link the actin cytoskeleton to cell-surface molecules important for cellular remodeling and growth regulation. This family of structurally similar molecules includes ezrin, radixin and moesin (ERM proteins) [31]. Merlin, like the ERM proteins, contains an amino-terminal Protein 4.1 cell-surface glycoprotein-binding domain (FERM domain; residues 1–313) followed by a predicted alpha-helical region and a non-conserved carboxy- terminal domain. Unlike ERM proteins, the merlin carboxy-terminal domain lacks conventional actin-binding sequences (Fig.). Recent studies on the FERM domain of merlin have demonstrated that it is composed of three subdomains that may mediate specific interactions with critical protein binding partners .[32,33]

Merlin is expressed in a variety of tissues relevant to the clinical features of NF2. High levels of merlin expression are detected in a large

number of tissues during embryonic development. In adult tissues, significant merlin expression is detected in Schwann cells, meningeal cells, lens, and nerve, accounting for the development of schwannomas, meningiomas, and lenticular opacities seen in individuals affected by NF2. Within cells, merlin appears to be localized in the cell membrane at regions involved in cell–cell contact and motility.

Familial NF2 is inherited in an autosomal dominant manner with almost 100% penetrance. It accounts for 50% of NF2[34]. As such NF2 was one of the first inherited tumour prone disorders to be localised to a specific genetic location. NF2 has the highest spontaneous mutation rate of any human genetic disorder (50%)[35.]

Fig2.Structure and potential function of the NF2 gene product, merlin.[1]



NATURAL HISTORY

Vestibular schwannomas (usually bilateral) occur in about 95% of adult patients with NF2, and adult-onset disease usually manifests with vestibular symptoms [36,26,38]. In contrast, children with NF2 often present with non-8th-nerve tumors and non-vestibular symptoms [35,39]. Recent studies have highlighted the occurrence of mononeuropathy in NF2 [40,41]. Peripheral neuropathy is common in NF2 patients with severe disease; in these patients, axonopathy can be caused not only by tumor growth, but also by multiple tumorlets and proliferation of Schwann and perineurial cells [42,43].

Vestibular schwannoma growth rates in NF2 are generally higher in younger patients but are extremely variable, both between patients and over time in the same patient [44,45]. Growth rates are highly variable even among multiple NF2 patients of similar ages in the same family [44]. This suggests that stochastic processes (random processes operating over time) or as-yet unknown factors influence vestibular schwannoma growth rates in NF2. For this reason, clinical management of multiple patients in NF2 families cannot be based on the expectation of similar vestibular schwannoma growth rates, even when other clinical aspects of disease severity are similar.

Age at diagnosis is, by far, the strongest single predictor of the risk of mortality, and therefore is a useful index for patient counseling and clinical management[47].

Actual survival rates in patients with NF2 based on long-term follow-up data have not been reported, however. Evans, et al[36], estimated that a likely median survival time for patients with NF2 was approximately 15 years following diagnosis. They also estimated that more than 40% of patients would be expected to die by the age of 50 years and that all patients would die by 70 years.

To summarize

(1) VS growth rates in NF2 patients are unpredictable

(2) One tumor in a single patient cannot be used as a control against the other

(3) Growth rates and hearing outcome do not correlate

(4) The significant majority of patients retain serviceable hearing; therefore, conservative management may be considered a favorable option for many patients.

Signs and Symptoms

The hallmark of NF2 is the development of bilateral VS. VS usually present with hearing loss, tinnitus or imbalance or a combination of the three symptoms. The other main tumour features are schwannomas of the other cranial, spinal and peripheral nerves; meningiomas both intracranial (including optic nerve meningiomas) and intraspinal; and some low-grade central nervous system (CNS) malignancies (ependymomas and gliomas). Individuals may present with cranial meningiomas or a spinal tumour long before the appearance of a VS.

The majority of individuals with NF2 present with hearing loss, which is usually unilateral at time of onset. The hearing loss may be accompanied or preceded by tinnitus. VS may also cause features such as dizziness or imbalance as the first symptom. Nausea, vomiting or true vertigo are rare symptoms except in late stage disease. A significant proportion of cases (20–30%) present with symptoms from an intracranial meningioma (headaches, seizures), spinal tumour (pain, muscle weakness, paraesthesia), or cutaneous tumour[36, 47,26,38]. Indeed, the first sign of more severe multi-tumour disease in early child- hood is often a non-8th nerve tumour (including a cutaneous tumour), or an ocular presentation [48]. Adult presentation is thus quite different to paediatric presentation, in which VS accounts for as little as 15–30% of initial symptoms. There also appears to be a tendency to mononeuropathy, particularly affecting the facial nerve causing a Bell's-like palsy, which does not fully recover years before the detection of a VS. Some children present with a

polio like illness with wasting of muscle groups in a lower limb, which again does not fully recover. In adulthood, a more generalised symptomtatic severe polyneuropathy occurs in about 3–5% of patients, often associated with an "onion bulb" appearance on nerve biopsy [36]. This can progress, leading to severe muscle wasting and even death.

However, around 40% of patients will show evidence of polyneuropathy on nerve conduction studies [42].

Mechanisms of Hearing Loss in Neurofibromatosis Type 2

Bilateral VS-associated binaural hearing loss will occur in an unpredictable manner over the lifetime of most NF2 patients [49,50,51]. Moreover, hearing loss patterns in one ear do not predict the clinical course of the contralateral ear in the same individual with NF2 [50]. Because of the uncertain clinical course associated with bilateral VSs and because of the lack of understanding of the mechanisms that underlie hearing loss associated with bilateral VS s in NF2, the management of these tumors has not been consistent or optimized.

The most common imaging findings identified in Bilateral VS associated hearing loss in NF2 was the presence of elevated intralabyrinthine perilymphatic protein and the presence of cochlear aperture obstruction on MR-imaging. Elevated intralabyrinthine protein on FLAIR MR-imaging in patients with SNHL has also been correlated with hearing prognosis and extent of hearing loss that will persist [52].

Elevated intralabyrinthine protein could be the result of cochlear aperture obstruction and disruption of the blood-CSF/labyrinthine barrier caused by permeable tumor vessels[53]. Another mechanism by which protein can accumulate within the perilymph associated with cochlear aperture obstruction involves impaired clearance caused by the Bilateral VS.

Other pathophysiologic processes of the inner ear structures have been implicated with hearing loss, including the development of endolymphatic hydrops and intralabyrinthine hemorrhage [54].

Imaging

Magnetic resonance imaging is the gold standard in detecting and visualizing VS. MRI, on the other hand, gives excellent soft tissue visualization but does not show the bony detail nearly as well as CT. The bony anatomy is demonstrated in excellent detail by high-resolution CT when performed with a bone algorithm. The cortical edges of the IAC are sharply defined, and intricate internal anatomy of the labyrinth is routinely visualized. The internal auditory canal is widened and eroded and tumour forms an acute-angle base with the petrous bone. VS are iso- hypointense with the brain in T1 and hyperintense in T2. It is centered on the porus acousticus, with an ice cream cone shape. On gadolinium infusion enhancement may or may not be homogeneous, depending on the presence of micro or macrocystic components[55] .

Screen for NF2 using contrast-enhanced MRI of the brain and entire spine. Contrast is important for detecting small schwannomas, particularly of the spinal nerve roots, as well as small intraparenchymal ependymomas. Newer sequences, such as high-resolution fast spin-echo (FSE) T2 cisternography and true inversion recovery, can aid evaluation of the cranial nerves.

As a result of its excellent contrast and multiplanar capabilities, MRI optimally depicts the number, size, location, and extent of the central nervous system (CNS) neoplasms found in NF2. However, MRI does not detect most of the ocular abnormalities associated with the disease; these are evaluated best using funduscopy. In addition, cortical and choroid plexus calcifications may be missed on MRI, particularly when using FSE techniques. These are visualized better on CT scan studies.

Diagnosis

The first case report of neurofibromatosis appeared in the early 19th century. It gradually became clear that there were two clinically distinct entities, ‘peripheral neurofibromatosis’, or von Recklinghausen’s disease and ‘central neurofibromatosis’. It wasn’t until 1987 that these were described as NF1 and NF2 respectively and diag- nostic criteria were established[56]. These have subsequently been reviewed and updated in 1990,1997(NNNF2) and most recently in 2011[57] .

The diagnosis of NF2 remains clinical, although in most cases can be confirmed with molecular testing.

Diagnostic methods

- Clinical and family history
- Examination including cutaneous and ophthalmic

  (Slit lamp)
- Craniospinal MRI
- Molecular analysis

All of the tissues may not be affected and all the potential genetic mutations have not been identified for a reliable genetic test. The diagnosis can therefore take years as many of the features are age dependant. The hallmark is bilateral vestibular schwannomas. The numerous changes to the diagnostic criteria reflect the difficulty in establishing a confident diagnosis as early as possible in those who do not (yet) have bilateral vestibular schwannomas, or a positive family history[58].

Diagnostic Criteria for Neurofibromatosis Type2

1991 NATIONAL INSTITUTES OF HEALTH CRITERIA

A. Bilateral vestibular schwannomas
B. First-degree family relative with NF2 *and* unilateral vestibular schwannoma *or* any one of the following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity

MANCHESTER CRITERIA

A. Bilateral vestibular schwannomas
B. First-degree family relative with NF2 *and* unilateral vestibular schwannoma *or* any two of the following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity
C. Unilateral vestibular schwannoma *and* any two of the following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity
D. Multiple meningiomas *and* unilateral vestibular schwannoma *or* any two of the following: schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity

NATIONAL NEUROFIBROMATOSIS FOUNDATION CRITERIA

A. Confirmed or definite NF2
    1. Bilateral vestibular schwannoma
    2. First-degree family relative with NF2 *and* unilateral vestibular schwannoma at an age younger than 30 years *or* any two of the following: meningioma, schwannoma, glioma, juvenile lens opacity
B. Presumed or probable NF2
    1. Unilateral vestibular schwannoma at an age younger than 30 years *and* at least one of the following: meningioma, schwannoma, glioma, juvenile lens opacity
    2. Multiple meningiomas *and* unilateral vestibular schwannoma at an age younger than 30 years *or* at least one of the following: schwannoma, glioma, juvenile lens opacity

A recent article devised a new diagnostic criteria for neurofibromatosis 2 labelled the Baser Criteria[57] . The criteria assigns different points for presence of spinal tumors, cutaneous schwannomas, cranial nerve schwannomas, mononeuropathy, cataracts, or peripheral neuropathies before or after the age

of 30. This study noted an improved sensitivity in the detection of neurofibromatosis type 2 at an earlier age.

Baser Criteria for diagnosis of NF2

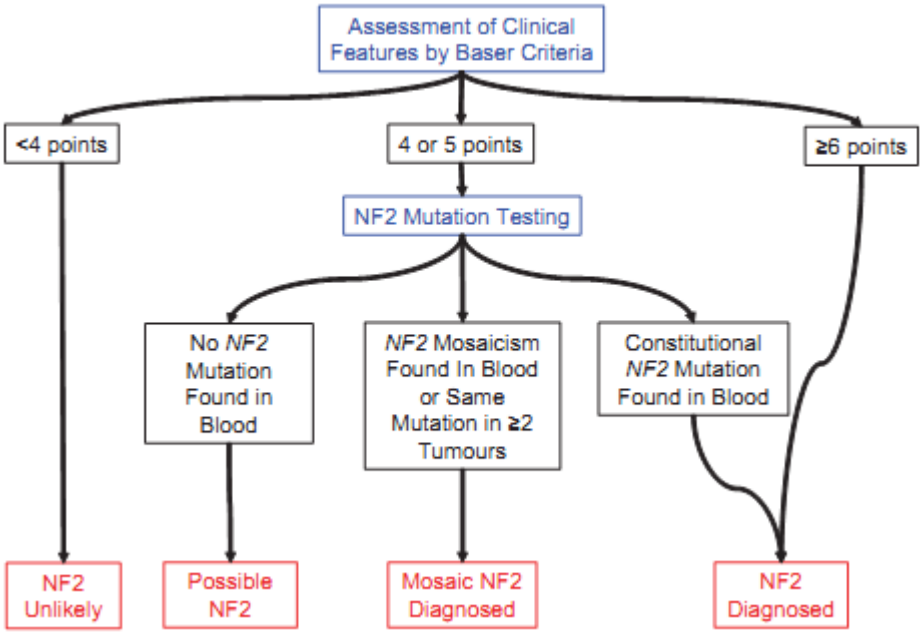
Box 2 – The Baser criteria for the diagnosis of NF2 (6)

Feature	Present at or before 30y	Present after 30y
First-degree relative with NF2 by these criteria	2	2
Unilateral vestibular schwannoma (VS)	2	1[a]
Second vestibular schwannoma	4	3[a]
One meningioma	2	1
Second meningioma (no additional points for more than 2 meningiomas)	2	1
Cutaneous schwannoma(s)	2	1
Cranial nerve tumour(s) excluding VS	2	1
Mononeuropathy	2	1
Cataract(s)	2	0

- A Diagnosis of definite NF2 is established if the total number of points is 6 or more
- NF2 mutation testing is indicated if the total number of points is 4 or 5.
  - A diagnosis of definite NF2 is established if a constitutional pathogenic NF2 mutation is found on mutation testing.
  - A diagnosis of mosaic NF2 is established if mosaicism for a pathogenic NF2 mutation is found in the blood or no detectable pathogenc NF2 mutation is found in the blood but the same pathogenic NF2 mutation is found in two separate NF2 associated tumours.
  - A temporary diagnosis of possible NF2 is made, pending further clarification. Clarification may occur if patient is diagnosed with a different condition eg schwannomatosis or if the disease evolves to permit diagnosis of NF2 by these criteria.

[a] Points are not given for unilateral or second vestibular schwannoma if the age at diagnosis is more than 70y.

Fig.3 Algorithm for diagnosis of NF2 using the Baser criteria



Comparison of five sets of criteria for the diagnosis of NF2 in the holdout subsets

Diagnostic criteria	Sensitivity	Specificity
1987 NIH[5]	64%	100%
1991 NIH[6]	67%	100%
Manchester[7]	70%	100%
NNFF[8]	64%	100%
NNFF + molecular testing[a]	70%	100%
Baser	79%	100%

Calculation of sensitivity and specificity was based on 67 patients with definite NF2 and 142 who definitely do not have NF2 at the age of onset of the first characteristic sign of NF2.

[a]Includes cases classified as "confirmed or definite NF2" by the NNFF criteria and also cases classified as "presumptive or probable NF2" by the NNFF criteria who were found to have a pathogenic *NF2* mutation on molecular testing (see text).

Recommendations for early diagnosis[59]

Clinical awareness of the genetic abnormality and its familial implications and timely screening makes early detection potentially self-perpetuating. In addition, there are numerous benefits of better outcome, maximum opportunity for hearing preservation and prevention of neurological sequelae. The early implementation of auditory, vestibular, tinnitus and facial nerve rehabilitation is thus possible.

The patient with NF2 diagnosed early can also benefit from timely genetic counselling, thereby decreasing the population of patients with NF2 and their contribution to the genetic pool. Genetic screening of first-degree relatives results in the early detection of other patients with this condition. MRI screening of families will also continue to contribute to the early identification of these patients.

The converse situation applies in the late diagnosis of NF2. The cascade of adverse events not only denies the NF2 patients optimal treatment, but also perpetuates the disease. Late detection carries a penalty borne both by the patient and the community. For the patient, there is the lost opportunity to prevent complications, implement rehabilitation and optimise the chance of hearing preservation. For the community, there is the missed chance of early detection of others with the condition, thereby increasing the prevalence of the disease and the subsequent financial burden of lifetime care.

In the last 10 years, there has been slow but steady progress in the management of this devastating condition. Microsurgical techniques, cranial nerve monitoring and advances in MR imaging have provided only a limited reduction in the morbidity and mortality of the NF2 patient. Molecular genetics carries the greatest potential for a cure for this challenging condition in the future. Until such time, the greatest advantage for both the patient and the surgeon in managing this condition lies in early detection.

Differential diagnosis

The main differential diagnosis of NF2 is schwannomatosis and some patients with multiple non cranial schwannomas turn out to have mosaic NF2 [34,35]. However, patients fulfilling the most sensitive Manchester criteria unlikely to be misclassified [57].

Antenatal diagnosis and genetic counselling

NF2 is an autosomal dominant disease with usually a 50% risk of transmission from an affected individual to their offspring, 50–60% of patients have no family history and represent de novo mutations in the NF2 gene [36,60,61]. Individuals who inherit a pathogenic mutation in the NF2 gene will almost always develop symptoms by 60 years of age [20]. Exceptionally, patients particularly in the pre MRI era will have not been diagnosed in their lifetime. Although the transmission rate is 50% in the second generation and beyond, the risk of transmission in an apparently isolated patient with NF2 is less than 50% due to mosaicism [62].

Because detection of tumours at an early stage is effective in improving the clinical management of NF2, presymptomatic genetic testing is an integral part of the management of NF2 families. Once a mutation has been identified in an affected individual, a 100% specific test is available for the family. In the absence of a genetic test a cumulative age at onset curve [63] can be used. Age at onset curves aid genetic counselling; for example, the risk of having inherited NF2 for an asymptomatic at-risk individual 25 years of age, prior to screening, drops to 25%. The risk to an unaffected 30 year old with a normal scan would be < 10%. Tumour analysis plays a vital role in providing genetic testing for the offspring of sporadic patients. At-risk individuals who are shown not to have inherited the mutated NF2 gene do not need further follow-up.

Even in the absence of identifying a mutation the residual risk of NF2 can be substantially reduced in the child of an apparently isolated case. In particular patients presenting with asymmetric disease over 40 years of age

with negative mutation analysis in blood would have a very low chance of transmitting NF2 to their children.

Because of the severity of NF2 there is a demand for prenatal diagnosis and pre-implantation genetic diagnosis. Use of the techniques above means that this is possible in the great majority of families.

Screening protocol

Children of affected patients should be considered to be at 50% risk of NF2 and screening for NF2 can start at birth. Cataracts can affect vision in early life and other tumour implications are present in the first ten years of life, particularly cranial meningiomas. Formal screening for VS should start at ten years, as it is rare for tumours to become symptomatic before that time even in severely affected families. Annual audiological tests including auditory brainstem response are still a useful adjunct to MRI [63]. Surgery is unlikely to be more successful for tumours < 6 mm than for tumours sized 6 mm, but VS growth is higher in younger patients, so for asymptomatic at-risk individuals without tumours, MRI screening every two years for those < 20 years old and every 3–5 years for those age > 20 years should be sufficient. The initial MRI scan could be at around 12 years of age, or 10 years in severely affected families. Once tumours are present, MRI screening should probably be at least annual. Spinal tumours are seen in 60–80% of NF2 patients on MRI [64-67]. While only 25–30% of patients with spinal tumours require a spinal operation from a symptomatic tumour, a full annual neurological examination is probably a wise precaution with spinal MRI only every 3 years or if there are new symptoms. If no tumours are present on the initial scan a further scan 5–10 years later may be reasonable.

In most families it is now possible to develop a genetic test so that screening can be targeted to affected individuals only. Identifying the affected patient's mutation not only allows testing of at risk relatives, but may also give important indicators as to the patient's own prognosis. As 25–30% of NF2

patients are mosaic frozen tumour should be taken at operation (with patient consent) for genetic tests.

NF2 screening protocol for at risk family members.

- Genetic evaluation protocol with blood sampling for gene defect.
- Audiology
- Pure tone audiogram
- Speech audiogram
- MRI of brain and spine with Godolinium.

Management of bilateral vestibular schwannoma

NF2 is a condition of multiple slow growing tumours which rarely turn malignant. The main ethos of management is therefore preservation of function, rather than cure[68].

NF2 presents many difficult management dilemmas. The mainstay of management of NF2 is surgical removal of symptomatic cranial and spinal tumours. The timing of removal of vestibular schwannomas is a more difficult area.

NF2 related Vestibular schwannomas are more difficult to treat than their sporadic counterparts. This is because they are often large by the time they are treated and they tend to be more aggressive in nature. Therefore, whatever the treatment modality, the risk of recurrence, facial nerve injury and other complications is higher[68].

The first priority is to evaluate the disease load and symptoms with full brain and spinal MRI, neurological examination, opthalmological examination, full hearing assessment including brainstem auditory evoked responses (BAERs),cutaneous examination [68].

There are three treatment options in the management of vestibular schwannomas in the NF2 patient: conservative treatment with annual surveillance, stereotactic radiotherapy and microsurgical removal. The choice

of the appropriate treatment option for each individual patient is based on numerous patient, tumour and treatment factors[59] .

Factors determining treatment of vestibular schwannomas in NF2 patient

Factors determining treatment of vestibular schwannomas in the NF2 patient
Tumour factors Size, bilaterality, brainstem compression, hydrocephalus, hearing, vestibular and facial function
Patient factors Patient's preference, age, tumour burden.
Treatment factors Previous treatment, primary and secondary rehabilitation of auditory, vestibular and facial function

The overall goal of treatment should provide a balance between preservation of neurological function and tumor control.

Watch and wait and rescan[59].

This generally involves a strategy of watchful waiting where tumours are treated when they become symptomatic or are clearly growing radiologically. There is still debate. Some advocate an early, anticipatory approach to stop tumours becoming symptomatic eg. the treatment of small VS with stereotactic radiosurgery (SRS) or hearing preservation surgery.

