# The Acoustic Neuroma:

Some clinical and histological aspects

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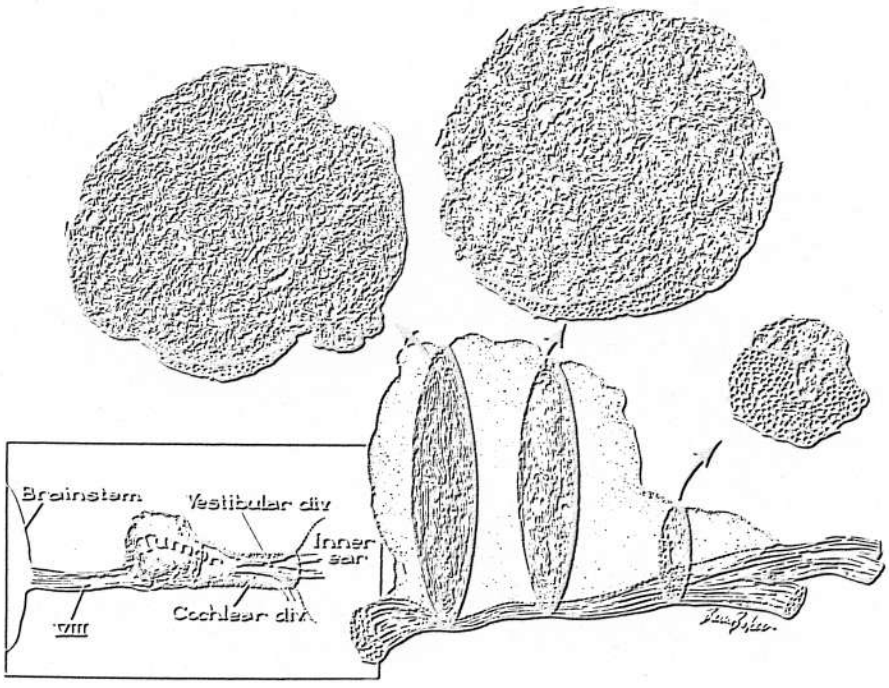
Enkele klinische en histologische aspecten




Glen E.J. Forton

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Some clinical and histological aspects

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Enkele klinische en histologische aspecten

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doctor in de medische wetenschappen aan de
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Antwerpen,
2001

Voor Dominique, Audrey en Laura

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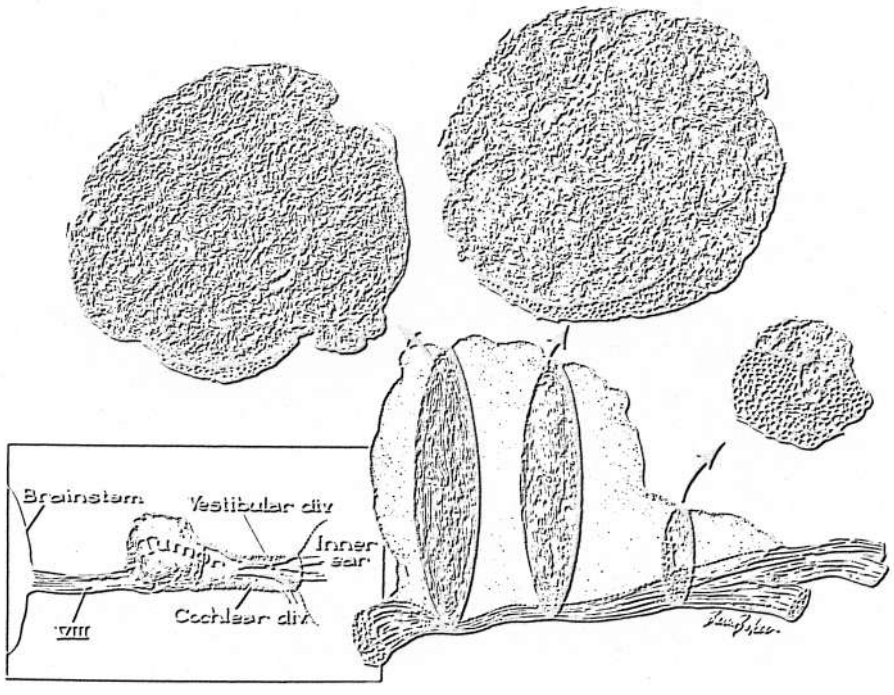
# Chapter 1

# Introduction and historical overview



## Semantics

Ever since Eduard Sandifort of Leyden (1742-1814) first described this pathological entity in 1777, controversy has existed and still exists as to the origin, histopathology, growth patterns and above all the surgical treatment of this benign tumor, commonly called “acoustic neuroma”.

The term “neuroma” was first used by Verocay in 1910 and is not generally accepted. Stout therefore suggested in 1935 to use the term neurilemmoma. Young also rejects this term, for the neurilemma is the innermost layer of endoneurium, also called the Plenk-Laidlaw sheath, that serves as basal membrane for the Schwann cells (1). Friedmann (2) finally, suggests that the term schwannoma should be preferred, for in his opinion; the tumor originates from the Schwann cells and not from the endoneurium in its narrowest meaning.

The term “acoustic neuroma” is therefore a misnomer; even more so because the tumor usually arises from the vestibular nerve and not the cochlear nerve. Vestibular schwannoma is therefore a more appropriate denomination, although not quite uniformly adopted.

This does not end the discussion, however, for Penfield et al. suggested as early as in 1932 that the tumor is of fibroblastic-mesodermal origin and they suggested it be called “perineural fibroblastoma”. Contemporary literature still is not unanimous on this matter. One of the problems is the uncertainty about the exact origin of the Schwann cells. There are, however, indications as to a mesodermal origin and there also are arguments as to an ectodermal origin.

These discussions notwithstanding, the terms vestibular schwannoma, neuroma and neurinoma are still being used interchangeably, even in reference textbooks.

## Epidemiology

The tumors originating from the eighth cranial nerve account for about 6 to 8% of all intracranial tumors and comprise approximately 78% of all cerebellopontine angle tumors (3)

According to Mattox (4), acoustic neuromas are found in about 1.5% of all routine autopsies. Hardy & Crowe (5) have reported back in 1936 a very high number of 2.5%. Their series has been reviewed, however, and four cases have been reclassified, yielding a more acceptable number of 0.8%. According to House and Hitselberger (6), only 0.1% of all these tumors eventually become symptomatic.

Interesting data, spanning no less than 19.5 years, were recently published by Tos et al. (7), offering a very reliable survey of the Danish situation (Table 1).

| | Number of new cases | Incidence per million |
|---|---|---|
| June 1976 – June 1983 | 278 | 7.8 |
| July 1983 – June 1990 | 337 | 9.4 |
| July 1990 – December 1995 | 355 | 12.4 |

*Table 1: the incidence of acoustic neuromas in Denmark according to Tos et al. (7)*

The authors observed a significant increase in the incidence of the acoustic neuroma during the last two periods, but this can be easily explained by the more refined radiological techniques allowing for earlier detection of smaller tumors. Indeed, the increase mainly consists of small and intracanalicular tumors (7).

According to House & Hitselberger (6) the mean age at diagnosis is 47.3 years with 51% of the patients being male and 49% female. In our own modest series, the mean age was 59.2 years and the male/female ratio was 0.46 (chapter 3).

## Clinical presentation

In the early days, an acoustic neuroma was usually only diagnosed after it had started compressing cranial nerves, such as the facial, trigeminal and vagus nerves. In a further stage the cerebellum, brainstem and the other cranial nerves in the vicinity, such as the VIth, Xth, XIth and XIIth eventually were compressed too and a life threatening condition with elevated intracranial pressure arose. Succinct clinical descriptions of what it means to die of an untreated acoustic neuroma were published by Sir Charles Bell (8) in 1830.

It was Toynbee (9) who first recognized an early acoustic neuroma confined to the internal auditory canal. His description was presented in 1853.

Not until the end of the nineteenth century however was the diagnosis made on the basis of clinical symptoms before death. Indeed, little was known of audiology before 1900. Julius Lempert (10) introduced the concepts of perceptive and conductive hearing loss in 1938.

The majority of patients present with a unilateral, slowly progressive sensorineural hearing loss as the principal symptom. There is, however, no such thing as a “typical” audiogram. As demonstrated in William House’s monograph I (11), four pure tone loss patterns can be roughly distinguished. Interestingly, 67% of all cases had a high tone loss type, defined as a perceptive hearing loss that sloped from low frequencies to high frequencies with a loss of at

least 25 dB through the speech frequencies and/or a total loss of hearing beyond 3000 Hz. A loss of hearing that did not differ more than 10 dB through the speech range was defined as a flat type loss.

| Pure tone loss pattern | Number of cases | Percentage |
|---|---|---|
| High tone loss | 31 | 67.4 |
| Flat loss | 11 | 24,0 |
| Low tone loss | 2 | 4,3 |
| Trough-shape loss | 2 | 4,3 |

*Table 2: Pure tone loss patterns, 46 cases (11)*

Up to 13% with an acoustic neuroma can present with a sudden hearing loss. Conversely, approximately 5% of all patients that present with a sudden hearing loss are found to have an acoustic neuroma according to Shaia & Sheehy (12). Also, perfectly normal hearing is possible in patients with acoustic neuroma, as reported by Vassalli et al. (13).

Many investigators have established the fact that excessive adaptation to a pure tone stimulus is most frequently associated with retrocochlear pathology.

Typically, acoustic or stapedius muscle reflexes are diminished or absent. In those cases where the stapedius muscle reflexes are still present, pathological reflex decay may be found.