Unless symptoms progress, patients should undergo regular annual neurological, ophthalmology and audiology assessment as well as brain MRI. Patients should undergo scanning every 6 months for 1 year and then annually thereafter . Spinal MRIs are generally performed every four to five years unless patients develop worrying symptoms or lesions.

Difficulties in Watch and wait policy.

1. MRI is expensive and patients may be lost to follow-up .

2. Tumours may undergo accelerated rates of growth after multiple years of stable period.

3 Patients who require surgery after observation are older and may suffer from more comorbidities which makes surgery potentially more risky.

4 Tumours with continued growth may no longer meet criteria for hearing preservation approaches or radiation therapy and may make facial nerve preservation more difficult.

Advantages with observation-

1 Potential elimination of the need for surgical or radiosurgical intervention.

2 Older patients may develop or have exacerbation of existing disease that may take precedence over treatment of the tumour (i.e., cancer, stroke, cardiac disease).

3 Younger patients may choose to observe the tumour to determine growth and choose intervention only when growth has been established.

4 Economic reasons, such as retirement, job changes, or insurance issues, may compel a-patient to choose observation as an initial option.

Inspite of all these pros and cons, surveillance may still be a feasible option in patients with multiple comorbidities and small tumours, in whom performing a craniotomy is a major undertaking (11).

Medical treatment [68]

There is an ongoing search for an effective medical treatment for NF2 related tumours. Phase 2 trials are under way for Lapatinib, a tyrosine kinase

inhibitor at EGFR receptors, Everolimus an immunosuppressant and Bevacizumab/Avastin. The latter is a monoclonal antibody that inhibits vascular endothelial growth factor and therefore tumour angiogenesis. It is currently approved for off label use in England under strict criteria including active schwannoma growth of at least 4mm or 60% volume in 12 months, in the context of severe multi tumour disease. It is suggested in situations where the tumour load is so high that targeted surgery would not be possible or beneficial or where there is loss of hearing secondary to growth in the only hearing ear, in an effort to re establish and preserve hearing for as long as possible. The initial observations are that Avastin is very effective at halting tumour growth and is therefore being increasingly used with rapidly growing tumours. The main disadvantages of Avastin therapy are that it poses a contraindication to surgery which is delayed until three months after stopping treatment and the benefits tend to last as long as the treatment, such that there is a risk of rebound on stopping. It also does not have any real efficacy against meningiomas.

New therapies

The NF2 protein appears to impact on multiple intracellular signalling pathways. These pathways include the PI3- kinase/Akt, Raf/MEK/ERK and mTOR pathways [69]. In particular, studies using NF2-derived tumour tissue reveal elevated levels of phosphorylated Akt. More recently, Akt- dependent phosphorylation of Merlin on 2 residues (Thr-230 and Ser-315) has been shown to target Merlin for ubiquitin-dependent degradation. Although no PI3 kinase or Akt inhibitors have yet been approved for treatment, there are multiple compounds in development – primarily for oncology indications. The Raf/MEK/ERK pathway has been implicated in NF2 tumorigenesis in part through identification of elevated levels of phosphor ERK and phospho-MEK.

The progress being made in cellular research especially with regard to pathways in which the NF2 gene product interacts raises the hopes of targeted therapy. Targeting the ERK1/, AKT, integrin/focal adhesion kinase/Src/Ras

signaling cascades, PDGFRbeta, phosphatidylinositol 3- kinase/protein kinase C/Src/c-Raf pathway, VEG-F and other pathways [69,70] means that drugs such as avastin, lotinib [71], lapatinib and sorafenib [72] may well bear fruit.

Stereotactic Radiosurgery

Radiosurgical techniques include single-session gamma knife surgery (GKS) and linear-accelerator (LINAC) technologies, as well as fractionated radiosurgery such as the CyberKnife. Of these, GKS is the best studied and most widely used.

Though the primary goal of surgical resection is complete tumour removal, the primary goal of radiation therapy is tumour control. It is widely accepted that Stereotactic radiosurgery is less effective in NF2 related VS. Relative growth ratios with contralateral controls indicate that SRS does have a beneficial effect in slowing tumour growth[74]. Tumour volume is the main determinant of outcome and that coupled with their propensity to grow, restricts the size of tumour suitable for treatment. The Sheffield group suggest a volume limit of $10cm^3$.[75] . There is a 5% risk of facial palsy and whilst there is great individual variation in the rate of hearing loss, overall SRS does not appear to slow the rate of deterioration[74].

Stereotactic radiosurgery could perhaps be advocated for the smaller tumors on the contralateral side. However, its long-term effects on theVIIth /VIIIth nerve complex and on VS growth have still not been conclusively established[73.]

Radiosurgery controls the tumor in 90% of patients and causes shrinking in approximately 20%[73]. However, secondary regrowth may occur and hearing may have a delayed deterioration. In NF2 patients, the risk of hearing loss following radiotherapy/ radiosurgery on the side of the smaller tumors is too high[73].

Many have concerns about the risk of malignancy, delivering radiation to a tumour prone condition. In contrast, others advocate fractionated

stereotactic radiotherapy in an attempt to preserve hearing and facial nerve function[75].

Radiotherapy has its inherent complications, may scar arachnoidal planes and may induce fibrosis and sclerosis, making surgery after previous radiotherapy extremely difficult[77].

Compared with microsurgery, potential advantages of GKS include faster recovery, reduced cost, and minimized morbidity and mortality.

Surgery

Surgery remains the primary treatment for NF2 related vestibular schwannomas. VS in NF2 are more difficult to treat than those of sporadic unilateral VS because NF2-related VS are often multifocal in the eighth nerve complex, and the potential for associated facial nerve schwannomas[68]. Most are large, in which case, hearing preservation surgery is not possible. Despite the great improvement in VS surgery over the last three decades, facial nerve damage and other adverse outcomes remain a real possibility during tumour removal, especially in the hands of less experienced VS surgeons[1]. Facial weakness may threaten the health of the eye as a result of loss of the protective blink reflex and as the lacrimal gland is also supplied by the facial nerve the loss of tear production will increase this risk. If facial nerve damage coexists with loss of corneal sensation from damage to the trigeminal nerve then the eye becomes exceptionally vulnerable to corneal ulceration and blindness[1].

The cornerstone of modern NF2 management is conservation of function, and the maintenance of "quality of life". The mere presence of a tumour is not an indication for its removal. Serious thought must be given to the benefits that are sought and the risks and complications of the surgery, and the treatment must be tailored to the needs of the individual patient[78] . Attempts at hearing preservation surgery should be limited to experienced centres who can offer a realistic chance of maintaining both the cochlear

nerve, but also cochlea function. If hearing is lost after apparent cochlear nerve preservation the patient may still be suitable for a cochlear implant. In many if not most instances the best policy will be to observe VS to decide on the best time to balance surgical morbidity against the almost inevitable loss of hearing[1].

The timing of surgery is a balance between hearing, facial nerve function and brainstem compression[68]. When there is no functional hearing, the threshold for surgery is lower, by which time the tumour may have reached a considerable size, increasing the risk of facial nerve injury and other surgical complications. Some advocate an early surgical approach to small intra canalicular VS by a middle fossa approach with hearing preservation rates of up to 50%[68].

The principle of minimal interference for VS applies equally to schwannomas on other cranial nerves, to intracranial meningiomas, and to spinal tumours[1]. It is very uncommon to have to remove a schwannoma growing on a cranial nerve other than the eighth because these tumours appear to have a much slower growth pattern than NF2 VS. Spinal tumours are mostly considered for excision if they are clearly producing symptoms or physical signs. In the absence of any dramatic growth of tumours, the head should be scanned every year and the spine every 3 years[1].

Surgery for vestibular schwannoma

The goal of surgery is complete tumour removal while preserving neurologic function if possible.

Surgical approaches are used for removal of VS:

1 Retro sigmoid Approach

2. Translabyrinthine Approach

3. Middle cranial fossa (MCF) Approach.

Choice of Approach

Depends on whether hearing can be preserved or not.The retrosigmoid and MFC are two surgical techniques most commonly used when attempting to preserve hearing.

1 Auditometry- Hearing preservation may be attempted when the pure tone average is 50 dB or less and speech discrimination is more than 70%.

2 Tumour size more than 2 cm is rarely amenable to hearing preservation despite initial hearing status.

3 Location of tumour - Tumours located far lateral in the lAC with extension into the cochlea or vestibule may not be amenable to hearing preservation.

Although many factors influence the choice of surgical approach, personal experience of the surgeon often determines the surgical approach.

1.Steps in retrosigmoid approach

1. Position -Modified park bench.

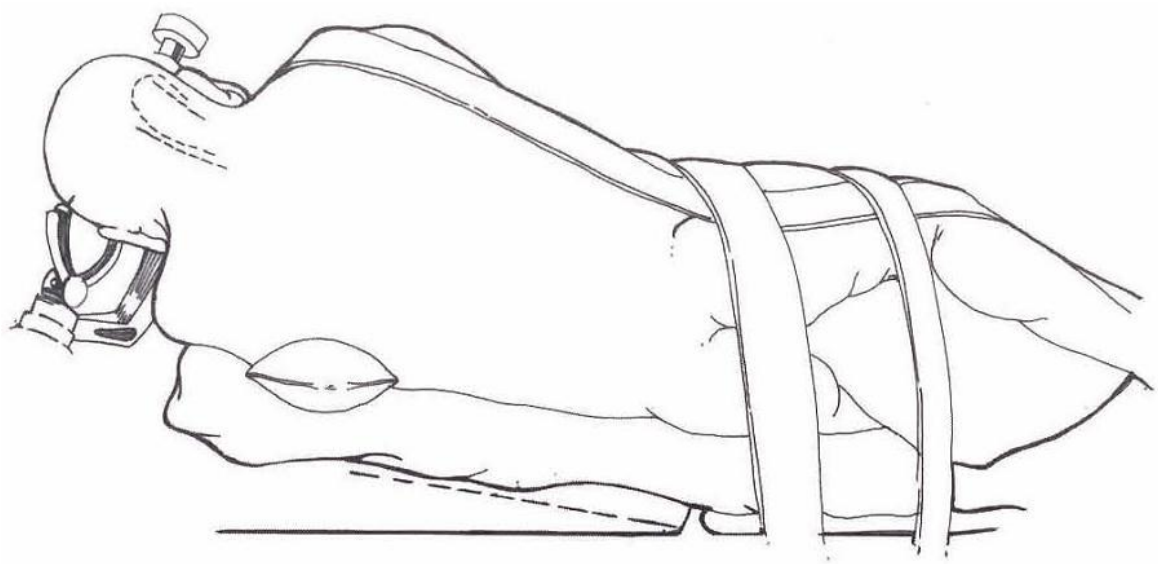


Fig 4. Lateral decubitus position.

2. Vertically oriented "S"shaped incision 4 cm posterior to the ear canal is made.

3. Small craniectomy is performed, anterior and superior limits of the craniotomy are the sigmoid and transverse sinuses, respectively. Laterally exposed mastoid air cells near the sigmoid sinus are occluded with bone wax to prevent transgression of CSF.

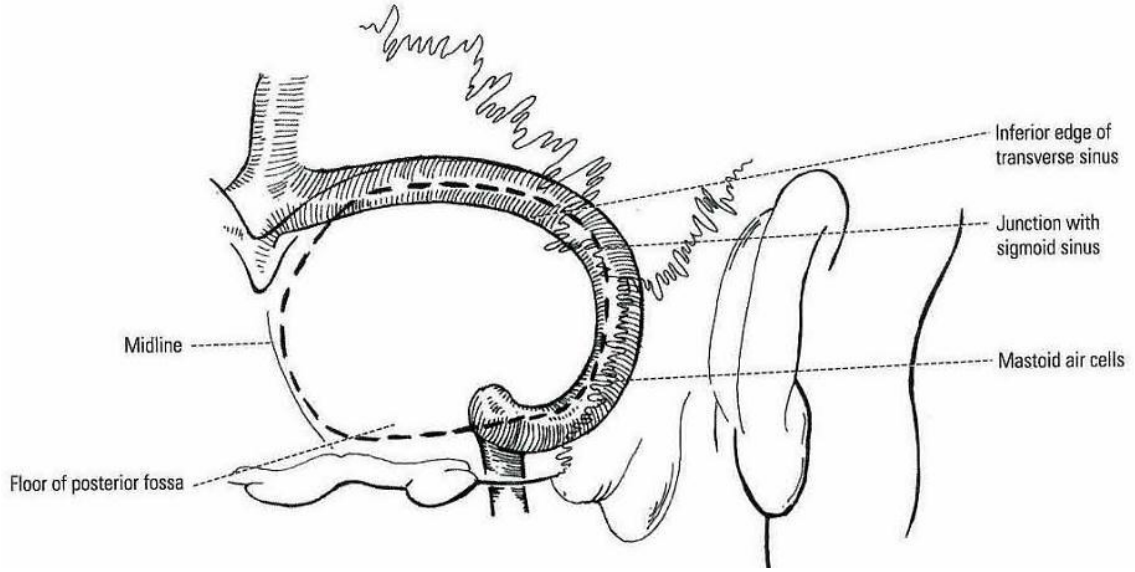


Fig 5. Anatomical boundaries retromastoid suboccipital craniectomy.

5. The dura is then opened and reflected.

6. Cisterna magna is opened to release the CSF which maximizes posterior fossa relaxation and minimizes the need to retract the cerebellum.

7. Once adequate exposure has been obtained, the tumor is clearly visualized along with the brainstem and lower cranial nerves. The facial nerve is displaced anteriorly and superiorly in the cerebellopontine angle. The tumor displaces the trigeminal nerve upward and the glossopharyngeal and vagus nerves downward.

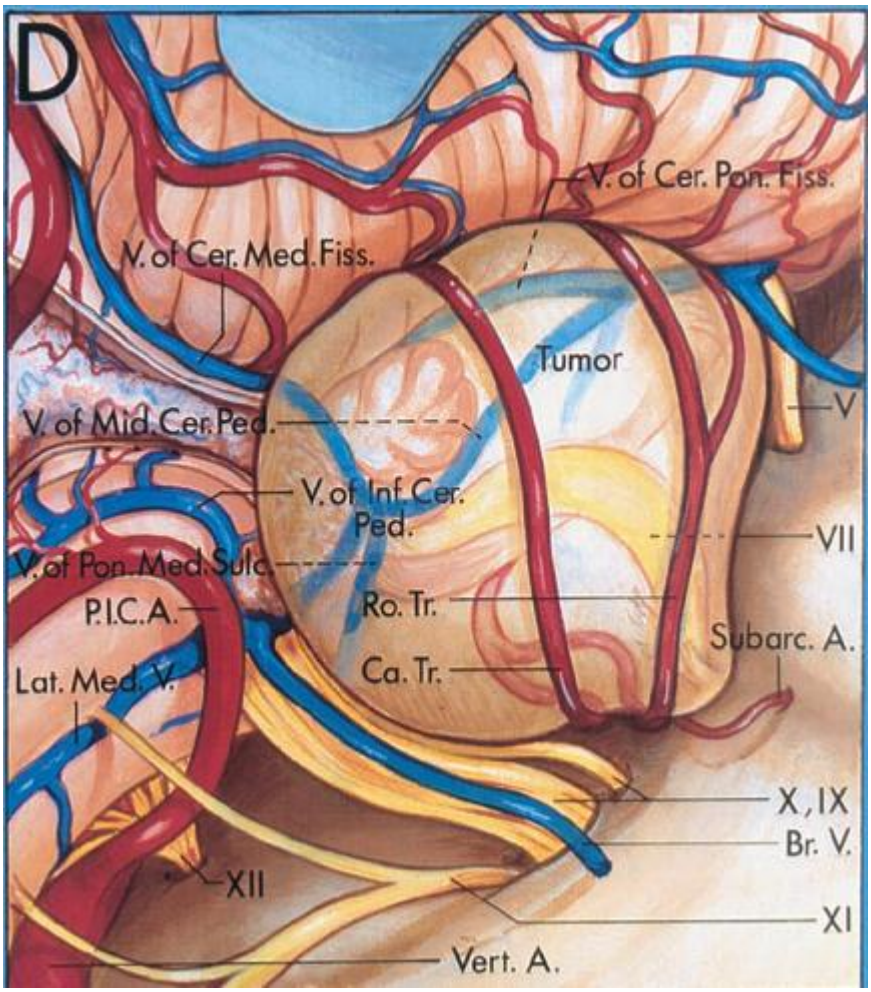


Fig 6. Relationships of an acoustic neuroma

8. The arachnoid over the tumor can be stripped away without coagulation, it provides not only the best plane for dissection but also a protective barrier for the cranial nerves and their small feeding vessels.

8. After peeling away the arachnoid, a nonstimulating area on the posterior tumor is coagulated with bipolar cautery and opened with microscissors and specimens are sent for pathologic study.

9. Debulking of the tumor is the next step and must be carefully performed under an operating microscope, using micro dissecting instruments, so as to maintain the anterior portions of the capsule if injury to cranial nerve VII and/or VIII are to be avoided. Depending on the size of the tumor, this process of

internal decompression followed by dissection and inward rolling the capsule may need to be repeated several times.

10. Once the tumor has been substantially debulked, the posterior wall of the internal auditory canal can be removed using a high-speed drill. Great care must be taken to avoid injuring the labyrinth while removing the posterior wall of the internal auditory canal. Drilling continues until the dura is seen. Drilling is stopped before the lateral edge of tumor is reached.

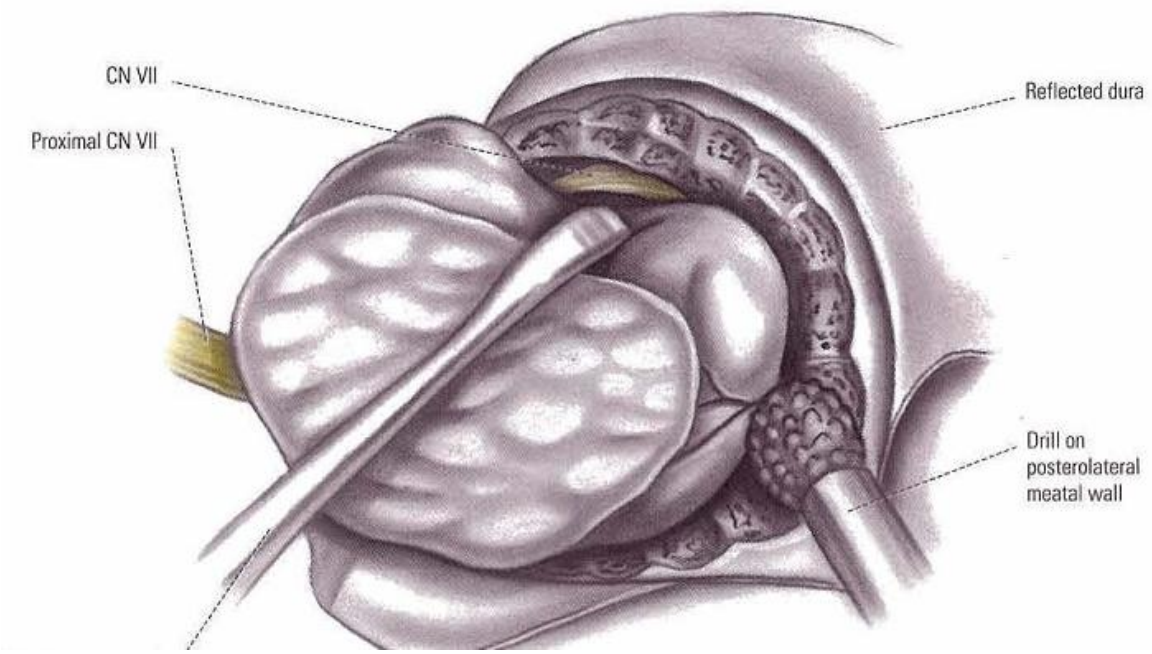


Fig 7 Exposure of VII th nerve in meatus.

11. Once the internal auditory canal is exposed, the dura is opened and the tumor is removed from it.

12. The superior vestibular nerve, inferior vestibular nerve, and tumour are identified in the posterior aspect of the canal. Gentle retraction of the superior vestibular nerve reveals the facial nerve, which is identified physiologically with a stimulator at minimal settings (0.05 rnA). The vestibular nerves are sectioned laterally, and tumour dissection is performed in the plane between the tumour and the facial and cochlear nerves in a lateral to medial fashion.

13 . Once the tumour dissection is complete, bone surrounding the lAC is sealed with bone wax and fibrin glue.

14. Eventually, the surgeon is left with the anterior portions of the capsule adhered to the brainstem and cranial nerve VII. As the tumor capsule is carefully removed from the brainstem, the root entry zone of cranial nerve VII can be identified. The capsule is then carefully removed from the facial nerve with as little trauma as possible. The facial nerve monitoring is of great help in this portion of the dissection to preserve the facial nerve.

All the lower cranial nerves and draining veins are preserved. Good hemostasis is secured, dura closed primarily and wound closed in layers.

Advantages -

1 .No tumour size limitation, can be applied to all acoustic tumors.

2 .Hearing preservation possible

3. Best wide-field visualization of the posterior fossa

4. Auditory brainstem implant placement possible .

5. Consistent facial nerve identification.

Disadvantages-

1 .Limited exposure of lateral lAC

2 .Intradural drilling

3. Postoperative headaches

4 .Cerebellar retraction

5. Facial nerve identification is relatively late in the dissection.

2. Translabyrinthine Approach

1. A C-shaped skin incision starts 1 cm superior to the auricle at the anterior-most aspect of the ear behind the sigmoid and extends to the mastoid tip.

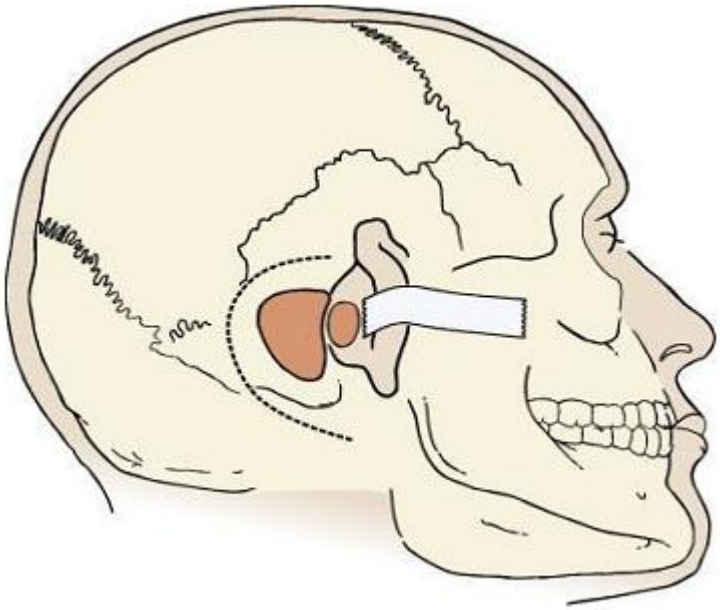


Fig 8. Translabyrinthine approach

2.Drilling follows that used for the retrolabyrinthine presigmoid approach. Once the mastoidectomy is completed to the point that the antrum is exposed, the incus is identified. The drilling is performed anterior to the facial nerve (facial recess), and the ossicles are fully exposed. The entire vertical portion of the facial nerve is drilled. The anterior bone of the facial recess is drilled to expose the incus and malleus.

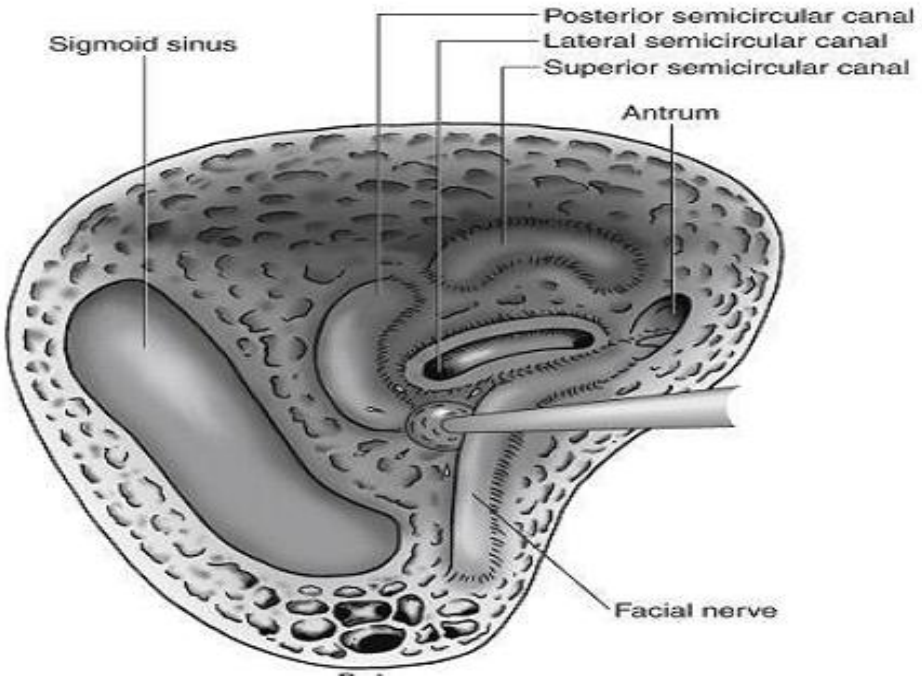


Fig 9.

3. The incus is removed and the tendon for the tensor tympani is cut.

4. The eustachian tube is identified and the middle ear are packed with temporalis muscle to minimize the risk of CSF leakage.

5. The vestibule (the junction between the lateral and posterior semicircular canals) that constitutes the lateral wall of the IAC is opened. The translabyrinthine approach exposes 270 degrees of the IAC. The facial nerve is anterior and the superior vestibular nerve is posterior to the vertical crest ("Bill's bar"),. Exposing the entry of the facial nerve into the IAC enables the transition between normal facial nerve involved with tumor to be identified.

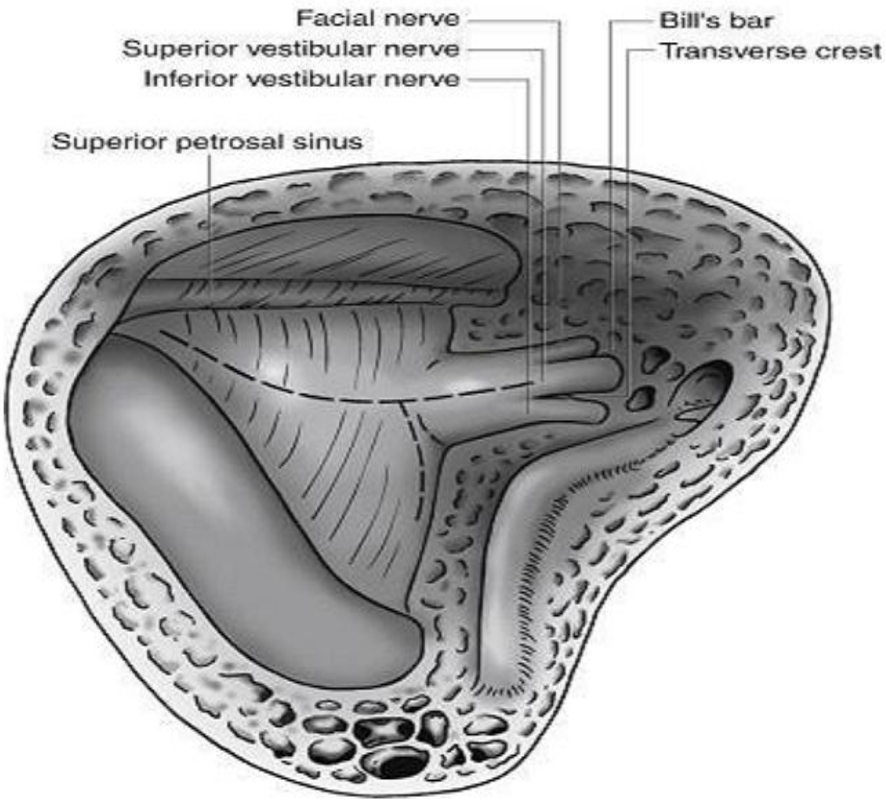


Fig 10

6. Once the dura is open, the entire subarachnoid, intracanicular, and vertical portions of the facial nerve are evident .

7. The facial nerve and the superior and inferior limits of the tumor are identified, and the tumor is debulked from it's core . Once a significant portion of the tumor has been removed, the superior and inferior vestibular nerves are cut and the tumor is peeled away from the facial nerve .The tumor is separated from the cerebellum using the intervening arachnoid plane. Finally, the facial nerve is decompressed completely .

8. Once the tumor is removed, the closure proceeds

Advantages-

1. It provides an option for resecting a tumor of any size.

2. It has excellent exposure of the posterior fossa.

3. It utilizes the least cerebellar retraction and the facial nerve is easily identified throughout the case.

Disadvantages-

1 Any residual hearing is sacrificed through this approach .

2 .CSF leak which necessitates abdominal fat graft placement

3. Unfamiliar anatomy to the neurosurgeon.

Steps in Middle Cranial fossa approach-

1. Supine position

2. Posteriorly based, U-shaped skin flap is designed.

3. 4 x 4 cm craniotomy is performed - two-thirds anterior to the external auditory canal and one third posterior.

4.. Middle fossa dura is elevated from the temporal bone medially to the petrous ridge. Dissection proceeds in a posterior to anterior direction to avoid trauma to the geniculate ganglion and greater superficial petrosal nerve, which may be dehiscent in upto 15% of patients. Anteriorly, dissection stops short of the foramen spinosum and middle meningeal artery.

5.Identify IAC, including the arcuate eminence overlying the superior semicircular canal, the greater superficial petrosal nerve, and the external auditory canal. The semicircular canal is blue lined in an anterolateral direction to expose the lateral extent of the canal near the lAC. The plane of the lAC can be approximated by bisecting the angle between the greater superficial petrosal nerve and superior semicircular canal.

6. Drilling along the petrous ridge helps localize the lAC safely. Drilling is extended laterally toward the fundus. While drilling directly over the canal, avoid injury to the underlying cochlea anteriorly and labyrinth posteriorly.

7. The facial nerve is traced laterally to expose the geniculate ganglion and the labyrinthine segment of the facial nerve.

8. The dura of the lAC is opened parallel to the long axis of the lAC. The facial nerve is identified in the anterior aspect of the lAC.

9. The tumour is dissected from the facial nerve throughout the lAC. Once the facial nerve is separated, superior and inferior vestibular nerves are avulsed laterally.

10. The tumour and vestibular nerves are dissected free from the facial and cochlear nerves in a lateral to medial fashion and tumour removed. Muscle or fat is placed in the lateral lAC. The temporal lobe is released and craniotomy is replaced.

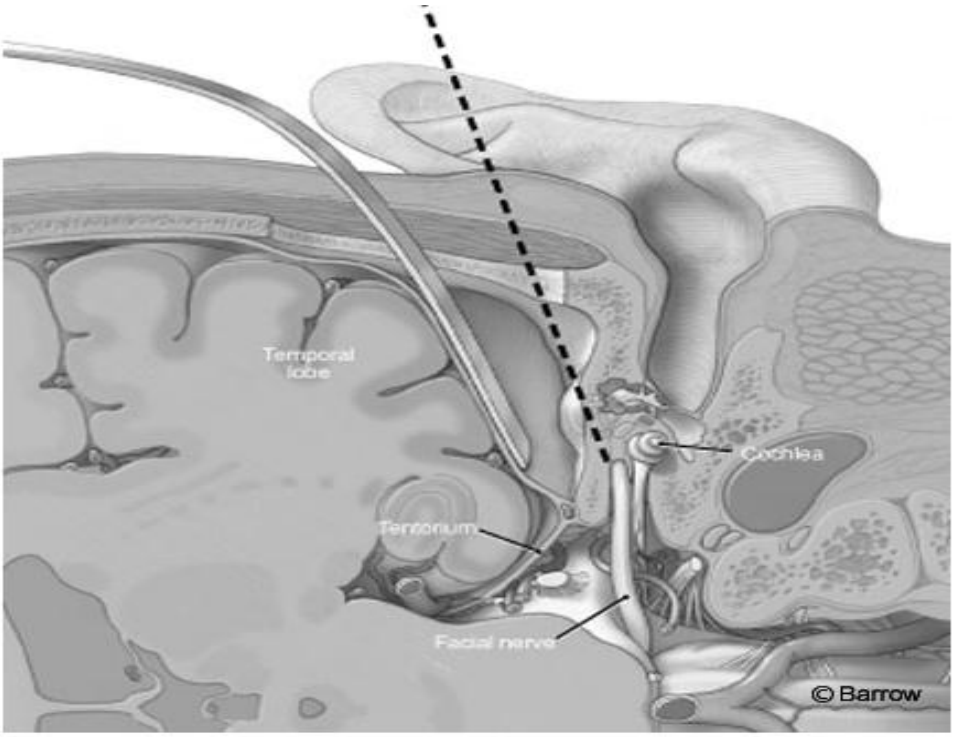


Fig11. Illustration shows the trajectory and angle of attack through the middle fossa for exposing the internal auditory canal

Advantages

1. The MCF approach is one of the approaches that allow hearing preservation.
2. Additionally it provides good exposure of the lateral internal acoustic meatus, CPA and clivus.
3. Drilling is extradural thereby decreasing morbidity.

Disadvantages

1. Size limits of tumors <2cm in greatest dimension.
2. Extensive temporal lobe retraction.
3. Limited exposure of the posterior fossa.
4. Required facial nerve dissection to access .

Complications of surgery

1. Recurrence

Recurrent tumour is the result of regrowth of residual tumour fragments. Despite total removal of all microscopically visible tumours, remnants of nerves may contain undetectable tumour cells. Recurrence is uncommon after acoustic tumor removal. Overall, the recurrence rate is 5-10% or lower. The desired mortality rate is below 1%; the current mortality rate is approximately 1–2% and, rarely, 1–3%[79].

2. Cerebrospinal fluid leak

The most common postoperative complication after VS resection and it occurs in approximately 10% of patients [80]. The MCF approach has a slightly lower rate than the other two approaches [81]. CSF leaks increase the risk of meningitis. Although the overall risk of meningitis is between 1% and 3%, a CSF leak raises the risk to roughly 14%[80] .Most leaks after the

translabyrinthine and MCF approaches present as rhinorrhea, while after retrosigmoid approach presents as rhinorrhea and incisional leaks.

3. Equilibrium

Most patients experience acute vertigo after surgery for VS. Recovery of balance is nearly universal by 6 to 9 months after surgery [82] .

4. Meningitis

Meningitis occurs in 1% to 8% of cases and may be either bacterial or aseptic.Aseptic meningitis occurs more commonly than bacterial and is secondary to inflammation from bone dust or blood. Any suspicion necessitates a lumbar puncture and aggressive therapy with broad-spectrum antimicrobial therapy and steroid prophylaxis while awaiting cultures. Aseptic meningitis responds quickly to steroids, which are slowly tapered over 3 to 4 weeks to prevent recurrent symptoms.

5. **Postoperative headache**.

Headache of over 3 months occurs in approximately 10% of patients with retrosigmoid (21%) approach having the highest incidence compared to middle cranial fossa (8%) and translabarynthine (3%) approaches[83] .

6. Tinnitus

Although more than half of patients without tinnitus preoperatively experience it postoperatively, nearly 50% of patients with preoperative tinnitus experience a significant reduction in their tinnitus postoperatively [85]. Most patients compensate well to the tinnitus and rarely are distressed by symptoms.

7. Seizure, hydrocephalus, and stroke represent <2% of cases and are rarely encountered [84].

Hearing Preservation and Augmentation

All NF2 patients should be referred to an audiologist for regular hearing assessments and training in anticipation of losing their hearing. Hearing and communication may be optimised by hearing aids initially. Lip reading, sign language and cochlear or auditory brainstem implants are options for those who have completely lost their hearing.

Of the surgical implants, cochlear implants provide a better quality of auditory input however they require an intact cochlear nerve. The scenario where this might occur in NF2 related VS is following attempted hearing preservation surgery or where there is a stable vestibular schwannoma with no hearing loss.

Auditory Brain Stem Implants (ABI):

ABIs are used to treat total deafness when there has been permanent damage to the cochlear nerves and hearing can therefore not be improved by other (more effective) means such as hearing aids or cochlear implant. Electrodes are placed on the cochlear nucleus at the auditory prominence, through the Foramen of Luschka in the lateral recess of the 4th ventricle, guided by electrophysiology recordings of the brainstem auditory evoked responses. This is connected to an external receiver and sound processor which convert sounds into electrical signals. The auditory sensations that are gained are a perception of environmental sound which can be a great aid to lip reading. Excellent speech perception is possible. ABIs are often placed immediately following removal of vestibular schwannomas in the same surgical sitting. In patients with NF2 and bilateral vestibular schwannomas, ‘sleeper’ ABIs are increasingly being placed with the removal of the first VS in anticipation of complete hearing loss as the opposite VS grows or is treated. There is some growing evidence that patients can derive greater benefit from their ABI if they have the opportunity to practice using it particularly whilst they have some residual.

AIMS AND OBJECTIVES

3. AIMS AND OBJECTIVES

1. To define the clinical characteristics of bilateral vestibular schwannoma.

2. To review the literature and compare our results with published series on bilateral vestibular schwannoma with regard to clinical manifestation, imaging features, diagnosis, surgical procedures and prognosis.

3. To assess facial nerve preservation and surgical outcome of surgically treated bilateral vestibular schwannoma.

MATERIALS AND METHODS

4. MATERIALS AND METHODS

Of 775 patients admitted with vestibular schwannoma during the period from January 1998 to September 2012 at the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala., 25 tumors in 19 consecutive patients with bilateral VS underwent surgery over a span of 14 years by a single senior author. Their surgical records during the same time period were reviewed retrospectively for the study.

The inclusion criterion for this study was the presence of bilateral VS on CT and/or MRI. Other patients with NF2 who had unilateral VS, with either a first-degree relative with VS, with associated meningioma or glioma or with juvenile posterior subcapsular lenticularopacity, were excluded from this study. However, patients with bilateral VS and the above-mentioned features, were included in the study

Record of all patients with bilateral VS were reviewed in order to analyse clinical data such as age, sex, presenting symptoms, signs, duration of symptoms to define the clinical characteristics. Presence of preoperative facial palsy, grade of facial palsy, presence or absence of compensated or uncompensated lower cranial nerve palsy, cerebellar signs were meticulously noted in all cases. Audiometry which included pure tone auditometry, speech reception threshold and speech discrimination was performed preoperatively in majority of patients unless they were neurologically too poor to be undergo the test. Extent of hearing loss (serviceable or non serviceable) was documented. Gardner Robertson Classification system was used to objectively define the extent of hearing loss. Serviceable hearing was defined as a four-frequency puretone average of better than 50 dB and a speech-discrimination score (SDS) of 50% or better.

Gardner Robertson Classification system

Class	PTA/SRT	SDS (%)
1	0-30dBHL	70-100
2	31-50dB HL	50-69
3	51-90 dB HL	5-49
4	>90 dB HL	1-4

Radiological investigations included conventional MRI imaging -T1 and T2-weighted imaging and Gadolinium-DTP.An enhanced Tl weighted MR images, Pre and postcontrast CT scans . Additionally, the tumour size was estimated by measuring the mean maximum anteroposterior and mediolateral diameters on the magnetic resonance imaging studies.

The tumors were then categorized according to the classification proposed by Jackler et al. as: (i) small, <1 cm; (ii) medium, 1–2.5 cm; (iii) large: 2.5–4.0 cm; and (iv) giant, >4 cm.

According to the classification of Samii et al[77].the tumor extent was defined as:

(i) T1 tumor, purely intrameatal.
(ii) T2 tumor, intra- and extrameatal.
(iii) T3a tumor, filling cerebellopontine angle (CPA) cistern.
(iv) T3b tumor, reaching to the brainstem.
(v) T4a tumor, compressing the brainstem.
(vi) T4b tumor, severely compressing the brainstem.

All patients underwent retrosigmoid suboccipital craniectomy and tumour excision in lateral position by the senior author. Standard microsurgical techniques were used in all patients. Adjuncts like cavitron ultrasonic surgical aspirator and facial nerve monitoring was done as and when required.Operation record of all patients were analysed for anatomical preservation of facial nerve, lAM extension. The extent of tumour removal was analysed and classified as either total or subtotal removal. Total removal was reported when operating surgeon on microscopic surveillance of the tumour bed found no tumour remnants. Subtotal removal was reported when operating surgeon had left behind tumour adherent to the brainstem, 7th nerve complex or into the internal auditory meatus. Tumour was sent for histopathological analysis. Surgically related complications were recorded and managed accordingly. All patients underwent elective postoperative CT scan on day 1. They were followed up on outpatient basis after discharge and follow up CT scan and or MR imaging was preformed.

Surgical outcome was analysed in terms of extent of tumour removal, postoperative facial nerve outcome and morbidity and mortality. The postoperative facial nerve function was assessed according to the House Brackmann classification system at discharge and 6 months postoperatively.

House-Brackmann Facial nerve paralysis Classification

		Characteristics			Estimated Function (%)
Grade	Description	Gross	At Rest	Motion	
I	normal	normal	normal	normal	100
II	mild dysfunction	slight weakness noticeable on close inspection, may have very slight synkinesis	normal symmetry & tone	forehead: moderate to good function; eye: complete closure w/ minimum effort; mouth: slight asymmetry	80
III	moderate dysfunction	obvious but not disfiguring difference between 2 sides; noticeable but not severe synkinesis, contracture, and/or hemifacial spasm	normal symmetry & tone	forehead: slight to moderate movement; eye: complete closure w/ effort; mouth: slightly weak w/ maximum effort	60
IV	moderately severe dysfunction	obvious weakness and/or disfiguring asymmetry	normal symmetry & tone	forehead: none; eye: incomplete closure; mouth: asymmetric w/ maximum effort	40
V	severe dysfunction	only barely perceptible motion	asymmetry	forehead: none; eye: incomplete closure; mouth: slight movement	20
VI	total paralysis	no movement	asymmetry	no movement	0

Patient were grouped into three depending on the degree of facial nerve palsy preoperative immediate postoperative and at last follow up

Group 1: Good facial nerve function: HB grade 1 or 2.

Group 2: Intermediate facial nerve function: HB grade 3 or 4.

Group 3: Poor facial nerve function: HB grade 5 or 6.

Surgical morbidity was assessed in terms of Glasgow outcome scale.

Glasgow outcome scale

1. Dead
2. Vegetative state
3. Severe disability- Able to follow commands/ unable to live independently
4. Moderate disability- Able to live independently; unable to return to work or school
5. Good recovery- Able to return to work or school.

Statistical Methods: Descriptive statistical analysis was carried out for data analysis. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number(%).