Jerger (14) initially described four types of Békésy audiograms of which the types III and IV are suggestive for retrocochlear pathology. In House's series of patients presented in his first monograph (11), 70 % indeed produced this type of pattern.

| Békésy audiometry results | Number of cases | Percentage |
|---|---|---|
| Type I | 3 | 7,3 |
| Type II | 9 | 22,0 |
| Type III | 12 | 29,3 |
| Type IV | 17 | 41,4 |

*Table 3: Békésy audiometry results, 41 cases (11)*

In 1977, Daly et al. (15) were the first to report on auditory brainstem evoked response audiometry in four patients with acoustic neuroma. Their results, along with the study reported by Selters and Brackmann (16) in the same year, indicated that ABR could be a very valuable tool for detecting auditory nerve lesions. Latency measures of ABR wave peaks have indeed excellent diagnostic potential. The three latency measures most often examined include: the absolute latency of wave V; the interaural latency difference (ILD)

between ears of wave V and the interpeak latencies (IPL) between waves I and III, I and V, and III and V. Several authors have described “normal” values for these parameters. The interaural latency difference should not exceed 0,3 msec in normal individuals. Selters & Brackmann (16) recommend a 0,1 msec latency correction factor for every 10 dB of hearing loss at 4000 Hz exceeding 50 dB in computing the ILD. The I-III and III-V interpeak latency are approximately 2 msec and the I-V interpeak latency therefore typically is 4 msec in normal subjects (17). An IPL value greater than 4,4 msec is considered abnormal. The acoustic neuroma typically causes a greater increase in the I-III IPL than in the III-V IPL.

An interaural difference in I-V IPL greater than 0,4 msec is considered pathological, again taking in to account a correction for a possible difference in hearing threshold at 4000 HZ between both ears.

It is generally agreed that when cochlear loss exists and all wave peaks are present, they are equally prolonged, thus not influencing the interpretation of an IPL increase.

It has been reported however that in less than 30% of all acoustic neuroma cases all three peaks (I, III and V) can be clearly identified. Finally, a desynchronized pattern may be found in case of profound hearing loss.

Oto-acoustic emissions will be absent in many cases, but they may be preserved as long as the afferent fibers of the cochlear nerve are still functional. This renders oto-acoustic emissions, whether click evoked or distortion products, unsuitable for acoustic neuroma detection. Distortion product oto-acoustic emissions are, however, useful in order to evaluate remaining cochlear function according to Oeken (18).

The acoustic neuroma patient may or may not present with tinnitus or disequilibrium.

Periodical unsteadiness or vertigo may be present, but in most patients the slowly progressive loss of peripheral vestibular function in the affected ear is hardly symptomatic due to central vestibular compensatory mechanisms. Simultaneous appearance of vertigo with nystagmus and hearing loss can occur, thus mimicking an attack of Ménière’s disease. In most cases caloric stimulation of the affected labyrinth will elicit hardly any nystagmus. In very large tumors with cerebellar compression, more complex nystagmus patterns can occur: e.g. asymmetrical gaze nystagmus or Brun’s nystagmus.

## Imaging

The first report on acoustic neuroma imaging was from the hand of Folke Henschen from Stockholm (19) who wrote, back in 1912: “diese Akustikustumoren den inneren Gehörgang erheblich erweitern und dass diese Erweiterung radiographisch darstellbar sein kann”. Indeed, the acoustic neuroma tends to enlarge the internal auditory canal and this is one of the most important radiological signs.

However, detailed radiological examination of the internal auditory canal started when radiologist like Stenvers, Guillen and Schuller published their methods. The main problem was avoiding the superimposition of the mid-face and the skull base. Hypocycloidal tomography together with iodocysternography were the techniques of choice from the 1950’s to the late 1970’s when CT-scan became the most accurate technique to study the inner ear. Several generations of CT-scanners followed one another, the latest generation being able to visualize very small anatomical structures and tumoral lesions. Typically, the acoustic neuroma is a tumor that is centered on the internal auditory canal and it shows marked enhancement after contrast administration. The enhancement usually extends into the internal auditory canal. The canal itself is usually widened with erosion of the posterior ridge. Also the crista falciformis shows marked erosion. An exception to this rule is, of course, the so-called “medial acoustic neuroma” as described by Tos et al. (20). This tumor is defined as an acoustic neuroma without tumor tissue located laterally in the internal auditory meatus. It is a relatively rare variant since it comprises about 2 – 3% of all acoustic neuromas. Tos et al. (20) found that these medial tumors were generally larger than the non-medial ones. The smallest medial tumor they found had an extrameatal diameter of 15 mm. Clinically, there seems to be no significant difference in symptoms or duration of symptoms between the two entities. Surgically, Tos et al. (20) found that the involvement of brainstem and cerebellum were significantly higher than is the case with non-medial acoustic neuromas.

The next important evolution was the introduction of magnetic resonance imaging in the 1980’s. Again, several generations of MRI scanners followed one another and more sophisticated sequences and software protocols are being developed in rapid succession.

Clinical studies were subsequently carried out to assess the sensitivity of MRI. One of these studies was a joint effort from the departments of radiology, neurosurgery and otorhinolaryngolgy of the University Hospital of Antwerp and will be discussed in chapter 3. After contrast administration, all tumors showed intense and greater than average enhancement (up to 300 %) on the T1-weighted images, except for one very small intracanalicular tumor that did not enhance. The enhancement was homogenous in 67% and

slightly inhomogeneous in 10%. Heterogeneous enhancement was encountered in cases with cystic degeneration (22%). The absence of enhancement after contrast administration in a pathologically proven acoustic neuroma is highly unusual, and as far as we could establish, our one patient is the only reported case. T2-weighted images may show mild to moderate peritumoral edema.

Today, visualization of the contents of the labyrinth is a reality. The 3DFT-CISS sequences allow us to detect extremely small lesions, such as intracochlear or intravestibular neuromas. A clinical report of a very small intralabyrinthine schwannoma of only 3.5 mm diameter that had been preoperatively diagnosed by means of MRI was published in the Annals of Otology, Rhinology and Laryngology (22) and the report is included in this volume (chapter 4). Until today, this case still is the smallest preoperatively diagnosed intralabyrinthine tumor in the literature.

A major contribution in this field has been made by the Flemish neuroradiologist from Bruges, J.W. Casselman, as demonstrated in his magnificent doctoral thesis (23). Recently, MRI imaging technique has evolved dramatically and now allows us to actually assess the cochlea's candidacy for hearing preservation surgery. Somers et al. (24) from Antwerp have recently demonstrated an astonishing correlation ($p < 0.05$) between a normal intralabyrinthine signal on 3DFT-CISS MRI images (being an iso-intense signal compared to the contralateral unaffected ear) and successful hearing preservation surgery. In their series of twenty six patients with an acoustic tumor, all being candidates for hearing preservation surgery, hearing was preserved in 50% of the ears where the tumor did not extend into the fundus (77% of the cases), but only in 33% of the cases where the fundus was obliterated by tumor (23% of the cases). Moreover, hearing preservation succeeded in 82% of the cases where a normal intralabyrinthine signal on 3DFT-CISS images was obtained, whereas in cases where the intralabyrinthine signal intensity was low, hearing was preserved in only 20%. In two cases with low pre-operative intralabyrinthine signal intensity but successful hearing preservation surgery, the post-operative control MRI showed that the intralabyrinthine signal intensity had returned to normal. The cause of the lower signal intensity is not exactly known, but the authors postulate that vascular compression due to mechanical obstruction by the tumor in the internal auditory canal might be responsible for this phenomenon. It is a well known fact that the presence of an acoustic neuroma causes significant biochemical alterations in the fluids of the inner ear, as described by Dix & Hallpike (25), Schuknecht (26), O'Conner et al. (27), Silverstein et al. (28) and others. The perilymph of acoustic neuroma patients appears to have a high protein level, which gives rise to altered light microscopic staining characteristics: Acidophilic staining precipitates are seen

in the perilymphatic spaces. Jahnke (29) studied the inner ear in case of an acoustic neuroma using electron microscopy. He describes high amounts of fibrous long-spacing collagen, significant thickening of the capillary basement membrane and even doubling of the capillary basement membrane, mucoid degeneration in the subepithelial space and severe degeneration of the sensory and non-sensory epithelia. The high protein content is ascribed to impaired terminal blood supply to the labyrinth secondary to vascular compression or even invasion of arteries in the internal auditory canal. The radiological finding of a signal decrease of the cerebrospinal fluid trapped in the fundus and of the intralabyrinthine fluid is in concordance with the histological findings. The study of the intralabyrinthine fluids by means of the 3DFT-CISS MRI sequence will yet increase our ability to select the best possible treatment for any given acoustic neuroma case.

## Histology

Harold F. Schuknecht (3) describes the macroscopical appearance of the acoustic schwannoma as follows: cochleovestibular schwannomas are usually firm, circumscribed, and encapsulated, and when small, they are round or ovoid in shape. Larger tumors tend to become lobulated, and then protrude from the internal auditory canal into the cerebellopontine angle. As the tumor grows, adjacent nerve roots are stretched over the surface of the mass or are incorporated into it. The internal auditory canal becomes enlarged and funnel shaped as the result of pressure erosion of the bone. Thus, the characteristic image of the “police whistle” or “champagne cork” arises.

Microscopically, the acoustic schwannoma is a generally cellular tumor with zones of low density alternating with zones of high nuclear density.