RESULTS

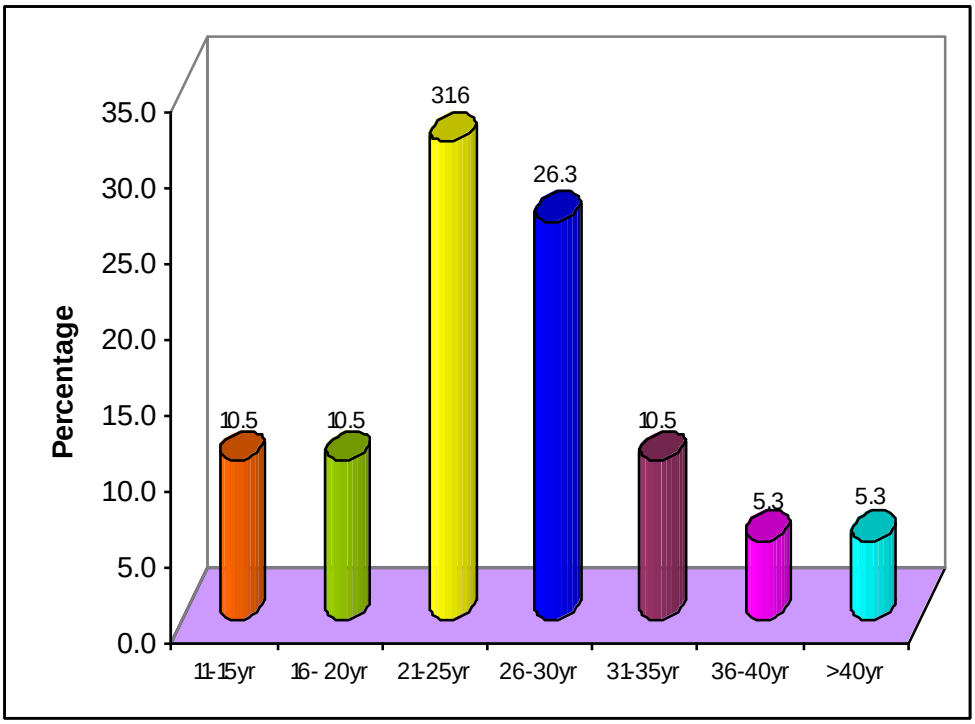
Results:

Of 775 patients admitted with vestibular schwannoma during January 1998 to September 2012 , 25 tumors in 19 consecutive patients with bilateral VS underwent surgery over a span of 14 years by a single senior author.

Table1. Percentage distribution of the sample according to age.

Age	n=19	Percent
11-15yr	2	10.5
16- 20yr	2	10.5
21-25yr	6	31.6
26-30yr	5	26.3
31-35yr	2	10.5
36-40yr	1	5.3
>40yr	1	5.3

Graph1. Percentage distribution of the sample according to age.

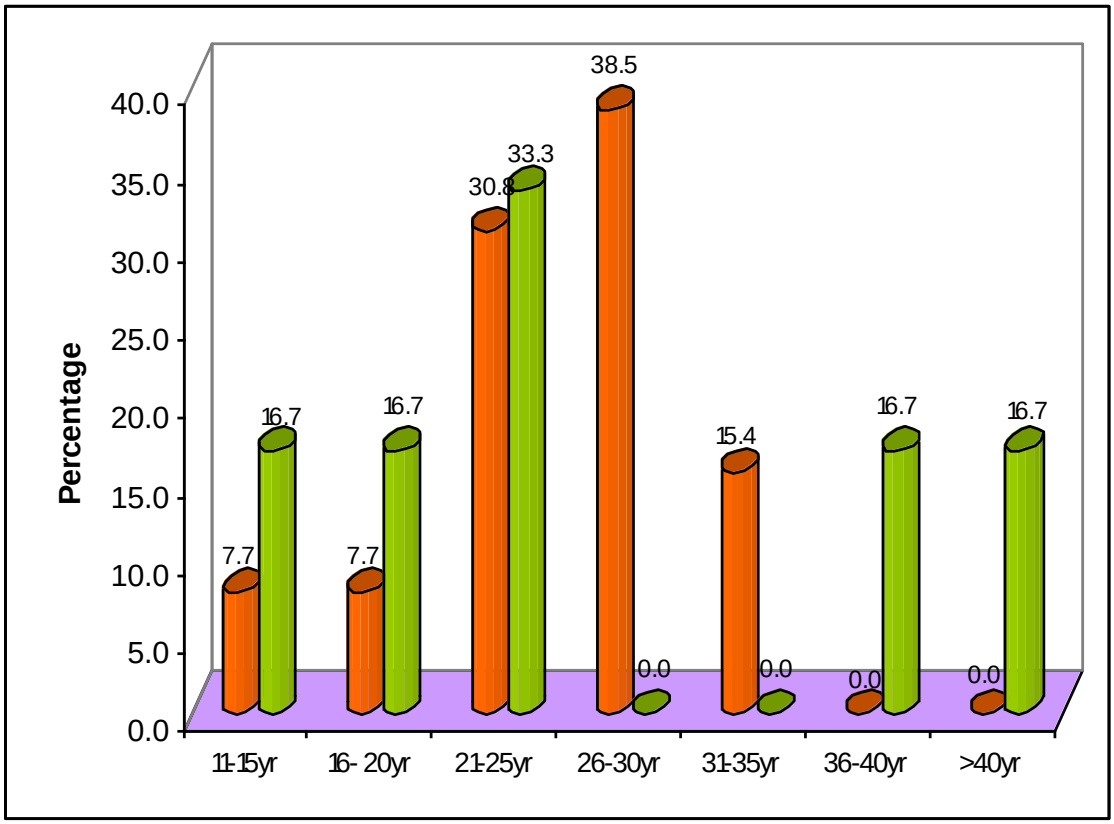


Mean age of bilateral VS presentation was 26.2 years with a range of 13 to 47 years. The most common age group was in 2nd decade.

Table 2. Distribution of the sample according to age and sex.

Age	Male		Female	
	n=13	Percent	n=6	Percent
11-15yr	1	7.7	1	16.7
16- 20yr	1	7.7	1	16.7
21-25yr	4	30.8	2	33.3
26-30yr	5	38.5	0	0.0
31-35yr	2	15.4	0	0.0
36-40yr	0	0.0	1	16.7
>40yr	0	0.0	1	16.7

Graph 2. Distribution of the sample according to age and sex.

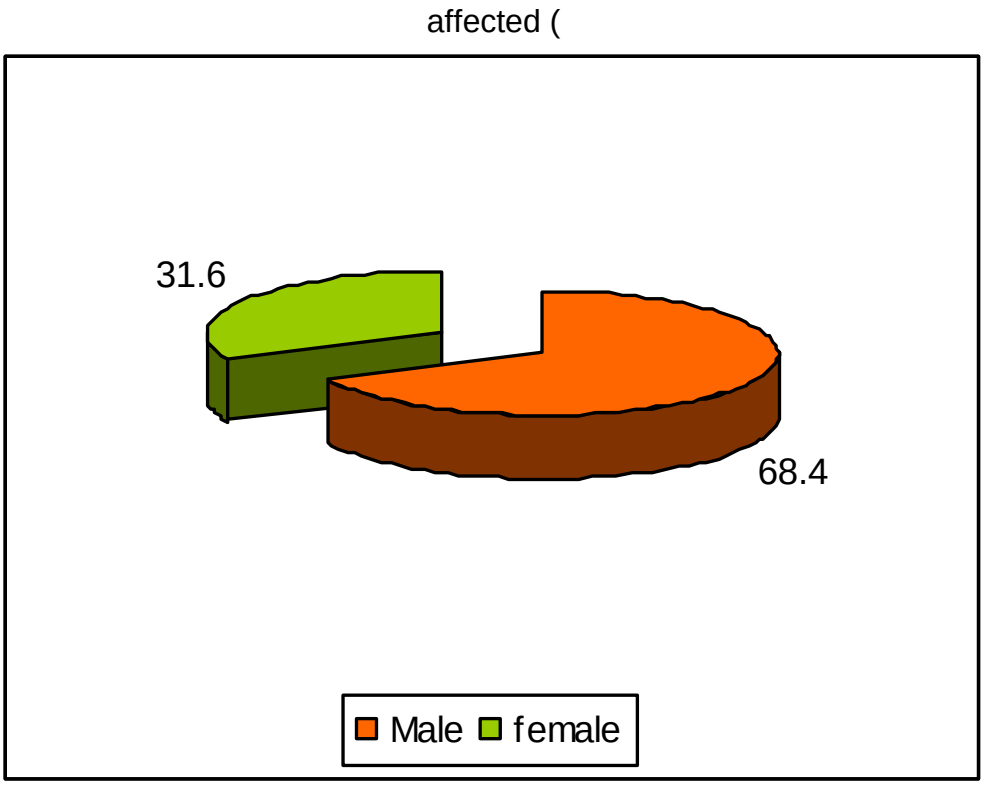


Family history of NF2 was present in four patients.

Table 3. Distribution of the sample according to sex.

Sex	n=19	Percent
Male	13	68.4
Female	6	31.6

Graph.3. Distribution of the sample according to sex.



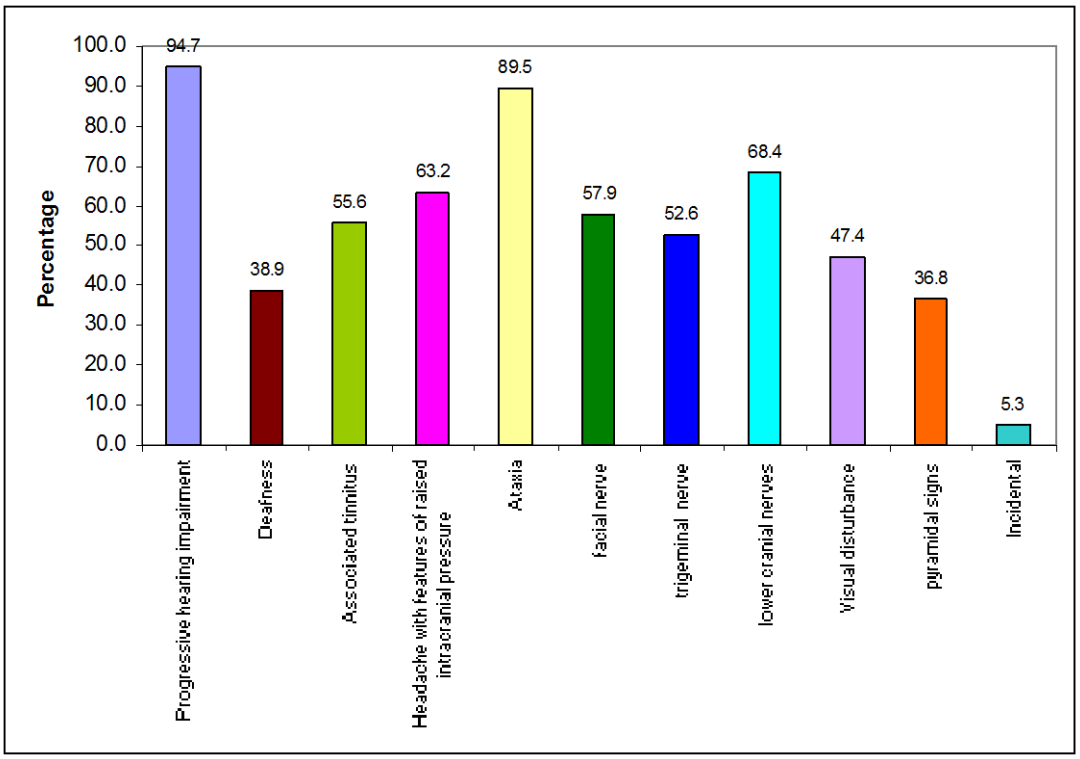
Males were most commonly 68.4%).Male to female ratio being 2:1.

Clinical findings in bilateral vestibular schwannoma.

Table 4. Pre operative clinical findings.

Pre operative clinical findings	n=19	Percent
Progressive hearing impairment	18	94.7
Deafness	7	38.9
Associated tinnitus	10	55.6
Headache with features of raised intracranial pressure	12	63.2
Ataxia	17	89.5
Facial nerve	11	57.9
Trigeminal nerve	10	52.6
lower cranial nerves	13	68.4
Visual disturbance	9	47.4
pyramidal signs	7	36.8
Incidental	1	5.3

Graph 4. Pre operative Clinical findings.

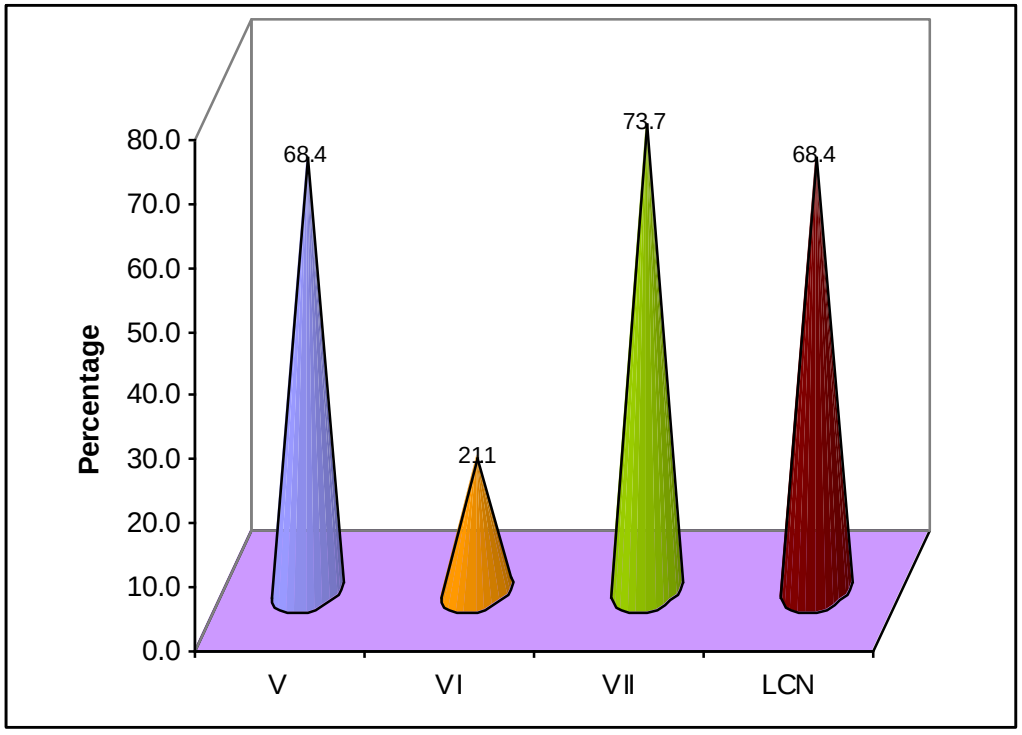


Progressive hearing impairment was the common initial symptom in 18 patients(94.7%) with preoperative deafness noted in 7 patients(37%) and associated tinnitus in 10 patients.

Table 5.Cranial neuropathy at initial presentation.

Cranial neuropathy	n=19	Percent
V	13	68.4
VI	4	21.1
VII	14	73.7
LCN	13	68.4

Graph 5. Cranial neuropathy at initial presentation.

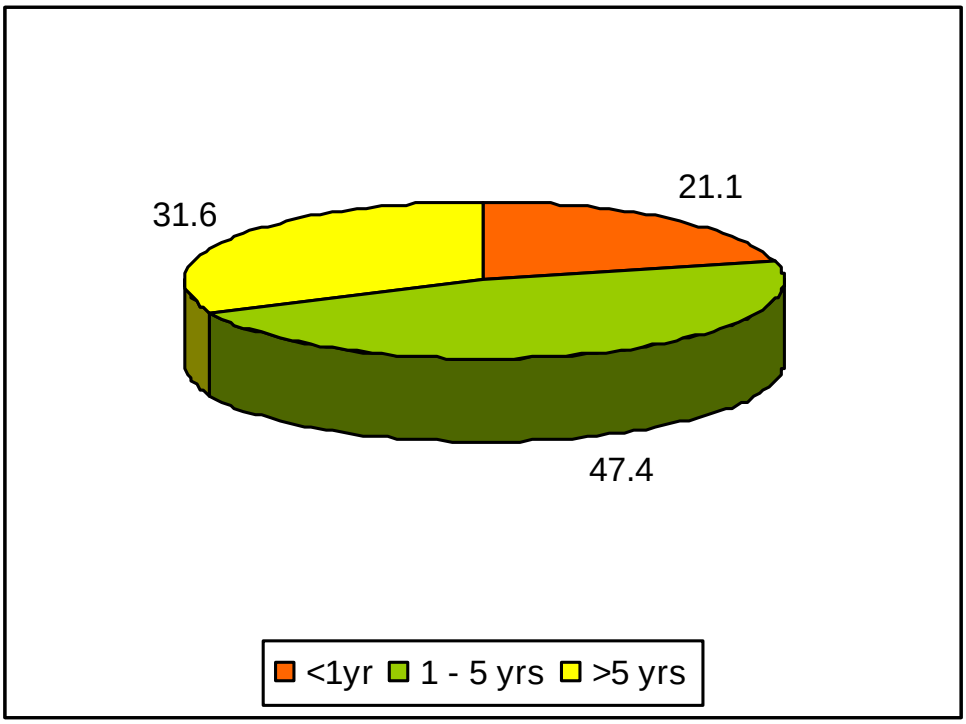


Other than vestibulocochlear nerve most common cranial nerve involved preoperatively at initial presentation in bilateral VS was facial nerve(73.7%).

Table 6. Duration of hearing impairment at initial presentation.

Hearing loss	Count	Percent
<1yr	4	21.1
1 - 5 yrs	9	47.4
>5 yrs	6	31.6
Mean ± SD	3.8 ± 3.7	

Graph.6 Duration of hearing impairment at initial presentation.

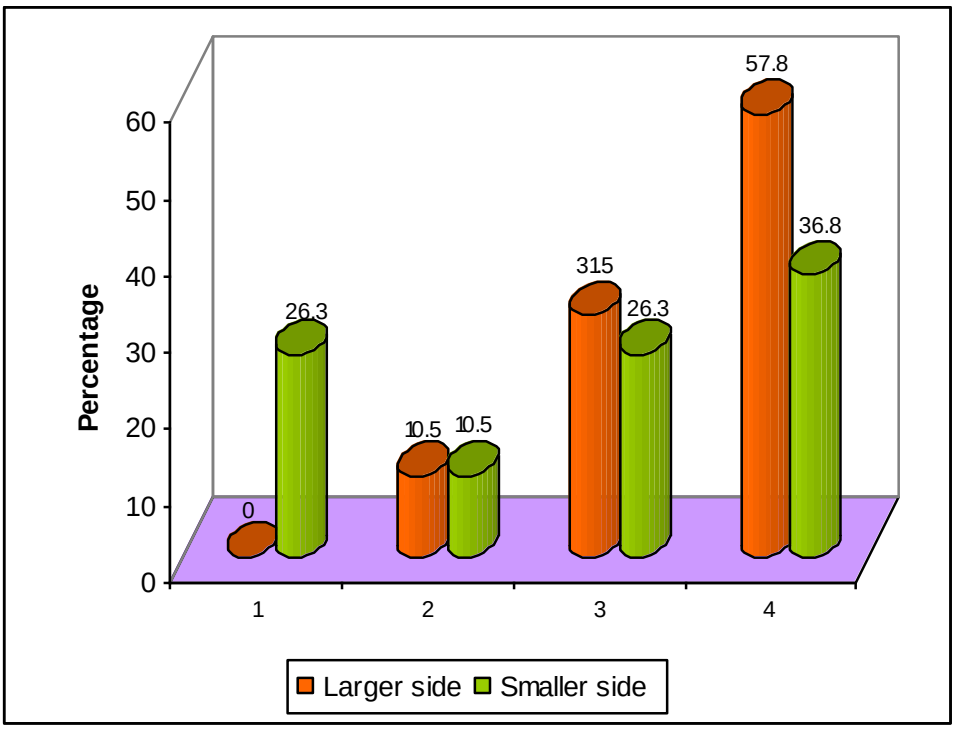


Mean duration of hearing impairement before diagnosis was 3.8 years at initial presentation.

Table.7.Preoperative hearing impairment (Gardner Robertson Classification system).

Class	Larger side n =19	Smaller side n =19
1	0	5(26.3%)
2	2(10.5%)	2(10.5%)
3	6(31.5%)	5(26.3%)
4	11(57.8%)	7(36.8%)

Graph.7.Preoperative hearing impairment (Gardner Robertson Classification system).



At initial presentation seventeen(89.3%) of these had no useful hearing on the side of the larger tumor .Thus, hearing preservation was not an issue during surgery for the larger tumors. On the side of the smaller tumors, seven(63.1%)

patients had no useful hearing whereas seven(63.1%) patients had mild to moderate hearing loss. These patients were placed on regular follow-up with an emphasis on learning lip-reading.

Table 8. Duration of symptoms related to facial nerve involvement at initial presentation

Duration of complaint	Count	Percent
<1 yr	6	54.5
>1 yr	5	45.5
Mean ± SD	1.8 ± 2.3	

Graph 8.Duration of symptoms related to facial nerve involvement at initial presentation.

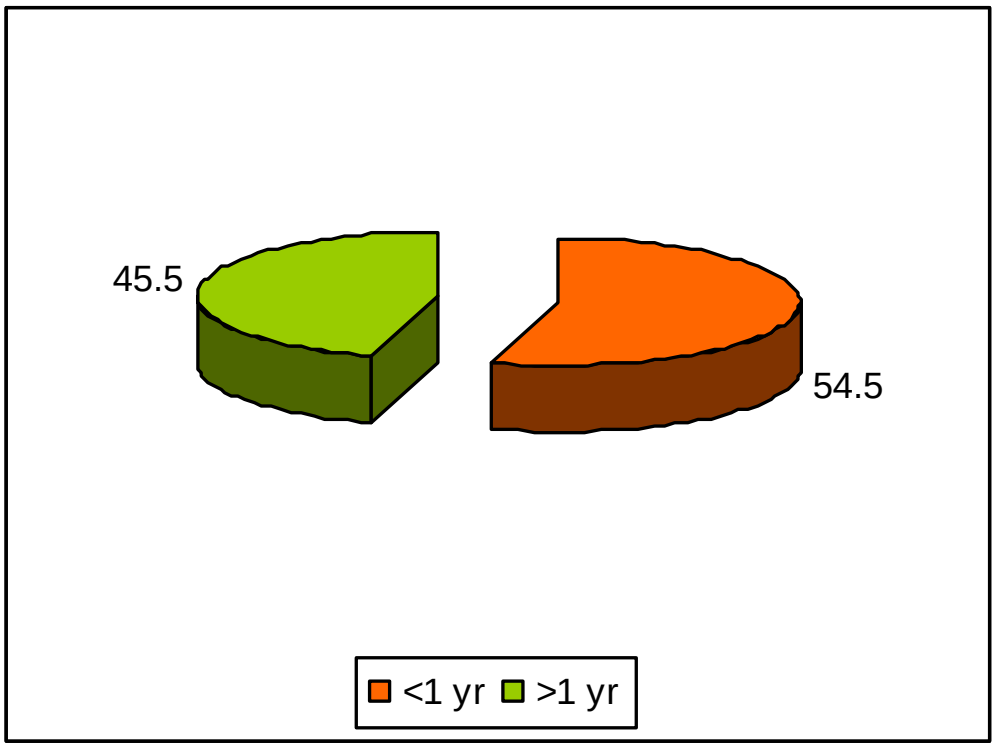


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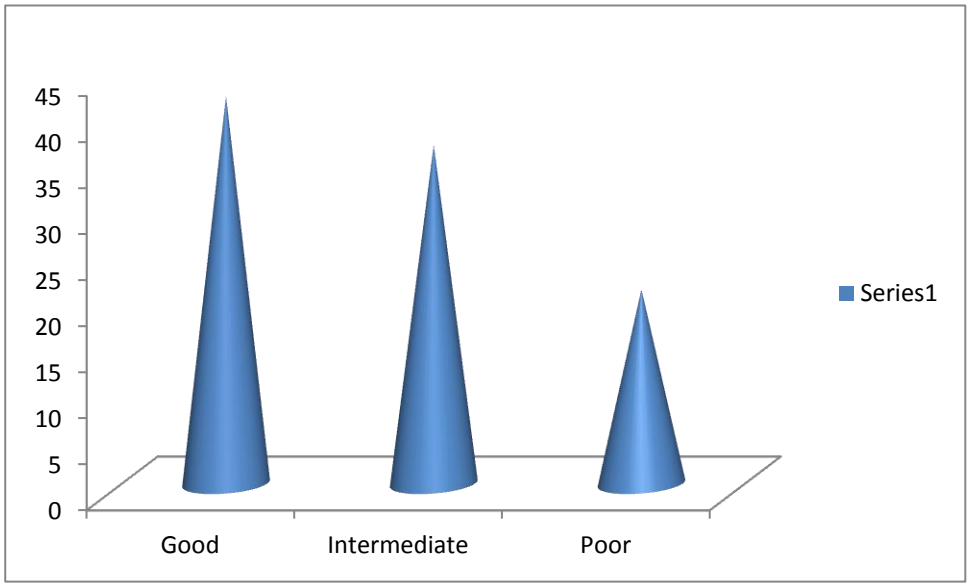
Table 9. Preoperative facial nerve function.

Facial nerve function	Preoperative n=19	
	Count	Percent
Good	8	42.1
Intermediate	7	36.8
Poor	4	21.1

Graph 9. Preoperative facial nerve function.

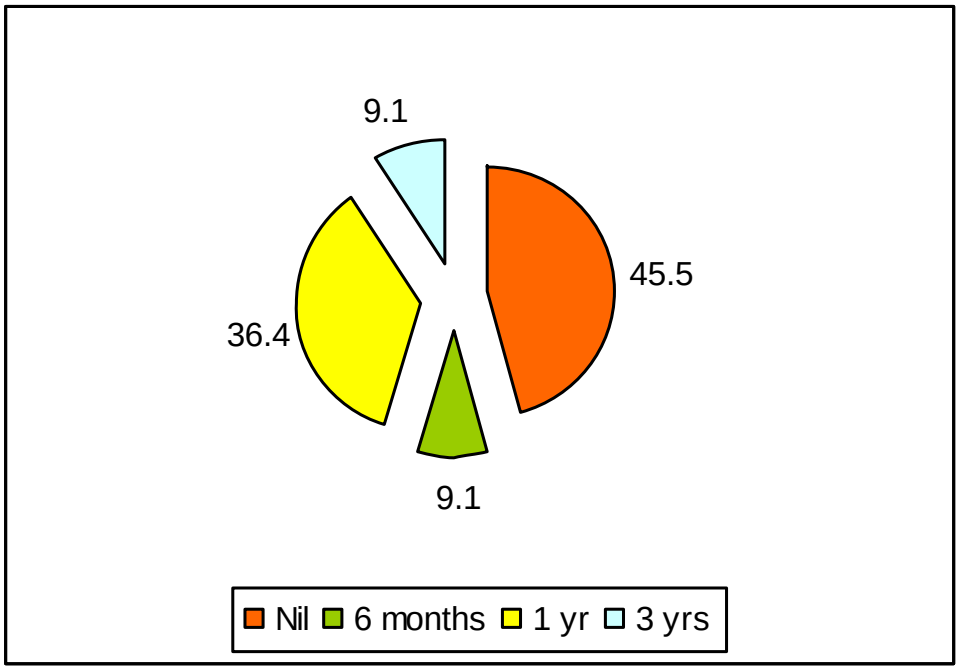


Preoperatively 42.1% patients had good facial nerve function(HB grade I and II),21.1% had poor function.

Table 10.Duration of symptoms related to trigeminal nerve involvement at initial presentation.

Duration of complaint	Count	Percent
Nil	5	45.5
6 months	1	9.1
1 yr	4	36.4
3 yrs	1	9.1
Mean ± SD	0.7 ± 0.9	

Graph 10. Duration of symptoms related to trigeminal nerve involvement at initial presentation.

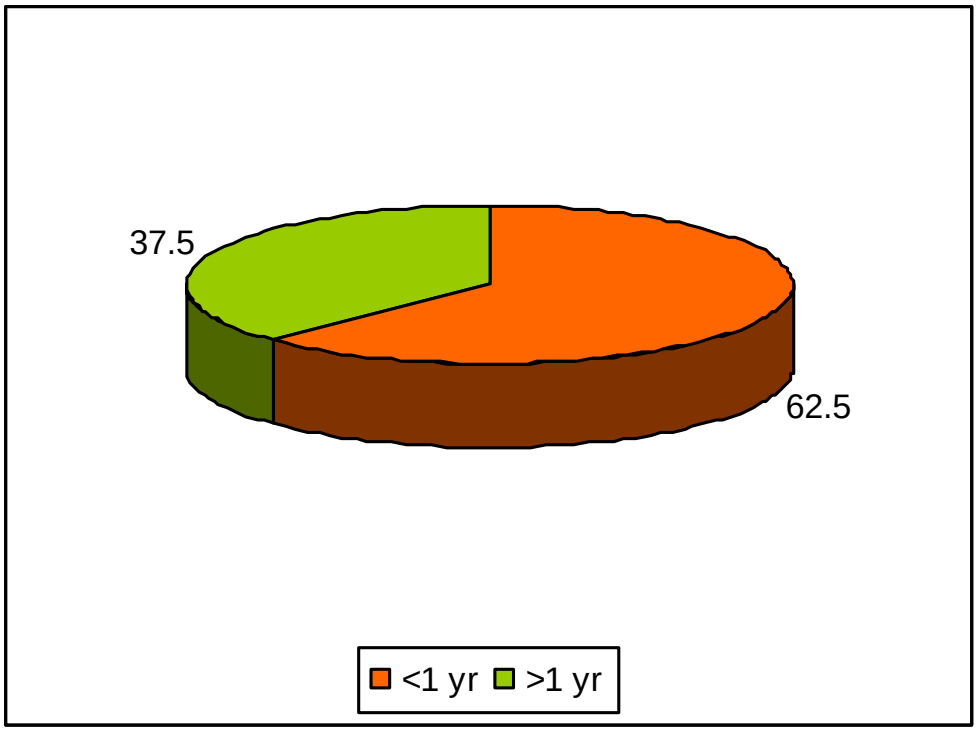


Trigeminal nerve was affected late in coarse of illness compared to hearing . Mean duration of symptoms before diagnosis was 6.4 months at initial presentation..

Table.11. Duration gait imbalance at initial presentation.

Duration gait imbalance	Count	Percent
<1 yr	10	62.5
>1 yr	6	37.5
Mean ± SD	0.8 ± 0.8	

Graph. 11. Duration gait imbalance at initial presentation.



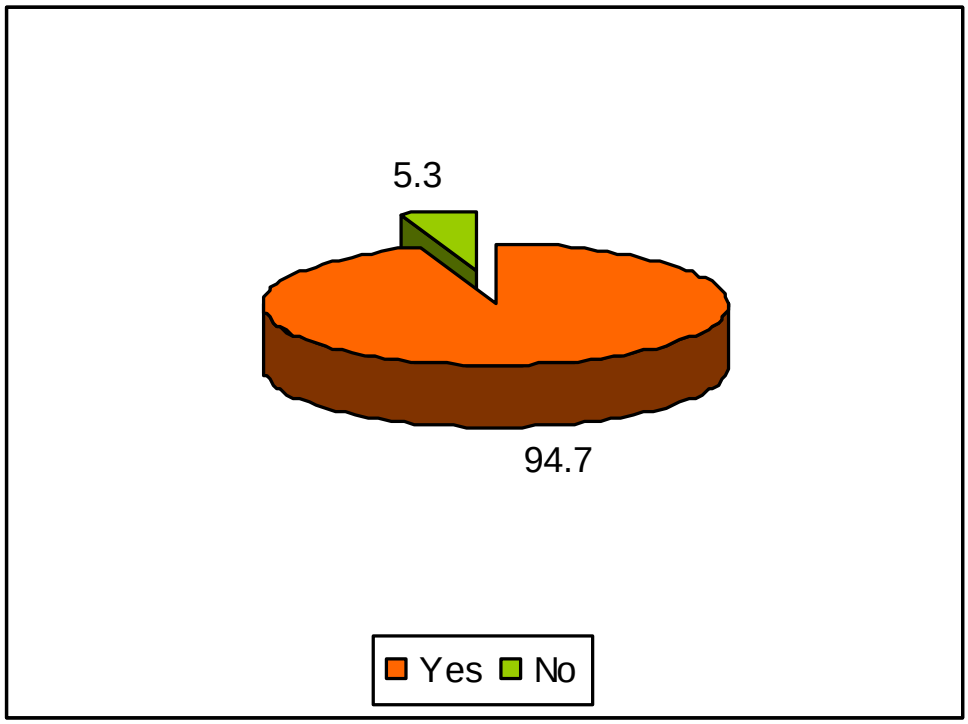
As with trigeminal nerve ,cerebellar involvement was late in coarse of illness compared to hearing and facial nerve . Mean duration of symptoms before diagnosis was 9.6 months at initial presentation..

RADIOLOGICAL FINDINGS

Table12. Preoperative obstructive hydrocephalus

Obstructive hydrocephalus	Count	Percent
Yes	18	94.7
No	1	5.3

Graph 12. Preoperative obstructive hydrocephalus

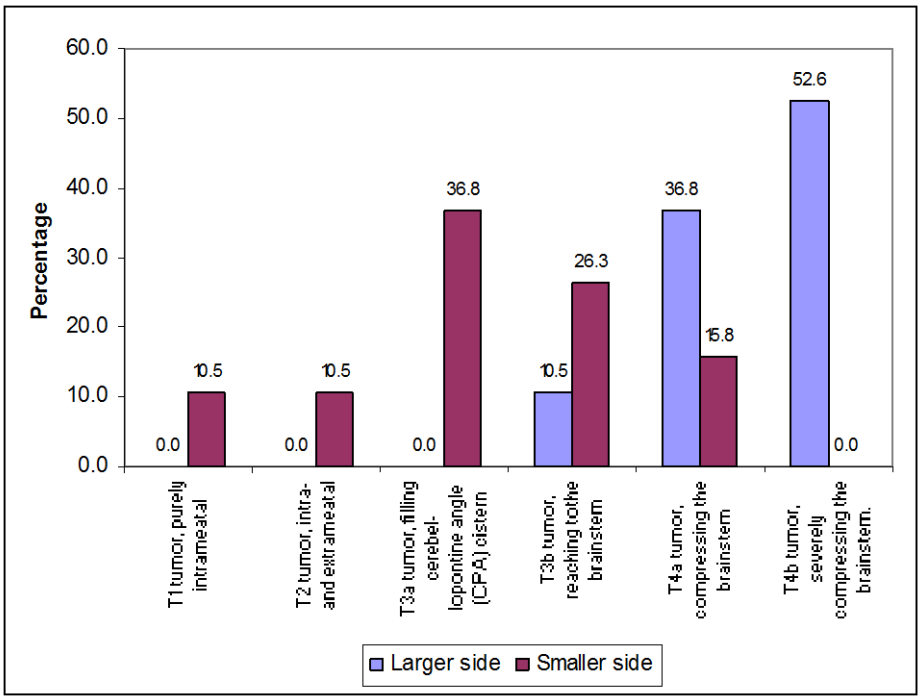


Most of the patients(94.7%) had obstructive hydrocephalus at initial imaging because of large tumors compressing over fourth ventricle.

Table 13. Tumor extension(Samii's classification).

Tumor extension	Larger side		Smaller side	
	Count	Percent	Count	Percent
T1 tumor, purely intrameatal	0	0.0	2	10.5
T2 tumor, intra- and extrameatal	0	0.0	2	10.5
T3a tumor, filling cerebel-lopontine angle (CPA) cistern	0	0.0	7	36.8
T3b tumor, reaching tothe brainstem	2	10.5	5	26.3
T4a tumor, compressing the brainstem	7	36.8	3	15.8
T4b tumor, severely compressing the brainstem.	10	52.6	0	0.0

Graph 13.Distribution of the sample according to tumor extension(Samii's classification).

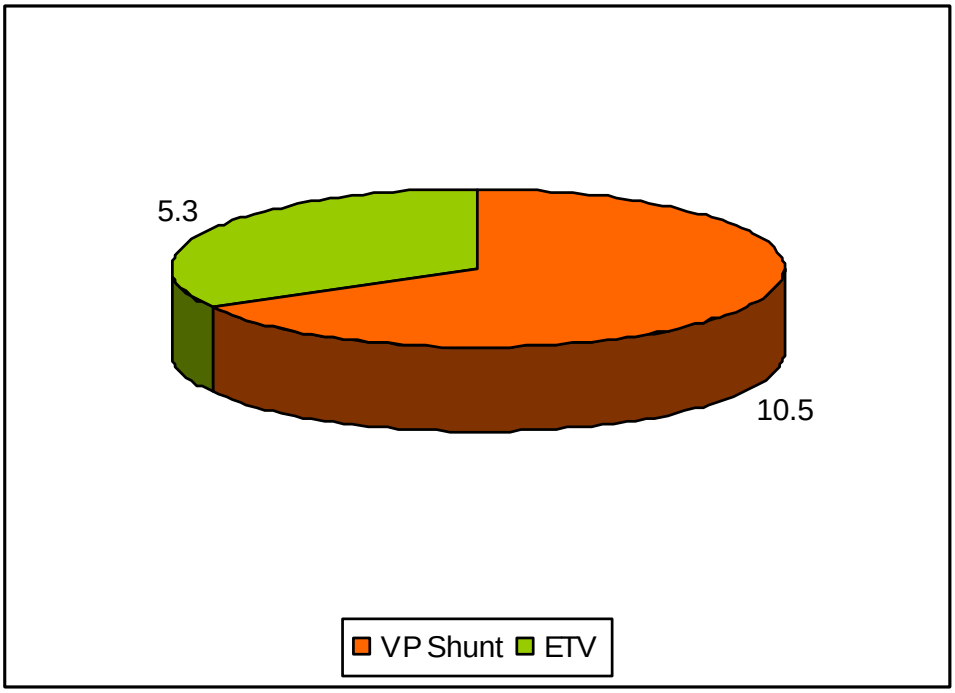


Most of the tumors on the larger side in bilateral VS were in the class of T4a and T4b (according to Samii's classification of tumor extension) with compression over brain stem and obstructive hydrocephalus.

Table14. Preoperative CSF diversion.

Preoperative CSF diversion	Count	Percent
VP Shunt	2	10.5
ETV	1	5.3

Graph 14.Preoperative CSF diversion



Three patients(15.8%) underwent CSF diversion for obstructive hydrocephalus before definitive surgery of VS .

Table15. Distribution of the sample according to size.

Size	Larger side n=15		Smaller side n=15	
	Count	Percent	Count	Percent
<1cm	0	0	0	0
1- 2.5cm	1	6.66	8	53.3
2.5-4cm	7	46.2	4	26.6
>4cm	8	53.3	4	26.6

Graph15. Distribution of the sample according to size.

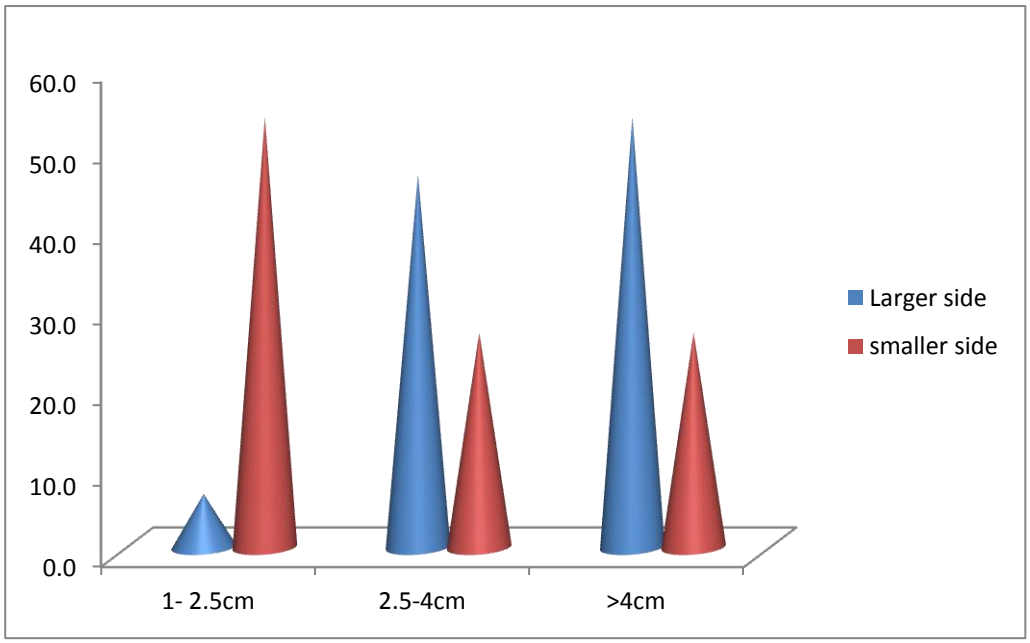


Table 16.Distribution of the sample according to average size.

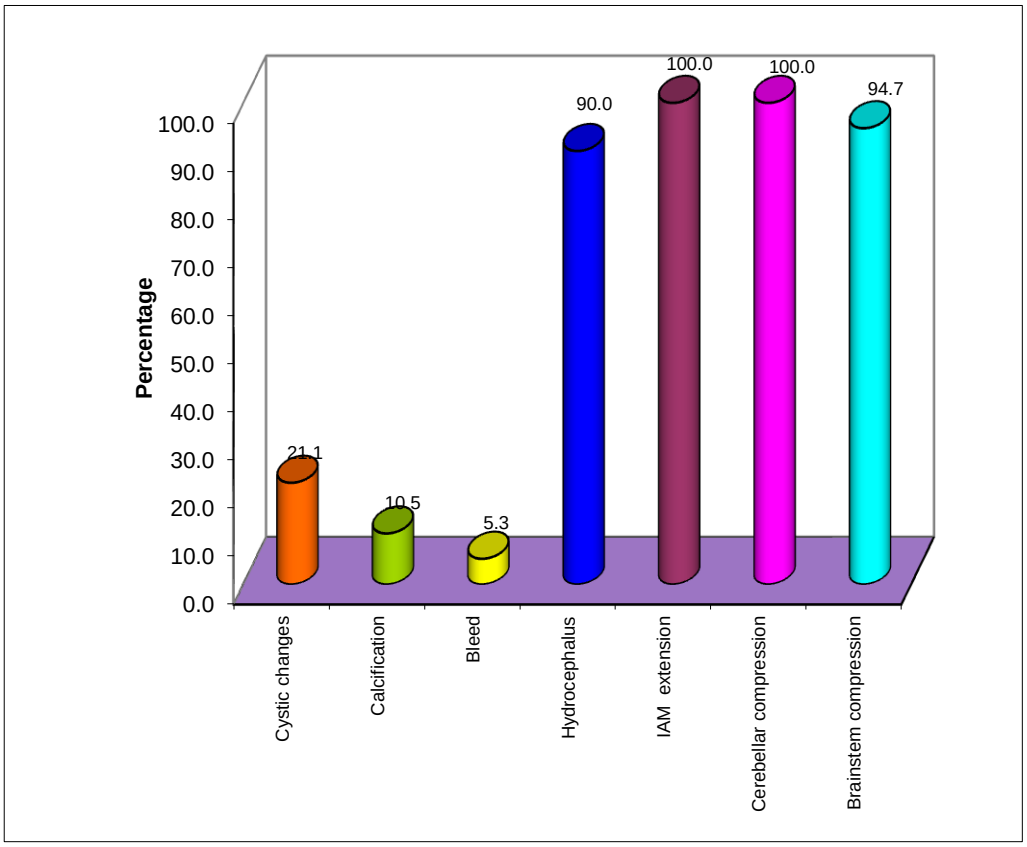
Average size	Mean	SD
Larger side	4.23	0.94
Smaller side	2.18	1.49

On imaging giant tumors (>4cm) were seen in 12 patients(79.9 %). Average size of tumor on larger side was 4.23 cm.