Antoni, in a 500-page monograph published in 1920, divided these tumors in two histologic types. Type A is composed of compact tissue of compact and interwoven bundles of long or oval shaped cells. In some areas, the cells are arranged in whorls, while in other areas there is a parallel alignment of the rather large nuclei, referred to as “palisading”. Streaks of collagen fibers are amply present. At times, the arrangement of nuclei and fibers creates formations resembling the tactile corpuscles of Meissner, known as “Verocay bodies”. Type B is a degenerate form, which often is intermingled with type A. It is characterized by loose texture and polymorphism of tumor cells. Nager (30) divided the type B in two subtypes. Subgroup 1 shows fatty degeneration leading to a honeycombed appearance of large pale tumor cells with small pyknotic nuclei. Subgroup 2 shows transformation of tumor tissue into

hyaline masses in which case the cell content is often reduced to a few stellate tumor cells embedded in an amorphous hyaline substance. All these types may coexist in one single tumor.

The typical whorls of collagen, sometimes forming so-called Luse-bodies, are of a particular kind: it is collagen type IV and V with a characteristic 130 µm band pattern, therefore called "long-spacing collagen".

Although several authors have described the presence of the S-100 protein both in the normal Schwann cell and in the acoustic neuroma (Harkin (31), Clark et al. (32)), this observation does not necessarily indicate that the schwannoma obligatory has to originate from the Schwann cells. Gould et al. (33) have described the abundant presence of vimentine in the cytoplasm of the tumor cells. Vimentine is a so-called intermediate filament and is typically considered as a mesenchymal marker protein. Peltonen et al. (34) reported on the presence of vimentine in perineural cells, thus indicating that these cells or not derivatives of epithelial or endothelial cells, but that they are of mesenchymal origin instead. Most specimens are also neuron specific enolase (NSE) positive.

One of the more recent developments is immunohistochemical staining using the monoclonal mouse antibody MIB-1 to demonstrate the Ki-67 nuclear antigen. This antigen is only expressed by nuclei that are not in the G0 resting phase of the cell cycle and is therefore a marker of cell proliferation or tumor growth. Several authors have reported on this issue (table 4).

| | Lesser et al. (35) | Charabi et al. (36) | Chen et al. (37) | Yokoyama et al. (38) |
|---|---|---|---|---|
| Proliferative cell fraction | 0.36 – 3.15 % | 0.4 – 38.0% | 1.16 – 3.40% | 0.37% - 6.61 % |

*Table 4: proliferative cell fraction (percentage of Ki-67 antigen positive cells compared to all cells).*

In the aforementioned studies, no correlation was reported between cell proliferation rates, and patient age, duration of symptoms or tumor volume. Clinical correlation in these studies suggests that lower proliferation rates are indicative of slower growth rates, but they are not conclusive.

Erlandson and Woodruff (39) have used electron microscopy to demonstrate that the tumor cells of the solitary schwannoma are provided with well-structured external laminae that form some kind of basement membrane for the tumor cells resembling the Plenk-Laidlaw sheath.

The cells have spindle shaped nuclei with one or two nucleoli. According to these authors, these findings indicated clearly that these cells are in fact differentiated Schwann cells.

These last observations are illustrative for the discussion and the speculations as to the true origin of the acoustic neuroma cells.

## Treatment

### Surgical treatment

#### The very early period

The first successful removal of an acoustic neuroma was reported on in 1894 (40) and was performed by way of a suboccipital approach by the English otologist Sir Charles Ballance on November 19th, 1894 on a 49-year-old woman. This patient was reported to be alive and well in 1906. She had a right facial palsy and she had lost function of the right trigeminal nerve. Furthermore, she had lost the right eye due to a corneal ulcer. In 1903, the German brain surgeon Krause (41) reported on a unilateral subocciptal approach for the removal of acoustic tumors. Unfortunately, bleeding was uncontrollable when it occurred in the cerebellopontine angle and the mortality rate was reported to be 85%. In 1904 the German otologist Panse (42) decided that the most straightforward way to remove an acoustic neuroma had to be through the labyrinth and he was thus the first to perform the translabyrinthine approach to the cerebellopontine angle. Due to lack of instruments and the limited exposure, mortality again was high. The first transsigmoid approach was devised and performed by Borchardt in 1905 (43), but again bleeding, this time from the lateral sinus, was a major problem and after a few attempts, this approach was abandoned.

In 1913, at the International Congress of Medicine in London, the then leading European neurosurgeons presented their results on removal of cerebellopontine angle tumors. The exact tumor sizes remain unknown.

| Surgeon | Number of cases | Number of fatalities | Percentage |
|---|---|---|---|
| Horsley (London) | 15 | 10 | 67% |
| Von Eiselsberg (Vienna) | 17 | 13 | 77% |
| Krause (Berlin) | 31 | 26 | 84% |

*Table 5: from House WF (Ed.). Monograph: Transtemporal Bone Microsurgical Removal of Acoustic Neuromas. Arch Otolaryngol 1964;80:667-677.*

As illustrated above, although brave attempts were made to surgically treat cerebellopontine angle tumors, morbidity and mortality were formidable.

**The Cushing era (1917 – 1935)**

This situation was unacceptable to Harvey Cushing (44), who in 1917 published his monograph "Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontine Angel", a milestone in the surgery of cerebellopontine angle tumors. He described 30 cases in great detail, 25 of which had tinnitus and hearing loss as their first symptom with the tinnitus preceding the hearing loss with several months. Of course, most of Cushing's patients had very large tumors and had ataxia, advance papilledema or even total blindness due to severely elevated intracranial pressure. He was the first to think of partial tumor removal via a wide bilateral suboccipital approach. The approach had to be bilateral, for in many cases they did not know which side the tumor was preoperatively. Thus, by performing intracapsular subtotal removal, he was able to dramatically lower operative mortality from 80% to 20%. By 1931, Cushing was able to report an operative mortality rate of only 4%! Some patients survived long enough to present with recurrence of symptoms due to regrowth of the tumor remnant. Cushing soon found out that the mortality rate was much higher with the second operation.

**The Dandy era (1922 – 1940)**

While Cushing continued to advocate subtotal tumor removal, other neurosurgeons, among which the famous Walter Dandy, started to pursue total tumor removal. The latter argued that a higher initial mortality rate was acceptable if better long-term survival was obtained. In 1940 Dandy reported (45) on 40 cases with a mortality rate of 10%. He also abandoned the bilateral approach and started doing a unilateral suboccipital approach. At that time, the clinical signs and symptoms were recognized in an earlier stage and the x-ray examination of the temporal bone usually indicated the site of lesion. Dandy dealt with smaller tumors than Cushing, was better equipped and realized that he could lower intracranial pressure by doing a ventricular or cisterna magna tap. While his exposure was still limited, he could gain better access to the cerebellopontine angle by resecting part of the lateral cerebellar hemisphere. In addition, anesthesia improved, blood replacement techniques became available and the electrocautery was invented.

**The pre-House era (1940 – 1961)**

In the post-Dandy era, the discussion on total or subtotal removal continued, but for three decades no major advances in clinical diagnosis or surgical treatment of the acoustic neuroma were made, in spite of improved equipment and patient care. More and more surgeons started doing this kind of surgery, which resulted in a higher cranial nerve deficit rate, while the mortality rate remained 20%. It is rather illustrative to note that during this span of time only one surgeon was actually attempting to save the facial nerve. In 1941, Olivecrona (46) reported on a series of patients in which he had been able to save the facial nerve in 65%.

Since Balance and Panse, and until well into the 1950's the otolaryngologist did not have an active part in the treatment of cerebellopontine angle tumors. If a patient presented with a unilateral progressive sensorineural hearing loss with tinnitus and cerebellar ataxia, the diagnosis would of course be considered, but an early diagnosis was unlikely. And even if a small tumor were diagnosed, the neurosurgeon would not operate until the tumor grew and became life threatening for the morbidity and mortality was still high.

**The House era (1961 - ?)**

The situation remained unchanged until the American otologist William House took up the challenge in 1961 when he presented his candidate's thesis to the American Laryngological, Rhinological and Otological Society. His work was called "Surgical Exposure of the Internal Auditory Canal and its Contents through the Middle Cranial Fossa" (47) and was the first presentation of a combined otologic-neurosurgical procedure designed for vestibular nerve sectioning and decompression. In 1964 he published his transtemporal technique (48) for total removal of acoustic neuromas, No longer were acoustic neuromas referred for the classic suboccipital approach, but operated by his oto-neurosurgical team via the middle fossa approach at first and subsequently via the re-instated translabyrinthine technique. House's modified translabyrinthine approach was revolutionary as it made use of all newly invented instruments, such as the operating microscope and diamond burrs (both introduced in the field of otology by George Shambaugh Jr.), and it allowed early visualization of the facial nerve. As refined audiologic techniques emerged and iodocysternography was introduced in the same year, earlier diagnosis was made possible and still smaller tumors were diagnosed and subsequently operated.

By December 1964, House published his first monograph presenting no less than 54 cases. The era of microsurgery of the cerebellopontine angle had begun. The co-operation of

House, an otologist, and Hitselberger, a neurosurgeon, inspired many teams all over the world.

**Modern microsurgery of the cerebellopontine angle: hearing preservation surgery (early 1970's)**

In the late 1960's and early 1970's, otolaryngologists throughout Western Europe, were inspired by House and started treating acoustic neuromas themselves instead of referring these patients to the neurosurgeon. We have tried to acquire some data from these pioneers.