Table 17.Radiological findings on CT and MRI.

Radiological findings	n=19	Percent
Cystic changes	4	21.1
Calcification	2	10.5
Bleed	1	5.3
Hydrocephalus	18	100.0
IAM extension	19	100.0
Cerebellar compression	19	100.0
Brainstem compression	18	94.7

Graph16. Radiological findings on CT and MRI.

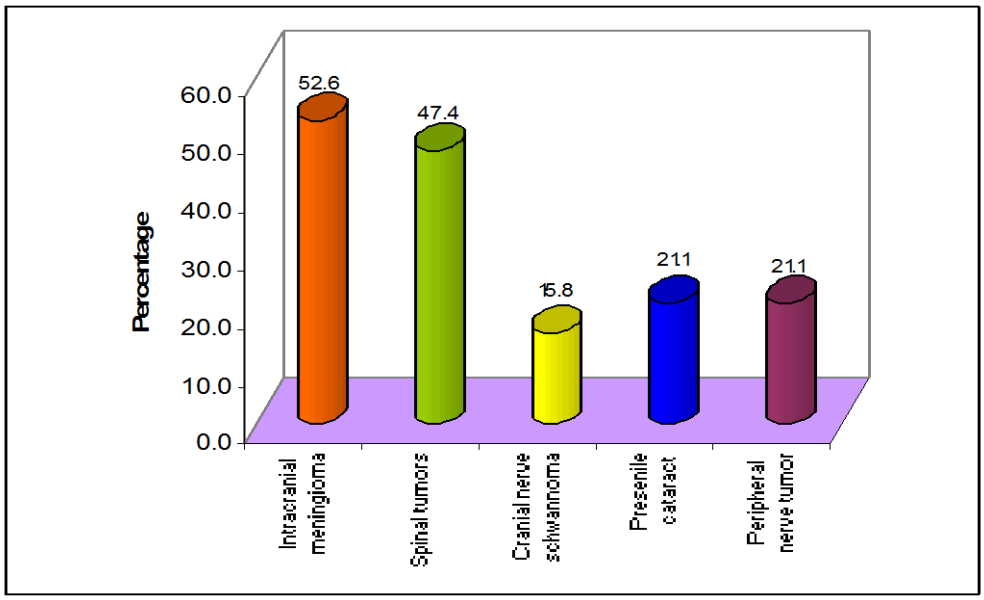


Since most of the tumors were larger , imaging showed obstructive hydrocephalus ,cerebellar compression,brain stem compression in >90% of patients.

Table 18. Other associated lesions of NF2.

The clinical manifestation of NF2	Count	Percent
Intracranial meningioma	10	52.6
Spinal tumors	9	47.4
Nonvestibular schwannoma	3	15.8
Presenile cataract	4	21.1
Peripheral nerve tumor	4	21.1

Graph 17. Distribution of the sample according to other associated lesions of NF2.



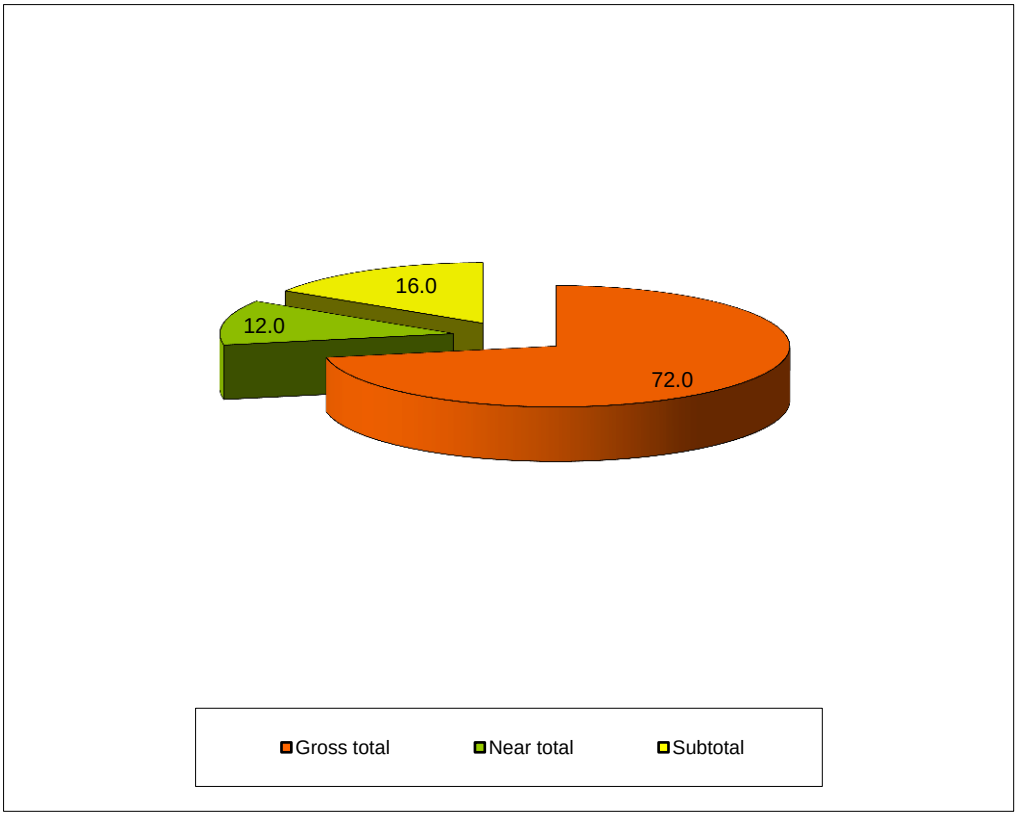
Other associated lesions of NF2 in our study other than bilateral VS were intracranial meningioma(52.6%), spinal tumors(47.4%),other cranial nerve schwannoma(15.8%) .

SURGICAL ASPECT

Table 19. Totality of surgical excision

Totality of Excision	N=25	Percent
Gross total	18	72
Near total	3	12
Subtotal	4	16

Graph18. Totality of surgical excision



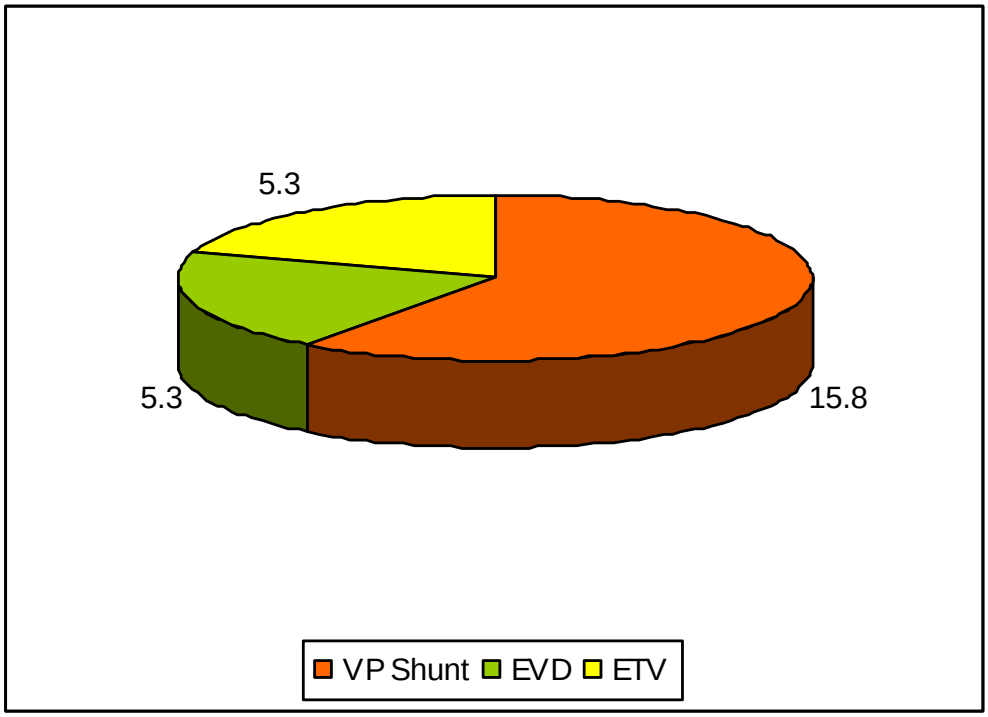
Initially all 19 patients underwent excision of one side tumour .On follow up 6 more patients without serviceable hearing underwent excision of nonoperated side VS for increase in size with brain stem compression.

In present study 72% of tumours underwent gross total excision inspite of larger size of lesions at presentation.

Table.20. Post operative CSF diversion.

Post operative CSF diversion	Count	Percent
VP Shunt	3	15.8
EVD	1	5.3
ETV	1	5.3

Graph 19.Post operative CSF diversion.



Postoperatively four (26.4%)patients underwent CSF diversion for hydrocephalus before resection of nonoperated side VS.

Table 21. Postoperative anatomical status of the facial nerve.

Postoperative anatomical status of the facial nerve	n=25	Percent
Anatomicaly preserved	10	40
Not preserved	9	60

Anatomical facial nerve preservation in present study was 52.6% even with larger size of tumors at diagnosis.

Graph 20. Postoperative anatomical status of the facial nerve.

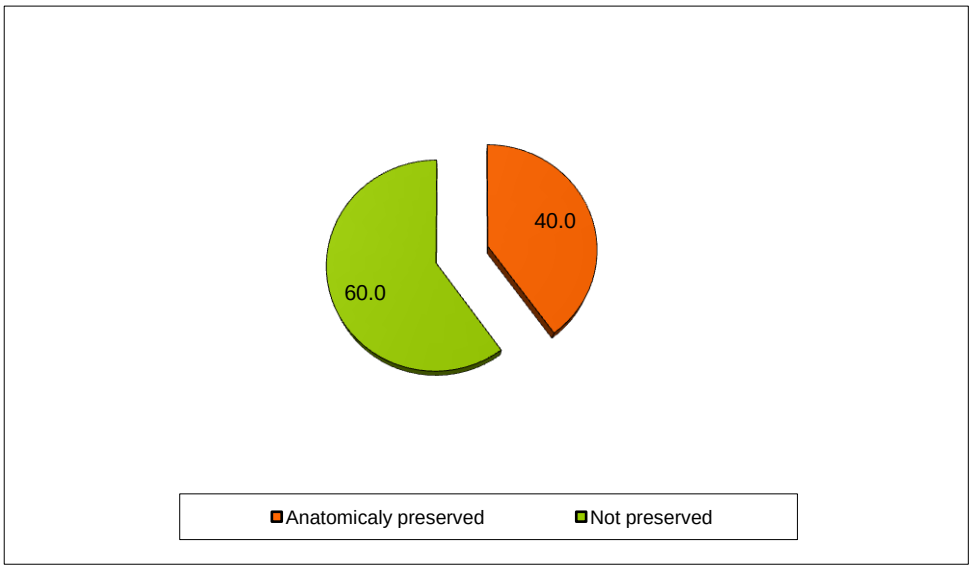
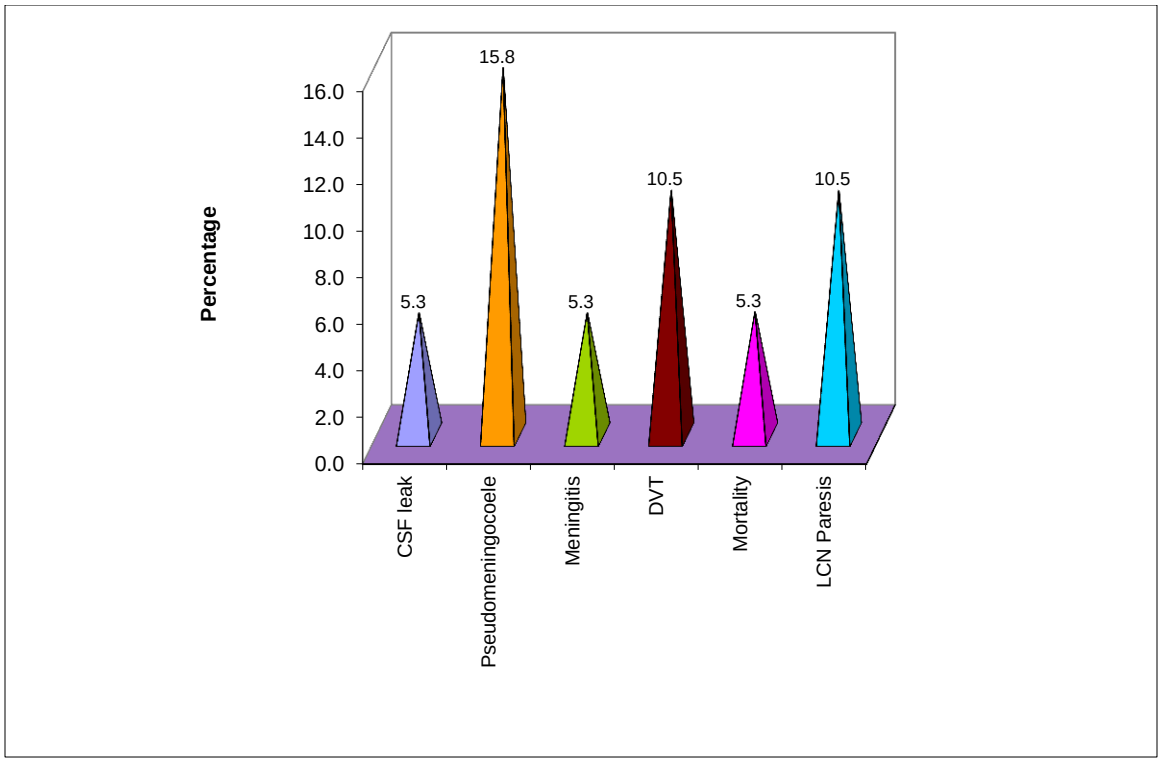


Table 22.Surgical complications.

Complications	Count	Percent	Treatment
CSF leak	1	5.3	Conservative
Pseudomeningocoele	3	15.8	Compression bandage
Meningitis	1	5.3	Conservative
DVT	2	10.5	Conservative
Mortality	1	5.3	-
LCN Paresis	2	10.5	-

Graph 21.Surgical complications.

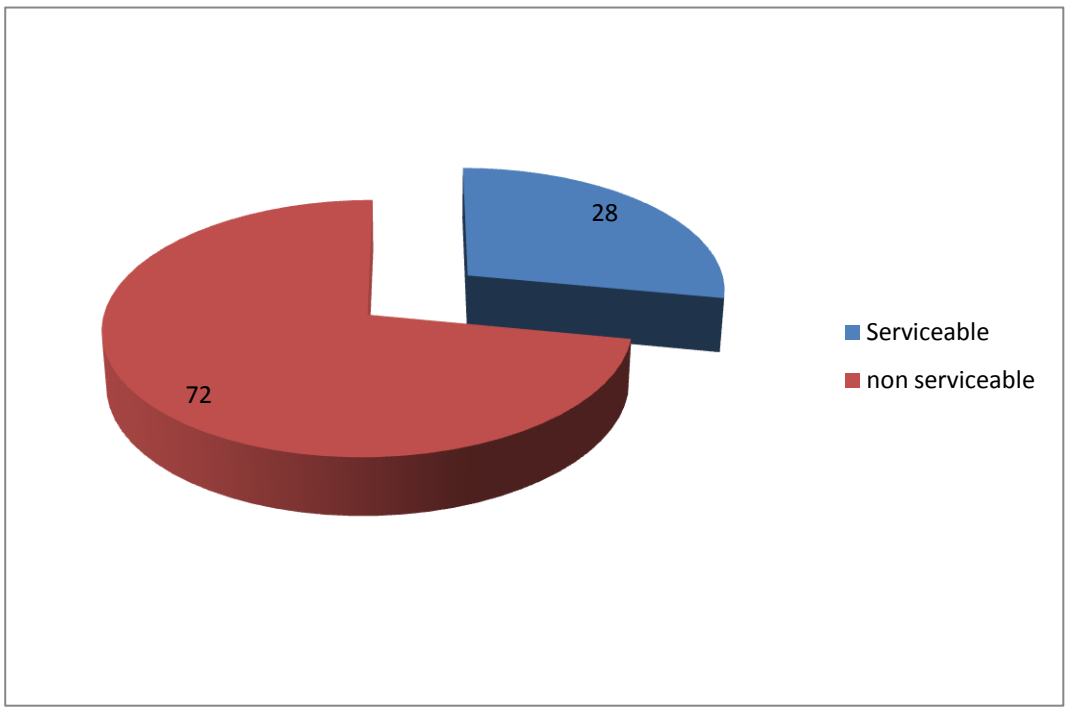


Common complication was pseudomeningocoele in 3 (15.8%)patients.DVT,LCN paresis in 2 patients. There was one mortality in this study.

Table. 23.Status of post operative hearing.

Post operative hearing	n=25	Percent
Nonserviceable	18.0	72
Serviceable	7.0	28

Graph 22.Status of post operative hearing.

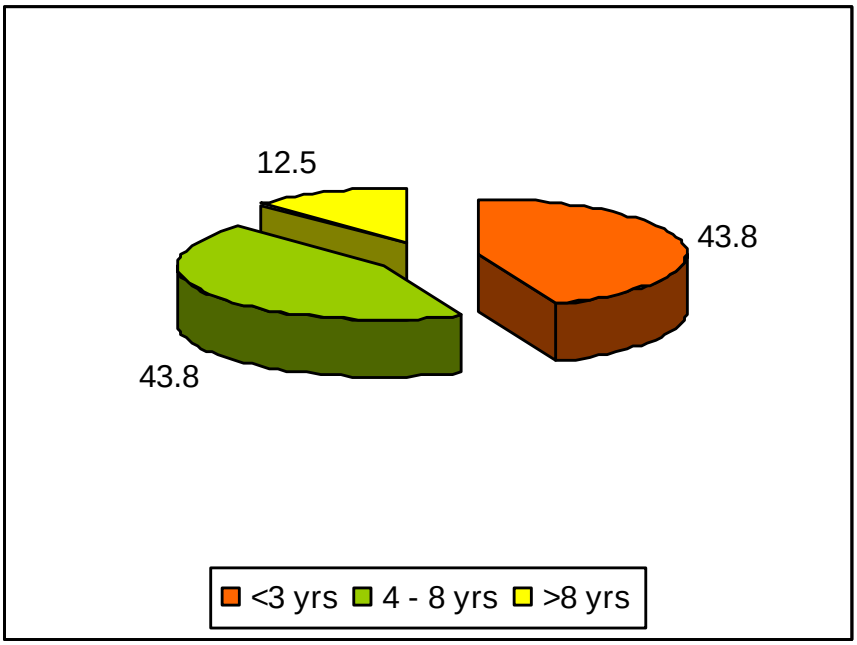


Postoperatively hearing was serviceable in only 28% of patients with 78% of patients having non useful hearing after surgery of 25 operated VS.

Table 24.Distribution of the sample according to duration of follow up.

Duration of follow up	Count	Percent
<3 yrs	7	43.8
4 - 8 yrs	7	43.8
>8 yrs	2	12.5
Mean ± SD	5.4 ± 5	

Graph 23. Distribution of the sample according to duration of follow up.

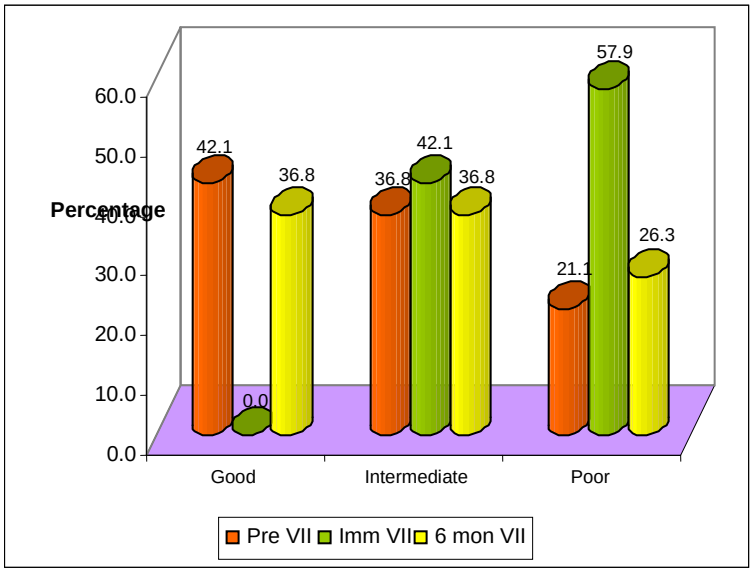


All the patients were followed up for a mean duration of 5.4 years with a range of 0-18 years

Table25. Distribution of the sample according to facial nerve function n=19.