One of the first was Ugo Fisch of Zürich, who did his first translabyrinthine and middle fossa approaches at the end of 1967 (49).

In the United Kingdom, Andrew Morrison from London, was the first to carry out translabyrinthine acoustic tumor surgery in 1968 (personal letter from A. Morrison). Except for the smaller tumors, these operations were performed in conjunction with T. King, a neurosurgeon. They started doing hearing preservation surgery in 1977, using the retrosigmoid route. In 1978 Richard Ramsden from Manchester started his impressive series of 778 cases (2000), using the retrosigmoid approach and the translabyrinthine approach fairly equally during the first 150 cases (personal letter from R. Ramsden). Later on, most of the tumors were operated via the translabyrinthine approach.

Jean-Marc Sterkers from Paris operated his first acoustic neuroma by means of the translabyrinthine approach on March 7$^{th}$, 1966 (personal letter from J.-M. Sterkers). He started using the suspetrous and the retrosigmoid approach in order to save hearing from 1972 on. In 1967, Michel Portmann of Bordeaux, another famous French pioneer, operated his first acoustic neuroma case using the middle fossa approach (personal letter from M. Portmann). He reported on his experience with the middle fossa approach in 1972 (50).

In 1972, Ed Marres started to do acoustic neuroma surgery at the University Hospital of Nijmegen, The Netherlands (personal communication).

In Germany, Malte Erik Wigand was a pioneer who performed his first acoustic tumor removal in 1973. He used the translabyrinthine approach for large tumors and chose the middle fossa approach for small and intracanalicular tumors. From 1973 on, he tried to preserve hearing in all cases up to 3 cm irrespective of the preoperative hearing! In all these cases he used the middle fossa approach (personal letter from M.E. Wigand)

In Italy, Mario Sanna from Piacenza performed a first translabyrinthine removal of an acoustic neuroma on June 29th, 1975. From 1978 on, the Piacenza-group also started using the retro-sigmoid and middle fossa approaches in order to save hearing (personal letter from M. Sanna)

Mirko Tos and Jens Thomsen introduced the translabyrinthine approach in Denmark in May 1976 (51, personal letter from J. Thomsen). The first middle fossa case was in 1989.

In Belgium, the late Jean Marquet of Antwerp was the first to adopt House's technique for translabyrinthine removal of acoustic neuroma in the early 1970's. He too advocated total tumor removal whenever feasible, for he was convinced that the tumor, although benign, actively grew into the adjacent cochlear nerve. Therefore, the cochlear nerve was to be removed in all cases. This premise was the impetus for this thesis: to prove the actual ingrowth of the schwannoma into the cochlear nerve, thus rendering hearing conservation surgery a futile exercise, for recurrences were bound to occur according to our late head of department. This fact explains why in our department, hearing preservation started only in 1990.

**Histological evaluation of tumoral ingrowth: the controversies**

The first spin-off of this histological research was a report on staining techniques to differentiate cartilage from bone in human fetal temporal bones and is included in this paper.

As we will demonstrate in subsequent chapters, there exists no cleavage plane whatsoever between the cochlear nerve and the tumor whenever adherences are present. Consequently, in case of adherences to the facial and/or cochlear nerve, a variable amount of tumor cells invisible to the surgeon will inevitably be left behind. Hearing preservation surgery in the same way is prone to leaving potentially viable tumor cells behind. In most cases of acoustic neuroma surgery, there are adherences between the tumor and the facial nerve. Therefore, in all cases, even without hearing preservation, potentially viable tumor cells are left behind on the facial nerve as demonstrated by Luetje et al. (52)

The discovery of tumoral ingrowth into the cochlear nerve in 1989 – 1990 at first lead us to believe that attempts to preserve hearing was a misconception for tumor recurrence was bound to occur, as Prof. Marquet had predicted. Therefore, the translabyrinthine approach combined with total tumor removal was advocated as the only correct way if dealing with an acoustic neuroma. The aforementioned statement to prefer the translabyrinthine approach in all cases was based on our histological findings and was made about ten years ago. Since

attempts to preserve social hearing continued elsewhere, a review of these attempts with special reference to tumor recurrence rate is presented.

However, as surgical techniques got better and still smaller acoustic neuromas were diagnosed in an earlier stage with hardly any loss of hearing, the idea of hearing preservation surgery gradually took form. Our research data, though providing ample evidence as to tumoral ingrowth in to the cochlear nerve, should therefore be interpreted in a different light.

As oto-neurosurgical teams in the late eighties and early nineties gradually mastered the three main approaches to the cerebellopontine angle (middle fossa approach, retrosigmoid approach and translabyrinthine approach), controversies and discussions as to which approach was best, flared. As always, the truth lies in the middle and each case has to be considered separately and then the most appropriate approach is to be chosen.

**The goal of hearing preservation surgery**

The goal of hearing preservation surgery is obviously maximal or total tumor removal, while at the same time avoiding major neurological sequellae, preserving facial nerve function and hearing in the affected ear. To achieve preservation of hearing, the labyrinth has to be left untouched, the cochlear nerve has to be dissected from the tumor and kept morphologically and functionally intact. This requires an intact blood supply to the labyrinth and the cochlear nerve. Thanks to the work of many distinguished otologic surgeons and neurosurgeons, we know now for a fact that preservation of social hearing is only an attainable goal in very well selected cases. An upper limit of tumor size of 15 mm extrameatal diameter in the cerebellopontine angle is generally accepted (53). Shelton et al (53) confirm that the rate of socially serviceable hearing preservation is much better for small tumors. A preoperative speech reception threshold better than 30 dB and a speech discrimination score better than 70 dB are broadly accepted values in order to consider hearing preservation surgery. The latter rule is also in accordance with George Browning's Glasgow Benefit Plot (54). Since this rule was originally devised to evaluate postoperative binaural hearing after middle ear surgery, it can easily be adapted to the evaluation of binaural hearing after hearing conservation surgery of an acoustic neuroma.

In the literature, a distinction is made between total (or near total) tumor resection and a deliberate partial removal.

Silverstein et al. (55) report on reoperations due to planned subtotal resection in patients over 65 years. All but two patients were operated via the translabyrinthine approach. The follow-up period ranged from at least one year to 13 years with an average follow-up time of

3.6 years. 50% had regrowth of their tumor at varying rates (0.09 to 0.76 cm/year) and 23% started to have symptoms due to their tumor regrowth. 14% of all cases had to have a second procedure. Olivecrona (56) reported a recurrence rate of 21% after subtotal resection and House (57) reported a recurrence rate of 23% after subtotal removal. Van Leeuwen et al. (58) report on a series of 106 patients operated on via a suboccipital approach of which 24 (23%) had total removal, 9 (8%) had near-total removal and 73 (69%) had a deliberate subtotal removal. The duration of follow-up ranged from 12 to 156 months. In the original group of 73 patients who had subtotal removal 19 patients (26%) developed tumor recurrence. In the group with near-total removal 2 of the 9 patients (22%) developed tumor recurrence. There were no recurrences in the total tumor removal group.

Though rather scarce, some reports exist that mention a second intervention due to tumor recurrence after incomplete tumor removal (59- 64).

Beatty et al. (59) report on 22 patients who needed a secondary procedure due to tumor recurrence from 1976 to 1985. All but three patients presented with symptoms and most of these with several symptoms. The primary procedure had consisted of a retrosigmoid approach in 21 patients and a middle fossa approach in one. Seven of these patients were known to have had incomplete tumor removal, while in 11 patients gross tumor removal was thought to have been accomplished. According to the authors, the interval between the primary and the secondary procedure ranged from 3.3 to 17 years with a median of 78 months. They advocate the translabyrinthine approach in case of re-intervention in those cases where a retrosigmoid approach has been used. They found that the translabyrinthine approach to the cerebellopontine angle through previously untouched tissues allow early definition of the facial nerve, delineation of the lateral extent of the tumor and access to a face of the tumor that often has less scarring.

Robertson et al. (60) report on 35 recurrent tumors after primary suboccipital resections. They all had a secondary procedure via the translabyrinthine approach. The interval between primary and secondary intervention ranged from 6 months to as long as 24 years, the mean being 69 months. The average size of the recurrent tumor was 2.6 cm, the largest measuring 6 cm. Interestingly, in only 3 of the 22 available patient records, the surgeon reported incomplete tumor removal. In all other cases, the surgeon believed to have accomplished total tumor removal.

Ohta et al. (61) on the other hand, report on a series of 81 patients treated for acoustic neuromas. In 8 of these cases, a thin layer of tumor was left overlying the facial nerve in order to preserve the nerve. Only one case showed regrowth 3.5 years after the operation.

In the other seven cases, the tumor remnants remained dormant during an observation period ranging from 4.5 to 8.5 years.

Cerullo et al. (62) have found tumor recurrence in 18 cases out of their series of 116 consecutive vestibular schwannoma cases. Their primary goal was preservation of facial nerve and cochlear nerve function, even if it meant leaving small fragments of tumor in situ. The authors found no correlation between recurrence and age, residual coagulated morsels of tumor, preoperative tumor size or opening of the internal auditory canal. The interval between primary surgery and detection of the recurrent tumor ranged from 6 to 148 months.

Gormley et al (63), report on 179 patients with acoustic neuromas, of which 84% were operated on using the retrosigmoid approach. They claim to have accomplished total tumor removal in 99% of their cases and they have not yet discovered tumor recurrence in this group in an observation period ranging from 3 tot 171 months. In one case, tumor removal was incomplete and this patient eventually required a secondary procedure due to symptomatic tumor regrowth.

In their retrospective series of 155 patients, Pace-Balzan et al (64) 143 (i.e. 92%) had “macroscopic” total tumor removal. However, in 21 of these cases, tiny fragments of tumor had to be left behind in order to preserve vital structures, the facial or the cochlear nerve. Of these 21 patients, 14 agreed to participate in a long-term follow-up using MRI. In 7 cases, a recurrence was found in an interval ranging from 6 to 150 months (mean 70 months).

All aforementioned authors agree that a very long surveillance period, some say lifelong, is mandatory. As hearing can deteriorate for a number of reasons, even after successful hearing preservation surgery at first, hearing loss does not necessarily equals tumor recurrence. Conversely, however, as a large number of operated acoustic neuroma patients are nearly always already deaf, hearing loss is no longer a useful clinical sign. Routine imaging is therefore the only safe method and, as recurrences will be small in the beginning, gadolinium enhanced MRI will be the method of choice due to its superior specificity.

A survey of more recent literature did not reveal new facts or new reports on large series.

**The facial nerve**

One of the main reasons to revert to subtotal tumor removal is to safeguard the facial nerve. A very nice review of postoperative facial nerve function (suboccipital approach) is offered by Van Leeuwen et al (58). They conclude that, in this series, the initial tumor diameter had very little influence on the postoperative facial nerve function. However, the number of

complications increased with tumor diameter. The authors also offer a very illustrative graph and a comparison with other centers.

| | Van Leeuwen | Sterkers | Tos | Van Leeuwen | Fisch | Haid | Shelton |
|---|---|---|---|---|---|---|---|
| Center | Nijmegen (NL) | Paris (Fr) | Copen-Hagen (DK) | Nijmegen (NL) | Zürich (SCH) | Erlangen (D) | Los Angeles (USA) |
| Year | 1994 | 1994 | 1992 | 1994 | 1988 | 1992 | 1989 |
| Number | 106 | 571 | 400 | 52 | 66 | 154 | 92 |
| Tumor diameter | all | < 40 | all | < 35 mm | < 25 mm | < 35 mm | * |
| approach | SO | RS/TL /MF | TL | TL/TO | TO | MF | MF |
| House I (100%) | 36% | 63% (I & II) | 67% | 78% | 70% | 53% | 81% |
| House II (80%) | 23% | 63% (I & II) | 12% | 10% | 15% | 25% | 9% |
| House III (60%) | 16% | 19% | 3% | 4% | 9% | 20% | 5% |
| House IV (40%) | 11% | 12% | 4% | 4% | 3% | 1% | 3% |
| House V (20%) | 6% | 6% | 4% | 0% | 3% | 0% | 1% |
| House VI (0%) | 8% | | 10% | 4% | | 1% | 1% |

*Table 6: Postoperative facial nerve function. SO = suboccipital approach; TL = translabyrinthine approach; TO = transotic approach; RS = retrosigmoid approach; * series selected for hearing preservation surgery (57)*

Undoubtedly, the facial nerve is not infrequently involved in the tumoral process, especially when the nerve becomes thin and stretched over the surface of the tumor. Luetje et al. (52) have demonstrated that it can be extremely difficult to define a surgical plane between the facial nerve and the tumor in those cases. They obtained microscopical evidence of the absence of a cleavage plane between the facial nerve and the tumor in three cases where excision of the compromised portion of the facial nerve "en bloc" with the tumor was required. They subsequently performed a direct primary VII-VII neuro-anastomosis by rerouting of the facial nerve. The authors conclude that histological involvement of the seventh and eighth nerves may be present without recognition by the surgeon.

Although the facial nerve may be involved in the tumoral process in a certain number of cases, the functional consequences of facial nerve involvement seem to be quite mild. Van de Heyning et al. (65) report that preoperative EMG recordings were pathological in 85 % of the studied acoustic neuroma cases, while electroneuronography was pathological in only 40

% of the cases. However, the progressive involvement of the facial nerve, as evidenced by the EMG recordings, only rarely provoked clinical signs. These findings may be explained by the phenomenon of collateral innervation, which reduces the loss of muscle power. Given the logarithmical relationship between mimic muscle power and facial movement, as described by Burres (66), one can readily understand that a fairly major reduction of functional facial nerve fibers is required before facial paralysis occurs.

Another interesting observation concerns the spatial relations between the intermediate nerve (Wrisberg) and the vestibular nerve. Although the intermediate nerve is considered to be a part of the facial nerve, it is more related to the vestibular nerve during its embryological development (67, 68). Involvement of the facial nerve by acoustic neuroma will therefore cause a loss of afferent functions before any clinical sign of facial paresis appears. An example is Hitselberger's sign.

There is also an important anatomical difference between the facial nerve and the acoustic nerve. The myelin sheath of the former extends far more medially than the myelin sheath of the cochlear nerve. The junction between the glial sheath and the myelin sheath therefore lies more medial to the brainstem. The well-developed myelin sheath of the facial nerve may also be partly responsible for the sparing of the facial nerve motor function.

These reflections are well illustrated by the clinical results (Table 4). As mentioned before, we cannot rule out the possibility of leaving tumor behind when preserving the facial nerve.

**Tumor-biological considerations**

Contemporary data clearly show that not all residual tumors grow, especially not if the morsels of tumor that are originally left behind are small and, according to some authors (61, 62) are cauterized. Some propose that there must be at least a certain volume of residual tumor, a “critical mass”, with its own blood supply and trophic factors in order to have a growing tumor again. Filipo et al. (69) have discovered the expression of the Transforming Growth Factor-β1 in the majority (83.87%) of the acoustic neuromas they studied. The expression was more important in Antoni A regions than in Antoni B regions. There was also a marked presence of TGF- β1 at the edges of the tumor. TGF-β1 is a multifunctional peptide that modulates cell proliferation and differentiation, embryonic development and maintenance of adult tissues. It is also involved in the development and function of the nervous system. Animal studies have shown that TGF-β1 is a major and potent mitogen for normal Schwann cells. Also, it is involved in the development of Schwann cell tumors with a different mechanism from GGF (glial growth factor). This growth factor could therefore

participate in the biological behavior of the acoustic neuroma and its recurrence after incomplete removal.

## Radiation therapy

The first “gamma-knife” in the world was installed at the Karolinska Institute in Sweden and was applied for acoustic neuroma treatment as early as 1969. The first unit in the United States was installed in Pittsburgh on August 4th, 1987. The latter unit has published their most recent results. In 1996, they treated 323 patients with an acoustic neuroma (70). The authors state optimistically that, although radiation therapy has until recently been reserved for patients who were either unwilling or unable to undergo microsurgery, they expect radiation therapy to replace surgery as method of choice by the year 2020. Although they present a nice survey of all possible hazards and complications regarding surgery, they fail to provide hard evidence as to the alleged superiority of radiation therapy and more important, they only assume that long-term tumor control will be good. Complications of radiation therapy are not discussed. A tumor growth control of 88% has indeed been reported by Maire et al (70) after no less than 45 Gy fractionated external beam radiotherapy. Norén et al (72) report on 110 patients: growth control was obtained in 90%, meaning that in 60% the tumor stopped growing and remained unaltered, while in 30% the tumor actually shrunk. Hearing was unaltered at first, but subsequently started to deteriorate. Only 30% of the patients maintained hearing at their preoperative levels. In a more recent paper, Thomassin et al. (73) report on their experience with 138 vestibular schwannomas treated with gamma knife surgery from 1992 to 1994, of which 104 patients were evaluated 3 years after irradiation. 70% of the patients who had normal hearing retained their normal hearing, while 50% of those patients with serviceable hearing kept their serviceable hearing

Stereotactic radiosurgery therefore is an alternative to offer patients who decline surgery or who are in a poor general condition. One has to keep in mind however, that it is not surgery at all and that the tumor, albeit irradiated, stays in place.

Recently, an intracranial sarcoma after gamma knife surgery for a vestibular schwannoma in a patient with neurofibromatosis was reported by Thomsen et al. (74). It is common knowledge that irradiation of the central nervous system is also capable of inducing tumors, especially when the dose exceeds 10 Gy (74).

Serious MRI studies as to the long-term results of radiation therapy have to be carried out and their results should be compared to the observed growth rates in the “wait-and-see” policy group.

## The “wait and see” policy

While in the eighties, a wait-and-see policy was restricted to those patients refusing any kind of treatment for their condition, the first results of this policy have led to a change in the management of a certain subgroup of acoustic neuroma patients.

Many authors have tried to establish a mean growth rate and came up with rather variable data. One of the issues at hand is *how* tumor growth is to be measured. The most accurate measurement, of course, would be the assessment of the tumor volume. Unfortunately, this kind of accurate measurements has only recently become available, again thanks to MRI. Before that, measurements were carried out on axial and coronal CT-scan images. Usually, the maximal diameter of the extrameatal portion of the tumor was measured. When comparing these data, one should keep in mind that the volume of a roughly spherical shaped object is directly related to the third power of its radius. Therefore, we have tried to seek correlations between two, and whenever available, three-dimensional measurements of the tumor, calculations of its volume and all available audiological and clinical data. These results are presented in a subsequent chapter. The same thought applies to the following data: growth rates are discussed, but it is not always clear how the authors measured growth.