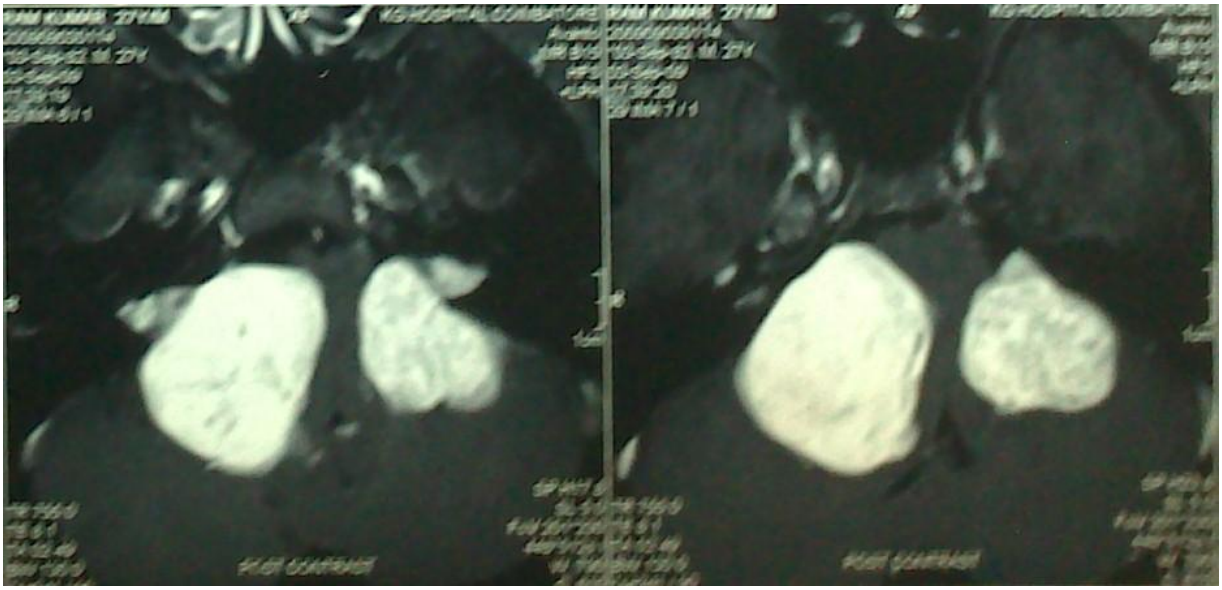
Facial nerve function	Preoperative		Immediate postop		6 months F/U.	
	Count	Percent	Count	Percent	Count	Percent
Good	8	42.1	0	0.0	7	36.8
Intermediate	7	36.8	8	42.1	7	36.8
Poor	4	21.1	11	57.9	5	26.3

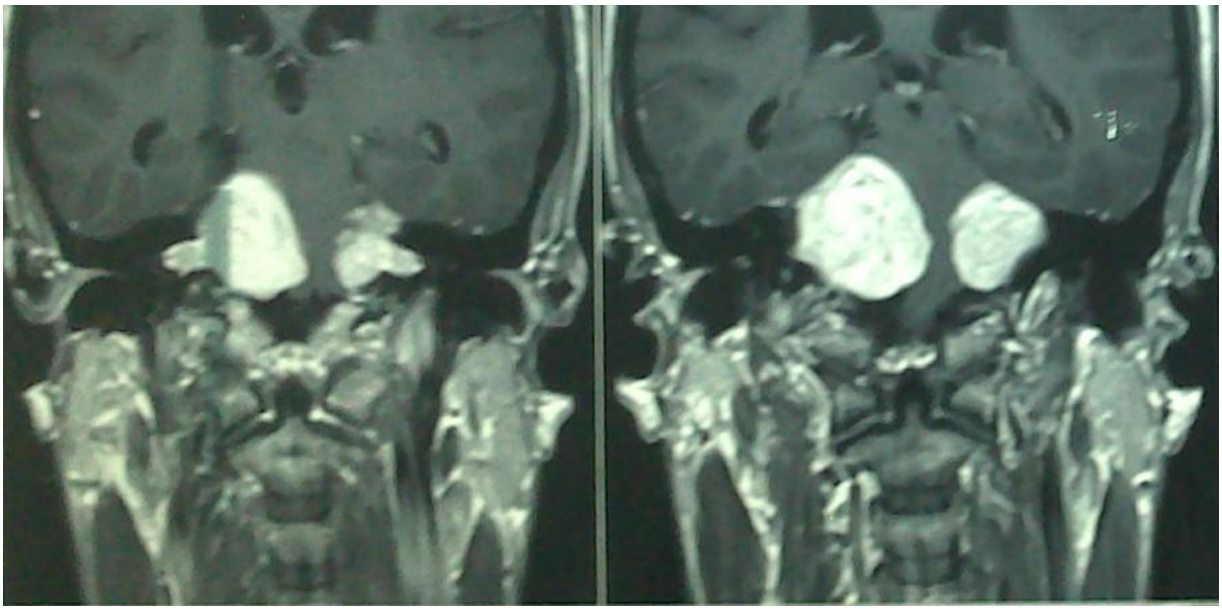
Graph 24. Distribution of the sample according to facial nerve function n=19.



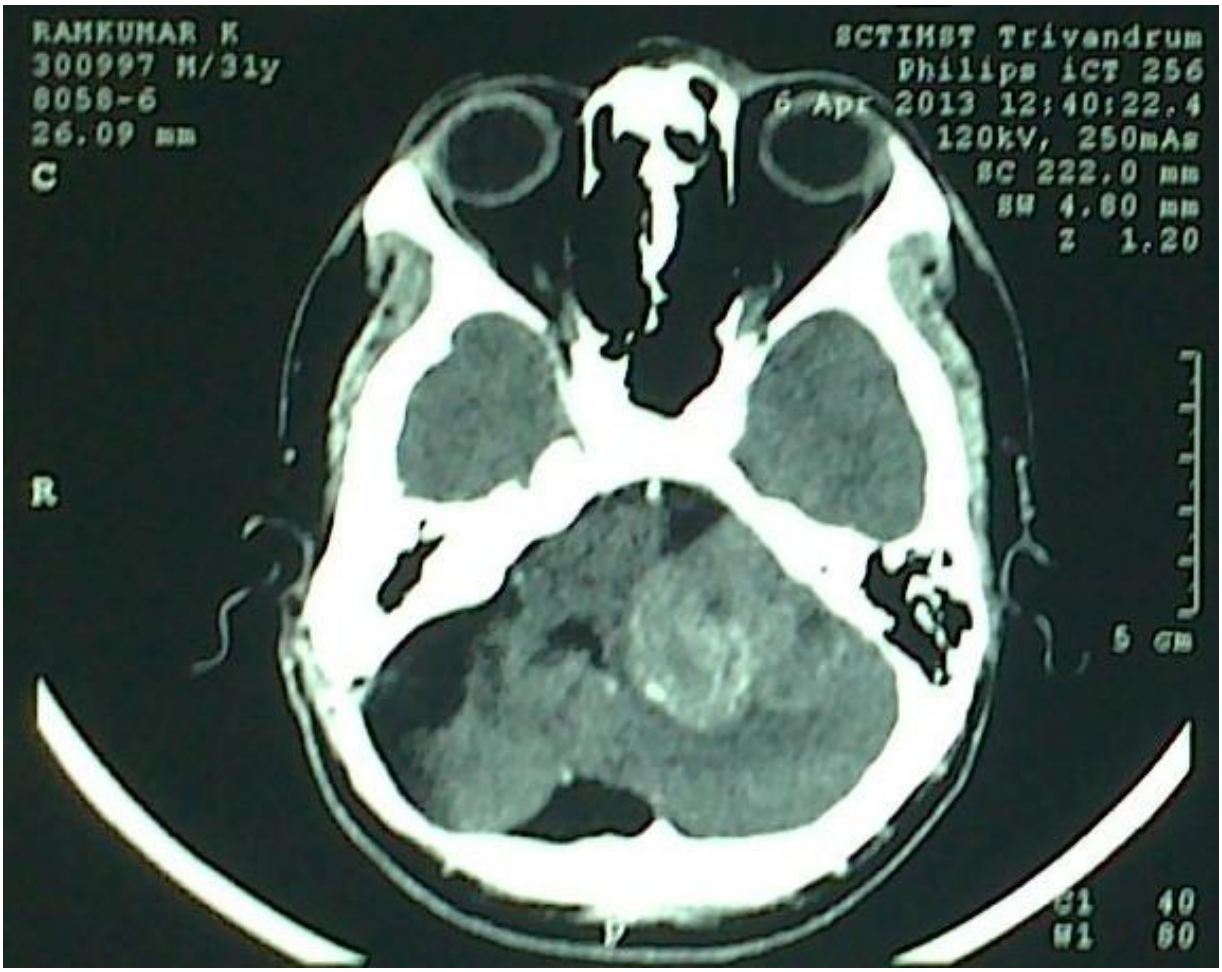
Preoperatively 78.9 % of patients had HB grade I-IV facial nerve function in present study. Follow up on immediate postoperative period all patients had deterioration to HB grade III-VI. At 6 months follow up facial nerve function in 73.6% patients improved back to preoperative status.

Patient no 8. Preoperative coronal and axial an d coronal T1 axial contrast MRI scan showing bilateral vestibular schwannoma T4b on right side and T4a on left side with IAM extension(According to Samii's classification).

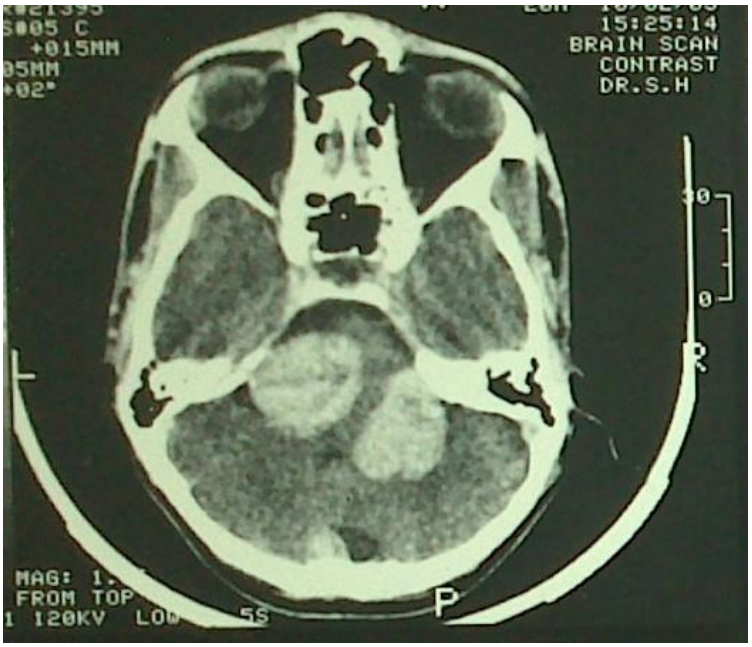




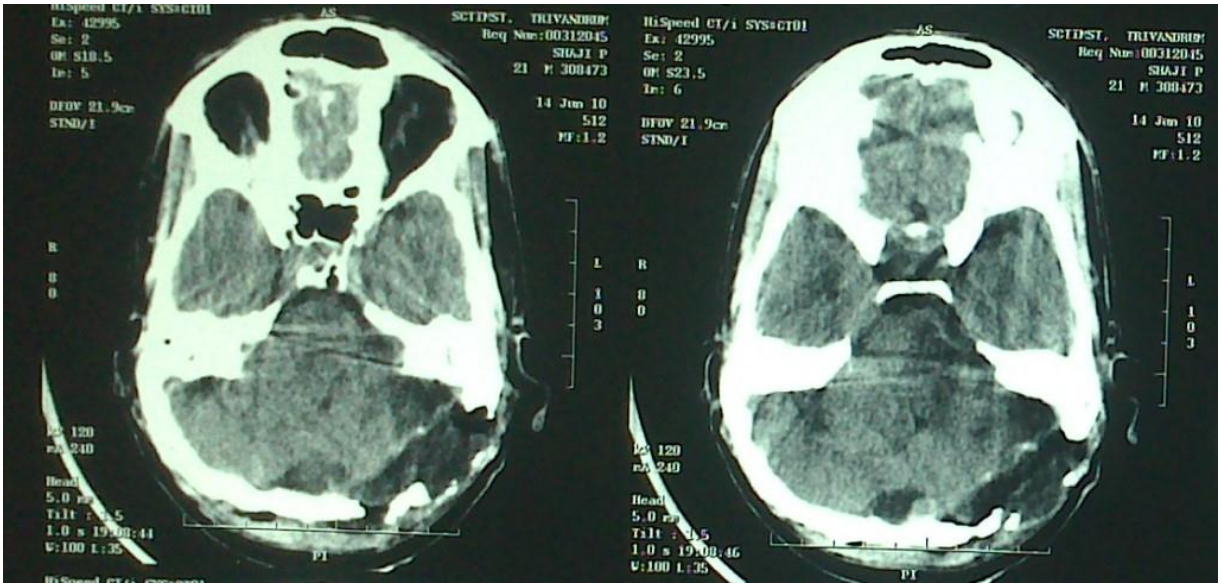
Patient no 8. Postoperative follow up contrast CT brain axial scan 4 years after right side vestibular schwannoma excision , showing no recurrence. Left sided lesion remaining almost of same size.



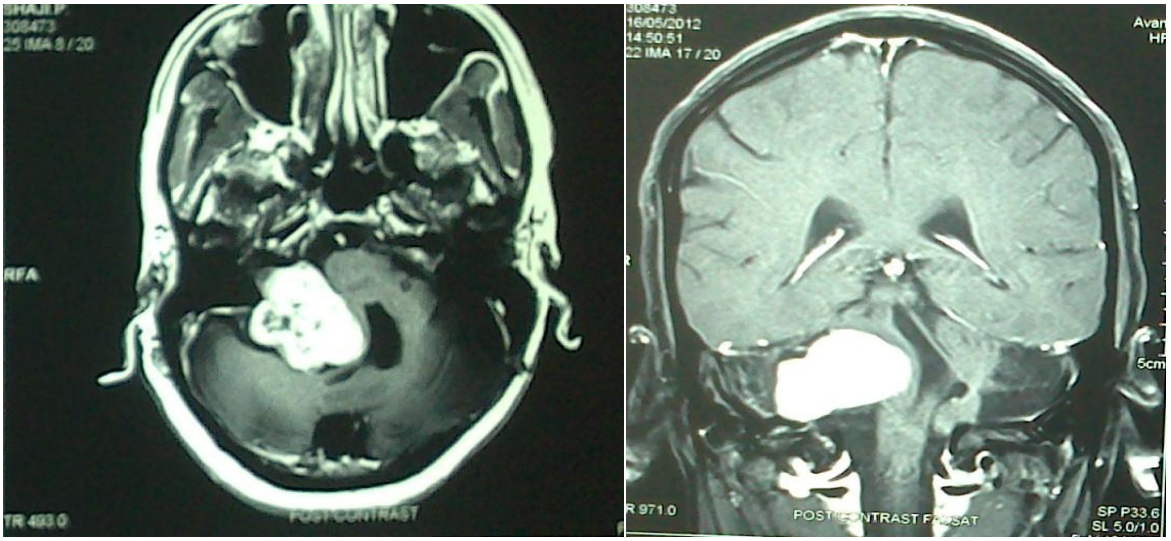
Patient no 9. Preopearative contrast CT brain axial scan showing bilateral vestibular schwannoma.



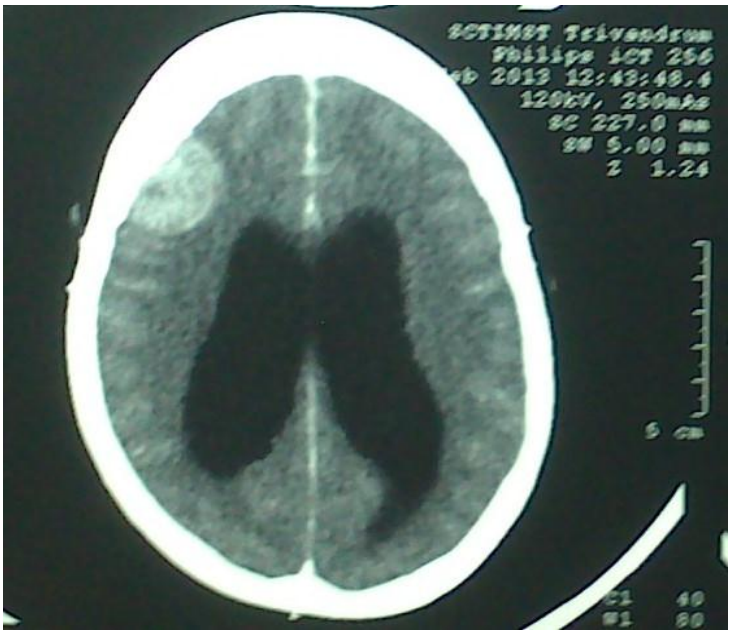
Patient no 9. Immediate postoperative axial contrast CT brain scan after excision of left VS.



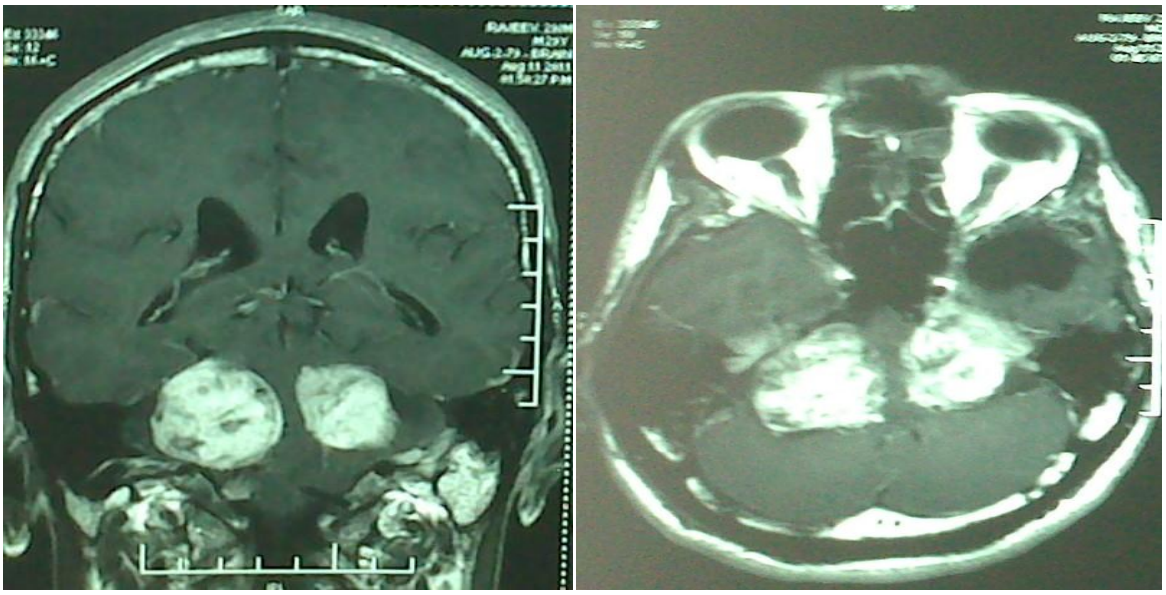
Patient no 9. Postoperative follow up axial and coronal T1 contrast MRI scan 2 years after excision of left VS.



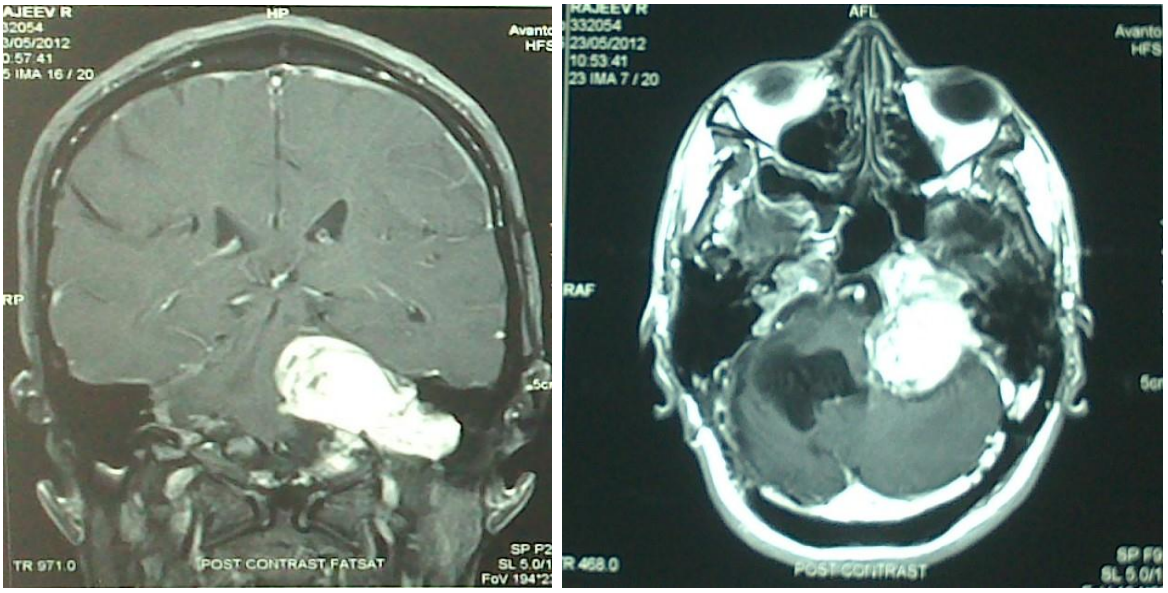
Patient no 9. Postoperative follow up contrast CT brain scan 3 years after excision of left VS showing supratentorial meningioma.