Strassnick et al. (75) found a mean annual growth rate of 1,1 mm (ranging from 0 tot 11 mm per year). Rosenberg et al (76) compared nonsurgical patients to patients who underwent subtotal resection. They found the growth in the nonsurgical group to vary from 0 to 17.1 mm per year, with a mean growth rate of 0.6 mm/year. The follow-up period ranged from 0.7 to 9.2 years with an average follow-up period of 4.3 years. Some patients eventually did require surgery due to rapid tumor growth. In the patient group that had subtotal tumor removal, the average growth rate *post*-operatively was 0.7 mm/year. The authors state that tumor growth rate can be readily monitored using MRI and that one can predict if and when problems, such as headaches, elevated intracranial pressure or cerebellar problems are to be expected. Surgery can therefore be postponed until it becomes really necessary, according to these authors.

We have to re-emphasize at this point, however, an observed growth rate based on the measurement of tumor diameter (e.g. by means of CT scan) does not accurately reflect the actual increase in tumor volume and its effect on the neighboring structures.

However, Thomsen et al (77) demonstrate that there seem to be several growth patterns, indicating that tumor growth rate may indeed vary over time.

Based on the observation of 123 patients with 127 tumors (6 cystic tumors and 9 NF2 tumors) from 1973 until 1993, they found no less than 5 growth patterns (fig. 1)

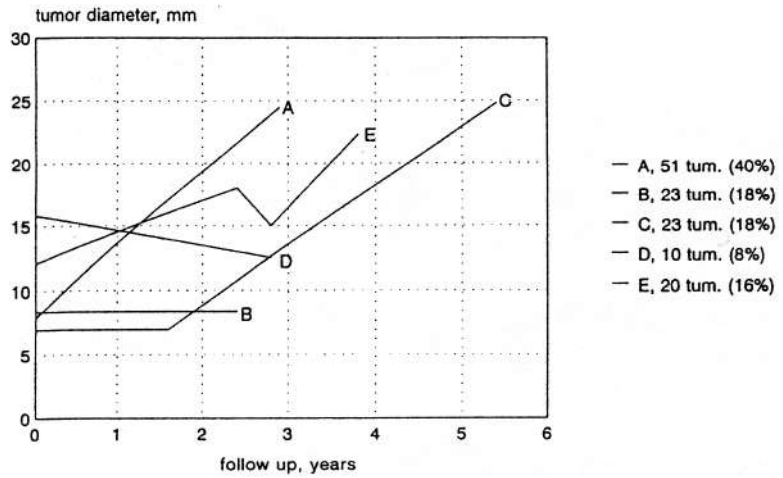



*Fig 1: From: Charabi S, Thomsen J, Mantoni M et al. Acoustic Neuroma: growth and surgical and nonsurgical consequences of the wait-and-see policy. Otolaryngol Head Neck Surg 1995;113:5-14*

In 74% of the available records on tumor volume, measurable growth occurred during the follow-up period. Continuous growth was noted in 40% (A), no measurable growth in 18 % (B), no measurable growth followed by continuous growth in 18% (C), tumor involution in 8% (D) and various growth patterns in 16% (E). The duration of symptoms was statistically unrelated to initial tumor diameter and initial (calculated) tumor volume. The authors conclude that the acoustic schwannoma typically grows slowly. However, the individual growth rate may vary. They found a mean growth rate of 3.2 mm/year (diameter) or 0.72 ml/year (volume). Again, we agree with the authors that diameters alone do not tell the whole story and that an attempt should be made to assess volume instead of diameters. MRI nowadays allows us to do just that, but where retrospective studies are concerned, volumes can only be estimated through calculations as we have attempted in our clinical chapter. Growth type C is of great importance as it demonstrates that tumors can remain "dormant" for some time and then start growing again. This is in contrast with other

publications, such as Rosenberg et al (76), where the authors state that the growth pattern and therefore the need for surgery can be estimated within a short evaluation period during which radiological assessment is carried out. Thomsen et al (77) submit this question to the reader: “How many tumors in group B will start growing during a longer observation period?” Tumor involution or negative growth is not as reassuring as it seems either, for some tumors in group E first shrunk and afterwards started growing again: a strange tumorbiologic phenomenon for sure. The authors conclude that tumors in patients with a short duration of symptoms prior to diagnosis grew faster than tumors in patients with a long prediagnostic duration of symptoms. In addition, cystic tumors tended to grow faster. The initials neuroradiological architecture of the tumor therefore has a prognostic value. Growth appeared no to be statistically related to age.

Finally, the authors state that before adapting a wait-and-see policy, duration of symptoms and the neuroradiological architecture should be studied, for a number of patients in their series lost their “candidacy” for hearing preservation surgery due to waiting too long. Therefore, patients who are considered candidates for hearing preservation surgery from the beginning, should decide from the start whether they want or do not want a maximal chance for hearing preserve and therefore choose for early surgery. Together with Nedzelski et al. (78), but contrary to other authors, Thomsen et al. (76) do not consider old age in itself a contra-indication for surgery.

Nedzelski et al. (78) concur that a wait-and-see policy is only to be suggested to selected individuals and that it implies strict follow-up on tumor growth by means of a high-definition CT or preferably MRI twice a year. If the tumor remains unchanged for three years, evaluation is carried out on a yearly basis. A growth rate exceeding 2 mm per year is an indication for surgery as is, of course, any tumor becoming too big and life threatening.

Shelton and Hitselberger (79) in 1991 presented a review of the results on no less than 2520 acoustic neuromas removed by members of the House Ear Clinic from 1961 until 1989. They compare surgery to radiotherapy and doing nothing (i.e. wait-and-see) and they concluded then that their surgical results were superior than the 22 % post-treatment total hearing loss obtained with radiation therapy and better than the 30% unaltered hearing mentioned by Norén (72). They point out the difficulties of saving the facial nerve when operating on an irradiated neuroma after it has started growing again. As for wait-and-see: they argue that their data confirm their intuition: the smaller the tumor, the easier it is to remove.

## Quality of life

Over the last five years, much attention has quite rightfully been paid to the quality of life after acoustic neuroma surgery. Questionnaires were developed and sent to the patients in an effort to evaluate how this kind of surgery had interfered with their lives. Andersson et al; (80) have evaluated the Swedish situation in 1997. They questioned 141 patients who underwent surgery via the translabyrinthine approach and concluded that normal to moderately impaired facial function (House & Brackmann I-III) was evident in 85.2% of patients. Most patients (80%) considered their hearing to be worse after surgery, 60% complained of tinnitus and 45% had balance problems. Headaches remained a problem in 22%. Work ability was affected in 23% and 37% reported a continued need for medical consultations, mainly due to facial problems or pain.

Van Leeuwen et al (81) in 1995, report on a survey of 134 patients of whom 108 underwent a suboccipital approach and 66 had a translabyrinthine or transotic approach. The patients operated via the suboccipital approach appeared to have more emotional problems afterwards than the translabyrinthine/transotic group. Irrespective of tumor diameter, more patients from the suboccipital group complained of headaches as compared to the translabyrinthine/transotic group. Overall, the quality of life of the patients was influenced to a limited extent by the surgical approach and whether or not a reoperation had been necessary. Suboccipital surgery led significantly more often to being declared unfit to work than translabyrinthine/transotic surgery. The main reasons were vertigo and hearing impairment. The surgical approach and the tumor size did not have any effect on hearing and tinnitus . A large portion of patients without vertigo preoperatively complained of vertigo after translabyrinthine/transotic surgery. Some patients with preoperative vertigo reported an improvement after suboccipital surgery. The most favorable facial nerve function was obtained after translabyrinthine surgery for a small tumor and the worst result after suboccipital surgery for a larger tumor. Recovery after the operation was always a slow process and recovery was not always complete. Patients had a poorer general state of health than their healthy peers, according to Van Leeuwen et al. (81).

## Development and aims of this thesis

In a first stage, staring in 1988, we have tried to select and adapt suitable histological staining techniques for our research project. The general idea was to demonstrate ingrowth of the schwannoma into the cochlear nerve. A first spin-off was the application of the Luxol fast blue MBS staining technique on human fetal temporal bone sections. This resulted in a first publication with F. Declau, using the Luxol fast blue staining technique in order to differentiate cartilage from bone in human fetal temporal bones. This paper comprises the first part of chapter two.

Parts two and three of the second chapter summarize our own histological research on the acoustic neuroma at the Experimental ENT laboratory of the University of Antwerp. We have applied a score of routine staining techniques and the Luxol Fast Blue staining technique to a series of intact small and medium sized acoustic neuromas that had been removed via the translabyrinthine approach by the late Prof. Marquet. The latter staining technique, however, did not help us to attain our ultimate goal: the identification of tumor ingrowth in the cochlear nerve. Therefore, we sought and found yet another technique: Verhoeff's old elastin staining technique. This time, we were able to clearly identify the nerve fibers and we could study the interface between tumor and nerve. This study was published in 1989 and comprises the second part of this chapter. This also explains why this study only deals with small and medium sized acoustic neuromas. The larger tumors could not be preserved as a whole without endangering the facial nerve or other vital structures.

In a following stage, immunohistochemical technology was applied. This time, we have tried to obtain microscopical sections that would prove beyond any doubt that there is actually no cleavage plane between the compromised nerves and the tumor, whenever macroscopically visible adherences were present between the nerve and the tumor. This study was published in 1990 and comprises the third part of chapter two.

In the third chapter, we offer clinical data of the subjects involved and we demonstrate some correlations. Also, we try to position our group of subjects in the general population of acoustic neuroma patients. In a second part, MRI data are discussed and the MRI characteristics of the acoustic neuroma are summarized.

Finally, atypical presentations of the schwannoma in the temporal bone are presented in the fourth chapter by means of case reports: one on facial nerve neuromas and one on a very small intralabyrinthine neuroma. A case report of a cerebellar astrocytoma was also included, because it perfectly mimicked an acoustic neuroma.