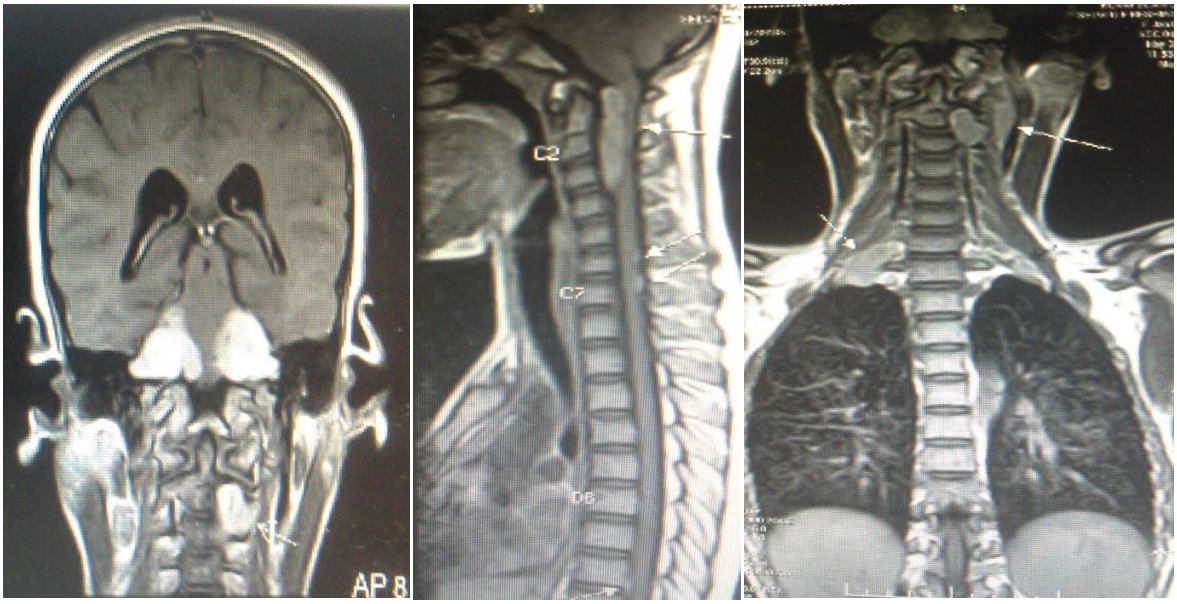
Patient no 11 . Preoperative contrast MRI brain coronal and axial scan showing bilateral vestibular schwannoma.



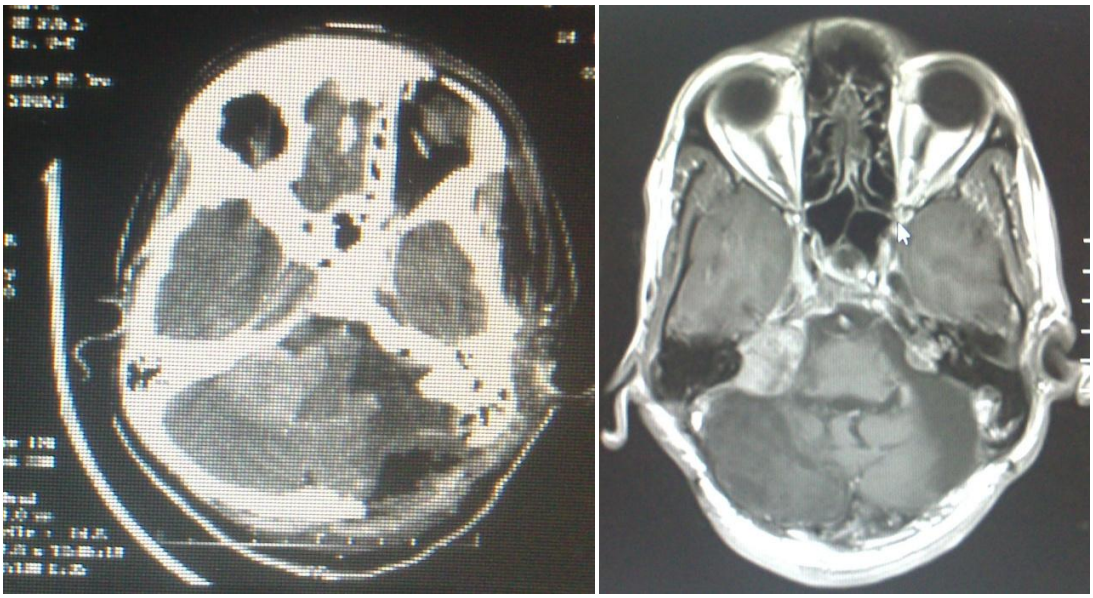
Patient no 11 . Postoperative coronal and axial T1 contrast MRI scan 1 year after excision of right VS showing no residue.



Patient no 17. T1 contrast MRI showing bilateral vestibular schwannoma and multiple spinal schwannomas.



Patient no 17. Axial contrast CT brain following excision of left VS, Axial T1 contrast MRI following excision of bilateral vestibular schwannoma, showing right trigeminal schwannoma .



6. DISCUSSION

Dealing with patients with neurofibromatosis type 2(NF2) and bilateral vestibular schwannomas (VS) is challenging. The potential for damage to the adjacent cranial nerves is greater and the frequency of cochlear as well as facial nerve preservation is lower when compared to patients with VS without NF2. However, with advances in microneurosurgical skills and expertise, a few authors have achieved results nearly equal to those for patients harboring sporadic VS. In India, the management of NF2 involves considerations quite different from that seen in European and American studies. In India, patients present with much larger tumors often with disabling cerebellar and long tract signs and raised intracranial pressure.

This study was undertaken to define the clinical characteristics of bilateral vestibular schwannoma, compare our results with published series on bilateral vestibular schwannoma with regard to clinical manifestation, imaging features, diagnosis, surgical procedures and prognosis .And to assess facial nerve preservation ,surgical outcome of surgically treated bilateral vestibular schwannoma.

This retrospective study was conducted in the Department of Neurosurgery, Sree Chitra Thirunal Institute for Medical Science and Technology, Trivandrum,Kerala. Of 775 patients admitted with vestibular schwannoma during January 1998 to September 2012 , 25 tumors in 19 consecutive patients with bilateral VS underwent surgery over a span of 14 years by a single senior author.

Table1. The incidence of bilateral VS.

Series	Bilateral VS/Total VS	Percentage
Present Series(2013)	19/775	2.45
R.N.Sahu et al[87](2007)	16/329	4.9
Moffat et al[59](2002)	25/59	42.37
Samii et al[21](1997)	82/1000	8.2
Baldwin et al[88](1991)	19/444	4.27

The incidence of bilateral VS among total number of VS varies among various series comprising 4.27% in Baldwin et al[88] to 42.37% in Moffat et al[59]. Incidence of bilateral VS in present series is low 2.45%.

Table 2: Mean Age distribution

Series	Mean age(yrs)	Range(yrs)
Present Series(2013)	26.2	13-47
Peyre et al[89](2013)	25.5	7-94
Eiji Ito et al[90](2009)	23	5-61
R N Sahu et al[87](2007)	25.7	13-45
Moffat et al[59](2002)	29	8-55
Samii et al[21] (1996)	27.5	11-62

The mean age distribution of bilateral VS in different series varied from 23-29 years. The mean age at the onset of disease-related symptoms in our

study patients was 26.2 years which is representative of the disease among the general population as described in population-based studies of NF2[91].

Table 3: Gender distribution

Series	Male	Female	Ratio
Present Series(2013)	13(68.42)	6(31.58)	2.16:1
Pyere et al[89](2007)	27(58.69)	19(41.31)	1.42:1
R N Sahu et al[87](2007)	12(75%)	4(25%)	3:1
Eiji Ito [90](2009)	10(37%)	17(63%)	0.58:1
Moffat et al[59](2002)	20(57.14%)	15(42.86%)	1.33:1
V F Maunter et al[45](2002)	20 (54%)	17(46%)	1.17:1
Sammi et al [21](1996)	41(50%)	41(50%)	1:1

In most series bilateral VS was more commonaly seen in Men than Women. In present series bilateral VS was more commonly seen in men than women (2.16:1) similar to most of studies. In Sammi et [21]al study sex distribution was equal.

Table 4: Neurological Symptoms/Signs of bilateral VS at initial diagnosis

Symptoms/ Signs	Present series	Eiji Ito et al[90](2009)	R N Sahu et al[87] (2007)	Moffat et al[59] (2002)	Baldwin et al[88] (1991)	Turgut et al[92](1998)
Hearing Loss	94.7%	56%	100%	77.1%	100%	92%
Imbalance	89.4%	-	93.8%	68.6%	-	48%
Lower cranial nerve involvement	68.4%	37%	50%		35%	16%
Headache	57.8%	-	-	28.6%	-	92%
Facial deviation	63.15%	3%	18.8%	12%	33%	48%
Facial numbness	52.6%	7%	81.3%	20%	-	32%
Visual disturbances	47.3%	11%	37.5%	-	-	48%
Pyramidal signs	36.8%	11%	-	-	-	32%
Incidental	5.26%	-	-	-	-	-

Progressive hearing impairment was the most common initial presentation in bilateral vestibular schwannoma in all series consistent with our series -94.7% followed by cerebellar signs. One patient in our study was incidentally diagnosed after road traffic accident.

In present study most common presentation was progressive hearing impairment . The mean duration of hearing loss was 3.8 years , most of the

patients having hearing loss duration in the range between 1 to 5 years. In one of the study conducted by Eiji Ito et al[90], the mean duration was 2.6 years with the range between 1 to 10 years.

Table 5. Preoperative facial nerve involvement

Series	Percent
Present	59.9%
Eiji Ito et al[90](2009)	3%
R N Sahu et al[87](2007)	18.8%
Moffat et al[59](2002)	98%
Turgut et al[92] (1998)	48%

As with other studies other than vestibulocochlear nerve most common cranial nerve affected preoperatively in bilateral VS was facial nerve (59.9%).

Radiological aspect

On imaging average size of tumor on larger side was 4.23 cm at initial presentation, where as 73.7% were giant VS (>4cm) . Most(89.4%) of the tumors on larger side in bilateral VS were in the class of T4a and T4b (according to Samii's classification of tumor extension) as with other study by R N Sahu et al[87]. This explains patients presentation with high rate of involvement of multiple cranial nerves, disabling cerebellar signs & raised intracranial pressure in bilateral VS.

Table 6. Other associated lesions of NF2

Other lesions of NF 2	Present study	Moffat et al[59](2003)	M. S. Dirks et al[91](2012)	R N Sahu et al[87](2005)
Intracranial meningioma	52.6%	45%	76%	25%
Spinal tumors	47.4%	60%	-	6.3%
Non vestibular schwannoma	15.8%	25%	23.5%	-
Presenile cataract	21.1%	15%	-	25%
Peripheral nerve tumor	21.1%	36%	-	12.5%

Other associated lesions of NF2 in our study were intracranial meningioma (52.6%), spinal tumors(47.4%),other cranial nerve schwannoma(15.8%) . These findings were similar to Moffat et al [59] series. Out of these lesions few patients underwent surgery for disabling symptoms.

Surgical decision making.

Total 25 VS operated in 19 patients with bilateral VS. Initially all 19 patients underwent excision of one side tumor .On follow up 6 more patients without serviceable hearing underwent excision of nonoperated side VS for increase in size with brain stem compression.

On the side of the larger tumor, since hearing was already compromised in most cases, both the retrosigmoid suboccipital craniotomy or a translabyrinthine approach could have been utilized for tumor removal. Both provide good access to the brain stem and its vascular supply and it is possible to remove extensions of the tumor into the supratentorial compartment, foramen magnum and into the cisterns anterolateral to the brain stem. The cranial nerves may be preserved or reconstructed using both these approaches. The

retromastoid suboccipital craniectomy was used in all our operations due to our familiarity with the approach and its versatility in removing larger tumors with facial movement, sensation and hearing preservation.

Preoperatively hearing was non serviceable in 89.3 % of cases on larger side of the tumor and 63.1% in smaller side. Thus, hearing preservation was not an issue during surgery for the larger tumors.

Serviceable hearing was present in only 2 patients (10.5%) on larger side of the tumor & 7 patients (36.8%) in smaller side. These patients were placed on regular follow-up with an emphasis on learning lip-reading. This was done so that if resection of smaller sized tumors was required then patient would be able to communicate.

Seventeen patients (89.5%) with severe mass effect due to larger tumors (tumor extent T3b–T4b) without serviceable hearing were operated on the larger side. Two patients (10.52%) with serviceable hearing on larger side and non serviceable hearing on smaller side underwent resection of smaller side of tumor to preserve hearing and to relieve brain stem compression.

Protocol of management of bilateral vestibular schwannomas based on the tumour classification by Samii et al [77].

Tumour Extension	Status of hearing	Larger side	Management plan	Smaller side	Management plan
T1	-	0	-	2	Observation
T2	-	0	-	2	Observation
T3a	Serviceable	0	-	3	Observation
	Non serviceable	0	-	4	Observation
T3b	Serviceable	0	-	0	-
	Non serviceable	2	Surgery	5	Observation
T4a	Serviceable	2	Observation	0	-
	Non serviceable	5	Surgery	3	one patient Observation and in 2 surgery
T4b	Serviceable	0	-	0	-
	Non serviceable	10	Surgery	0	-

In present study 72% (18/25) of tumors underwent gross total excision even with larger size of tumors at diagnosis. This is comparable to international

literature where, in bilateral VS a total surgical resection of 76-87-5% is reported[88,77,76].

Postoperatively all the operated patients had non serviceable hearing on operated side as in preoperative period. The higher incidence of postoperative deficits in present series is probably due to large tumor size and an attempt at complete tumor removal. In other series[77,92,93] hearing preservation was 36,30,70% as they operated on tumors of relatively smaller size in view of hearing preservation .

Even with giant tumors anatomically facial nerve was preserved in 40% c of ases, comparable with other studies [87,21]. Preoperatively 78.9 % of patients had HB grade I-IV facial nerve function . Follow up on immediate postoperative period all patients had deterioration to HB grade III-VI. At 6 months follow up facial nerve function in 73.6% patients improved back to preoperative status as in other studies[21,93].

All the patients were followed up for a mean duration of 5.4 years with a range of 0-18 years. One patient was lost to follow up after surgery. One patient (5.26%) expired in postoperative period. Mortality in other series[77,92] were 2.5% to 28%.One patient (5.26%) lost to follow up after surgery. Another patient expired after excision of cervical intramedullary tumor in different setting.

25 year old lady underwent excision of bilateral vestibular schwannoma at an interval of 8 years. Following excision of VS in the same setting she underwent Grade II excision of postmeatal petrous meningioma & partial excision of foramen magnum meningioma. on 1st postop day , patient developed sudden cardiopulmonary arrest and succumbed.

No other significant postoperative complications observed in this study other than meningitis and CSF leak in one each, pseuodomeningocoele in two patients and deep venous thrombosis in two patients.

Of total 16 patients followed, six patients (37.5%) with nonserviceable hearing underwent excision of nonoperated side of tumor for increase in size &

brainstem compression. Three patients (17.8%) had increase in size of nonoperated side tumor but with preserved serviceable hearing without mass effect/hydrocephalus/new deficits ,seven patients of (43.75%) nonoperated side tumor with preserved serviceable hearing and tumor size remaining same are kept on close follow up.

On follow up scan six patients (23.07%) of 25 vestibular schwannoma operated had recurrence of lesion of size <2cm without mass effect/hydrocephalus/new deficits. These patients are kept on regular follow up. One patient, whose disease was stable, died 8 years after surgery from reason unrelated to the present disease. Other studies reported recurrence of 0 to 16%[92].

This study along with study done by R N. Sahu et al[87] shows that in Indian scenario patients with bilateral vestibular schwannoma present very late in course of illness with large tumour, disabling neurological deficits and brain stem compression. So hearing reservation was not an issue during surgery for larger tumours with nonserviceable hearing. Main management strategy was to decompress the brain stem from mass effect and conserve the serviceable hearing if present.

The limitations of present study were study design (retrospective study),smaller sample size, presentation of patients with giant tumors with irreversible deficits.

7. CONCLUSIONS

- Bilateral vestibular schwannomas are one of the most challenging conditions to treat.
- Patients with bilateral VS are younger, have larger lesions, poorer preoperative hearing and are more likely to lose either auditory and/or facial nerve function during attempted total resection of the tumor. Depending on their clinical status, patients can be offered watch & wait & rescan or surgery as management option. Conservative management is advised in patients with medium-size tumors until one or both become life threatening or the hearing deteriorates.
- Hearing preservation remains a challenge in these patients, but can be optimised by the early detection of tumours in the NF2 patients.
- The detection of small VS with useful hearing is possible by minimizing delay in diagnosis and adopting a tight surveillance programme. Early diagnosis of NF 2 remains the single most important factor for the best outcome in this condition.

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Proforma for patients with bilateral vestibular schwannoma

General instructions:

Please fill in all questions

Write yes/no/ NA wherever applicable

If the response is not known, please write unknown

If additional info is available please elaborate

Plesase use separate proforma for each admission

A. GENERAL INFORMATION:

1.Name

2. Age

3. Sex

4. Hospital no.

5. Address

6. Phone number

7.Mobile no.

8 e-mail address

9.Date of admission

10.Date of discharge/death

B. PRESENTATION:

1. Hearing loss

2.Tinnitus

3.Vertigo

4.Diplopia

5. Headache

6.Raised intracranial pressure

7.Blindness

8.Facial numbness

9.Dysguesia

6.Seizure

7. Pyramidal signs

8. Hemiparesis

9. Ataxia

10.Altered sensorium

11. Incidental

C. SYNDROMIC ASSOCIATION:

1. Neurofibromatosis

2.Associated tumours

D. EXAMINATION :

1. Neurocutaneous markers

2. Fundus

3.Posterior subcapsular catract

4. Visual deficit

5.Cranial nerve deficits

6.Hearing

7.Cerebellar signs

8.Focal deficit

E. IMAGING

1. X-ray

1a.Normal

1bSigns of raised ICP

1c. IAM widening

1d. Jugular bulb

1e. Calcification

2. CT scan

2a.Contrast CT Right Left

2a1.Hypodense

2a2. Isodense

2a3. Hyperdense

2a4. Mixed

2a5. Calcification

2b.CECT Right Left

2b1.Homogenous

2b2. Heterogenous

2b3. Non- enhancing

3. MRI

3a T1WI Right Left

3a1. Hypontense

3a2.Isointense

3a3. Hyperintense

3B. T2WI Right Left

3b1 . Hypontense

3b2. Isointense

3b3. Hyperintense

3c contrast Right Left

3c1. Homogenous

3c2. Heterogenous

3c3. Cystic changes

4. Special sequences

5.Size

6.Tumor extension

7.Brainstem compression

8.Cerebellar compression

9.Hydrocephalus

10.Intratumoral bleed

F8.Tumor extension (classification of Samii et al.) Right Left

(i) T1 tumor, purely intrameatal

(ii) T2 tu-mor, intra- and extrameatal

(iii) T3a tumor, filling cerebel-lopontine angle (CPA) cistern

(iv) T3b tumor, reaching tothe brainstem

(v) T4a tumor, compressing the brainstem

(vi) T4b tumor, severely compressing the brainstem.

Tumors other sites-

G.AUDIOMETRY Right Left

SDS

PTA

SRT

I.SURGERY

1. Grade of excision

1a. Total

1b. Subtotal

1c. Subcapsular

2. Operative Approach

2a. Retromastoid suboccipital

2b. MIddle fossa approach

2c. Translabyrinthine

3.Preoperative CSF diversion

3a.ETV

3b.VP Shunt

3c.EVD

4.Postoperative CSF diversion

4a.ETV

4b.VP Shunt

4c.TP Shunt

4d.EVD

J. COMPLICATIONS

1. CSF leak

2. Meningitis

3. Cranial nerves involvement

3a. 3rd CN

3b. 4th CN

3c. 5th CN (sensory/ motor)

3d. 6th CN

3e.7th CN(House-Brackmann)

3f.Hearing

3e. Lower cranial nerves

4. Postoperative hematoma

5.Pseudomeningocele

6.Paradoxical CSF Rhinorrhea

5.Cerebellar signs

J.HISTOPATHOLOGY

K.RADIOSURGERY

L. FOLLOW UP –GLASSGLOW OUTCOME SCORE

1. At discharge

2. 6 weeks

3.6 months

4. 1 year

5. 2 year

6. Duration

7.Hearing

8.Facial nerve function(HB)

9.Equilibrium

M. MORTALITY

1. Operative

2.Follow up

N. RECURRENCE

1. Yes

2. No

O. RESURGERY

1.Yes.

2.No

If recurrence/new lesion, use separate proforma