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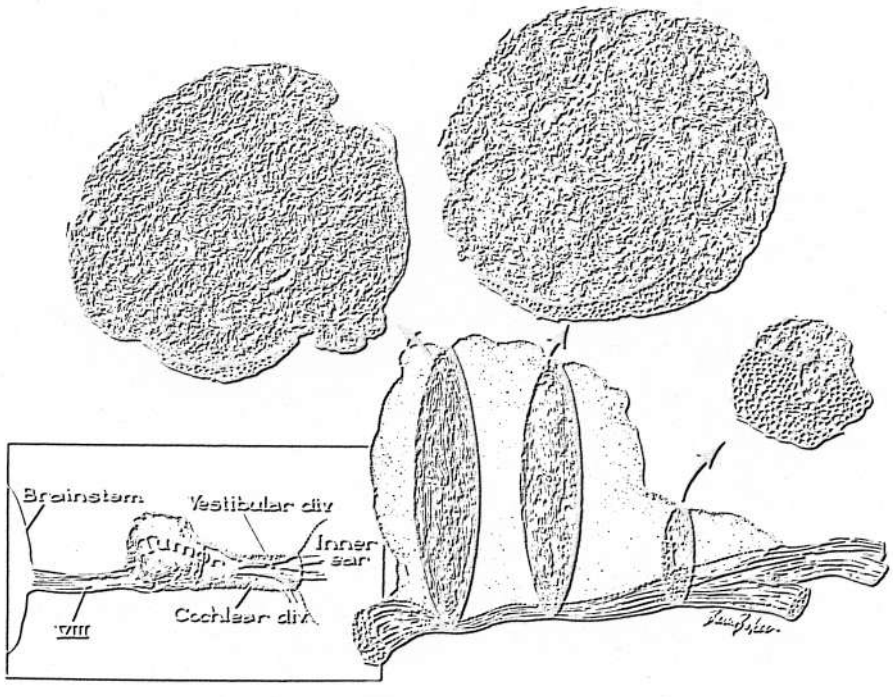
# Chapter 2

# Histology



## Chapter 2a

# Differentiation of cartilage and bone in human fetal temporal bones with Luxol fast blue stain

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## Samenvatting

Een gemodificeerde Luxol fast blue techniek werd op punt gesteld om de ontwikkeling van het os temporale te kunnen bestuderen. De gemodificeerde kleuringstechniek laat toe een duidelijk onderscheid te maken tussen het aanwezige primitieve kraakbeen en het nieuwgevormde bot. Alhoewel beide weefsels een grote hoeveelheid collageen bevatten, zijn hun kleuringseigenschappen na de Luxol fast blue kleuring duidelijk verschillend en dit door de verschillende fysicochemische eigenschappen van de respectievelijke collageentypes in beide weefsels. De differentiatie van het mesenchymateuze weefsel tot ligamenten en gewrichten kan fraai in beeld worden gebracht met deze techniek. Ook bij de studie van de endochondrale botvorming binnen het otisch kapsel en het middenoor geeft de gemodificeerde Luxol fast blue kleuring complementaire informatie bij de standaard kleuringsmethoden.

## Summary

A modified Luxol fast blue technique was used to study the development of the temporal bone. This staining method makes it possible to make a clear distinction between the primitive cartilage present and the new forming bone. Although these tissues both contain a significant amount of collagen, their staining properties with the Luxol dyes are widely dissimilar, due to the different physicochemical properties of the collagen types involved in these tissues. The differentiation of mesenchymatous tissue into ligaments and joints can also be very clearly demonstrated with this technique. In studying the endochondral ossification process of the otic capsule and middle ear, the modified Luxol fast blue stain is a valuable technique that is complementary to more conventional staining methods.

## Introduction

The Luxol dye technique was developed by Klüver and Barrera (4) in 1953 for staining the myelin sheath of nerve fibers. The staining properties of the Luxol dyes are based upon their chemical structure. Luxol fast blue is a diarylguanidine salt of an acidic dye. The specific structure of the latter is not responsible for the staining reaction produced (2). In their early publication, Klüver and Barrera (5) used the du Pont product, Luxol fast blue MBS, a phtalocyanine dye, but similar results were obtained with azo-dyes: Luxol fast blue type ARN and type G (9, 10). Following its discovery in 1953, the Klüver and Barrera method was

generally accepted in many laboratories as a highly specific staining technique for myelin (7). However, it became clear quite rapidly that this method or its modifications (6) were not al all very specific and a significant number of artifacts were described, particularly since the Luxol dye techniques also stain red blood cells, elastic tissue and collagen (3).

Salthouse (11) reported a selective staining method for collagen and elastin by the application of Luxol fast blue G in a saturated methanol solution. Clasen et al. (2) also found that collagen stains with the Klüver-Barrera technique if the slides are only slightly differentiated. Both authors attribute this staining of collagen to the action of the Luxol dyes as milling dyes.

Although “non-specific”, the staining of collagen and elastin tissue gave us the idea of using the Luxol dye technique to investigate the endochondral ossification of the otic capsule and middle ear in fetal temporal bones. In man, the cephalic mesenchyme surrounding the inner ear differentiates into cartilage in the 8th postovulatory week (1). The subsequent process of ossification starts at 16 weeks menstrual age as the result of hypertrophy of the chondrocytes in their lacunae. While calcium is deposited in the cartilaginous matrix, cellular masses invade and contain chondroblasts, many undifferentiated cells and blood vessels; the cartilage cells and matrix are then rapidly destroyed and replaced by proliferating and differentiating cells.

Osteoblasts form bone around the spicules of the cartilage matrix that are left. This kind of bone formation constitutes endochondral ossification. With the conventional staining methods that are routinely used in the laboratory (i.e., hematoxylin-phloxin-safranine, trichrome-Masson or periodic acid-Schiff), we have never been able to obtain a good differentiation between the primitive cartilage and bone tissue.

## Materials and methods

The Luxol fast blue method, here described, is a modification of the techniques reported by Klüver and Barrera (4, 5) and by Margolis and Pickett (6). Our material consisted of 8 fetal temporal bones between 14 and 22 weeks menstrual age. These temporal bones were preserved in 4% formaldehyde. The non-decalcified specimens were embedded in polymethyl-methacrylate (Technovit 7141) and sectioned coronally by a semi-automatic (Exakt2) cutting system so that tissues were 1.3 mm thick. Afterwards, sections were decalcified with 5% trichloro-acetic acid, dehydrated and embedded in paraplast.

The initial 1.3 mm semithin sections were cut on a Leitz microtome so that their final thickness was 8µm. They were then stained with hematoxylin-phloxin-safranine, trichrome Masson, periodic acid-Schiff and the modified Luxol dye technique, as described in detail in Table 1.

## Results

With the conventional techniques for the demonstration of collagen, little contrast could be obtained in the endochondral ossification process of the otic capsule: cartilage and bone differ only in shades of color. With our modified Luxol fast blue technique, a clear differentiation between the primitive cartilaginous spicules and its surrounding bone tissue could be obtained (Fig.1); the cartilaginous matrix only stains with cresyl violet while the osteogenic cells and bone matrix stain blue with the Luxol dye.

The features of the developing ossicular chain are also well illustrated with the Luxol dye technique: as in the otic capsule, the endochondral ossification of the ossicles is quite well differentiated. Ligaments, the synovial membrane and periosteum also stain blue. In contrast, the articular cartilage of the joints only stains with cresyl violet.

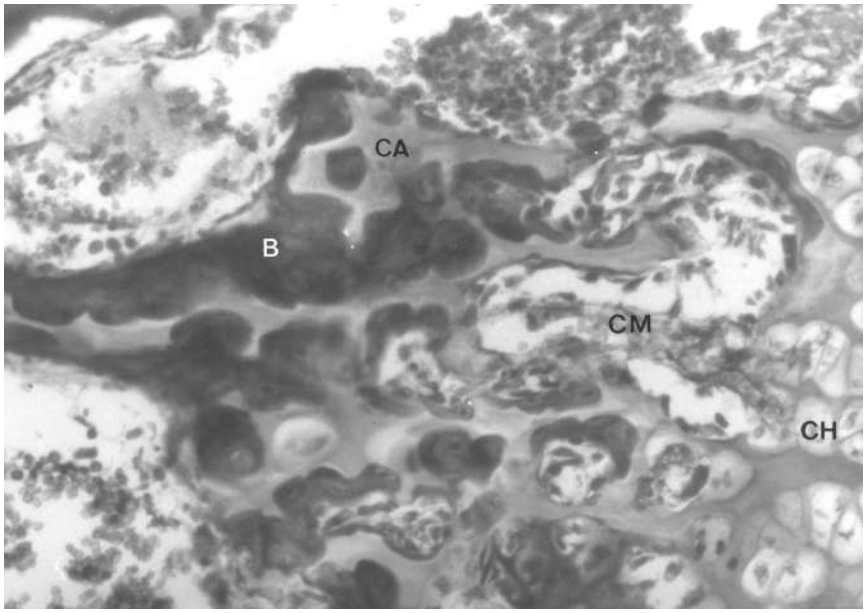


*Fig. 1: Visualization of the endochondral ossification process in the developing otic capsule at 18 weeks of gestational age. At this stage, the chondrocytes (CH) are hypertrophied. Cellular masses (CM), containing chondroclasts, blood vessels as well as osteogenic cells, invade the calcified cartilaginous matrix (CA)). The osteogenic cells differentiate into osteoblasts and intercellular substance of bone (B) is laid down on the remnants of the calcified cartilage. (Modified Luxol fast blue stain; 62.5 x)*

## Discussion

Although cartilage and bone both contain collagen, they differ widely in their staining properties. The exact staining mechanism of the Luxol dyes is not quite clear. Investigations on the molecular organization of the myelin sheath have revealed the existence of a glycoprotein and glycolipid coat in the extra-cellular space between adjacent cellular lipid layers (12).

Clasen et al. (2) reported diminished staining properties of myelin with the Klüver-Barrera method when tissue sections were first subjected to alkaline hydrolysis. However, such hydrolysis leads to disrupted proteins and bound lipids.

Salthouse (11) described a reduction in collagen staining after tanning. Tannic acid affects the properties of collagen as a polymer and also blocks keto-imide groups known to be important for this type of dye binding. Clasen et al. (2) and also Salthouse (11) have suggested that the staining of the myelin sheath and of collagen and elastin is due to the presence of hydrophobic sites (non-polar amino acids) in the fixed substrate. The same hypothesis can explain our results with the modified Luxol fast blue-cresyl violet method. Our findings show that this technique will not stain all types of collagen, but only those fibers with hydrophobic properties. Indeed, cartilage and bone contain different types of collagen: cartilage contains chiefly type II and bone type I collagen.

Type I collagen is more glycosylated then type II. The glycosylation of the collagen may greatly modify their physicochemical properties, including hydrophobicity. Type II collagen contains twice as much water as type I, due to quite large amounts of hydrophobic carbohydrates.

Elastin also stains properly with the modified Luxol dye technique and is a very hydrophobic protein, due to non-polar amino acid groups (8). As a consequence, elastic cartilage also stains with the Luxol dye in contrast to hyaline cartilage. The mucinous matrix of the mesenchymatous tissue which contains highly hydrophylic proteoglycans, is not al all stained by the Luxol dye.

## Staining solutions

Make a 1% solution of Luxol fast blue MBS by dissolving 1 g in 100 $cm^3$ 95% ethanol. Add 0.5 $cm^3$ of 10% acetic acid. Filter before using.
Make a 0.1% aqueous solution of cresyl violet.
Cresyl violet differentiator: add 90 $cm^3$ 95% ethanol to 10 $cm^3$ chloroform and use 3 drops acetic acid.

## Method for staining paraffin sections

Immerse fetal temporal bone sections in 95% ethanol for 2 min.
Rinse with 95% ethanol
Stain overnight in solution A at 37° C.
Immerse in 95% ethanol for 10 sec.
Wash in distilled water for 10 sec.
Begin to differentiate with 0.05% aqueous solution of lithium carbonate for 5 sec.
Continue differentiation in 70% ethanol for 3 sec.
Wash thoroughly in distilled water
Stain with solution B for 2 min.
Wash briefly in distilled water
Rinse in 70% ethanol
Differentiate with solution C by washing the slides in 95% ethanol
Dehydrate in the usual manner

*Table 1: Technique for the preparation of modified Luxol fast blue MBS and cresyl violet solutions.*

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## Chapter 2b

# The involvement of the cochlear nerve in neurinomas of the eighth cranial nerve

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## Samenvatting

In dit hoofdstuk wordt enerzijds de ontwikkeling van een geschikt histologisch kleuringprotocol besproken en anderzijds worden de microscopische bevindingen ter hoogte van de grenszone tussen tumor en nervus cochlearis beschreven. Onze bevindingen hebben geleid tot twee publicaties, die hier weergegeven worden.

Als kleuringstechnieken werden de klassieke trichroom-Masson kleuring, de Luxol Fast Blue techniek van Klüver en Barrera, de elastinekleuring volgens Verhoeff en een immunohistochemische techniek op basis van monoclonale muis-antilichamen tegen humane neurofilamenten gebruikt. Samengevat kwamen wij aldus tot de volgende conclusies:

De Trichroom-Masson kleuring is een waardevolle routinekleuring voor acousticusneurinomen en laat een mooie differentiatie tussen de myelineschede en het omringende perineurale bindweefsel toe.

De Luxol fast blue kleuring is geenszins een specifieke myelinekleuring: zowel myeline als collageen kleuren op vergelijkbare wijze. Deze kleuring is dan ook van weinig of geen nut wanneer men geconfronteerd wordt met een specimen dat beiden bevat, zoals acousticusneurinoma's.

De elastinekleuring volgens Verhoeff levert een duidelijk beeld op, waarin eventueel aanwezige zenuwen voldoende opvallen. Er ontstaat voldoende contrast tussen het tumorale stroma enerzijds, en het collageen bindweefsel, waaronder het perineurale bindweefsel, anderzijds. De myelineschede wordt echter niet duidelijk gekleurd.

Een specifieke immunohistochemische techniek is noodzakelijk wanneer men de zenuwvezels met absolute zekerheid wil definiëren of wanneer men het verloop van zenuwvezels in de tumormassa wil bestuderen. Met behulp van deze techniek konden wij tumorale ingroei in de Nervus Cochlearis aantonen, tenminste op die plaatsen waar ook macroscopisch zichtbare vergroeiingen bestonden tussen de tumor en de zenuw. Wij troffen typische schwannoom cellen aan temidden van zenuwvezels van de Nervus Cochlearis, terwijl er omgekeerd ook zenuwvezels werden gevonden omgeven door manifest schwannoom. Een duidelijk klievingsvlak is niet aanwezig.

Op histopathologische basis kan bijgevolg gesteld worden dat de N. Cochlearis ten minste gedeeltelijk betrokken is in het tumorale proces in die gevallen waar macroscopische adherenties waarneembaar zijn. Het microscopisch correlaat is de afwezigheid van enig klievingsvlak tussen tumor en zenuw

## Summary

In view of recent controversies concerning the preservation of hearing in acoustic neurinoma surgery, we examined the courses of the vestibular and cochlear nerve fibers in 12 intact acoustic neurinomas studied in our department. Due to its lack of specificity, the Luxol fast blue stain was found to be inadequate for our study of the nerve fibers. In contrast, Verhoeff's stain proved to be satisfactory when combined with a highly specific immunohistochemical technique. There were macroscopically visible adherences between the tumor and the cochlear nerve in 9 out of the 12 specimens. From those specimens, histological sections were obtained in which both the cochlear nerve and tumor could be clearly identified. In these specimens the cochlear nerve was involved in the tumoral process and there was no clear cleavage plane between the nerve and the tumor. However, all these patients suffered only from minimal losses of hearing as a result of their tumors.

## Introduction

It is well known clinically that the neurinoma of the acoustic nerve usually arises from the inferior branch of the vestibular nerve. The differentiation between cochlear and vestibular fibers, however, remains a matter of debate. To seek evidence as to the involvement of the cochlear nerve in the tumoral process, we initiated an investigation to determine the courses of both the cochlear and vestibular nerve fibers in acoustic neurinomas, particularly since there have been recent tendencies for surgeons to spare the cochlear nerve during removal of acoustic neurinomas. Indeed, from a histological point of view, the surgical concept of hearing preservation in cases of cochlear involvement is doubtful. The functional implications of such surgery and the fate of the facial nerve have been omitted from the present study and will be the subject of a separate report.

A number of authors seem to have different opinions about whether the cochlear and vestibular nerve fibers are myelinated or not. Kimura et al. (4) found that 92% of all the human spiral ganglion cells they had examined were of the unmyelinated or partly myelinated type, with more unmyelinated neurons (i.e. 99%) under the age of 40. Neely (10), on the other hand, reported that a vast majority of the cochlear fibers is myelinated. One can find analogous controversies concerning the vestibular nerve. For example, Perre et al (11) wrote that there are no myelin sheaths around the vestibular ganglion cells. Ylikoski (17) confirmed that the vestibular ganglion cells are ensheathed by a single layer of Schwann cell cytoplasm and that there is no real myelin sheath. In contrast, Ballantyne and Engström (1)

indicated that the majority of the vestibular ganglion cells are provided with a characteristic, multiple myelin sheath. In 1986, Schefter and Harner (13) published a histological study of the vestibulocochlear nerve and found that both the spiral ganglion of Corti and the vestibular ganglion of Scarpa are provided with a myelin sheath and that the myelin sheaths of the vestibular fibers appear more medially than those of the cochlear fibers.

The previous findings have thus shown that the histological picture on cross-section largely depends on the site where the section is removed from the eighth nerve. Schefter and Harner (13) suggested that the most reliable characteristic for discrimination of cochlear from vestibular fibers is the density of the nerve fibers on a cross-sectional view. The cochlear portion appears more compact and darker in its staining appearance than the vestibular portion, because the latter contains only about half the number of nerve fibers, though it is usually larger than the cochlear part. Thus, a double staining appearance arises. These observations by Schefter and Harner, however, were made on normal vestibulocochlear nerves. In neurinomas, on the other hand, the anatomy is quite often considerably disturbed by the growth of the tumor and the presence of numerous bands of collagen, which makes it all the more difficult to identify the cochlear and vestibular nerve fibers.

In 1953, Klüver and Barrera (5) introduced their Luxol fast blue MBS technique as a “specific” stain for myelin sheaths, neurons and glia nuclei. A few years later, Margolis and Pickett (6) published their new applications of the Luxol fast blue myelin stain. That this technique causes both collagen and elastin fibers to stain was first described by Salthouse (12) in 1965 and confirmed by Clasen et al. (2) in 1973. The latter authors used Luxol fast blue G in methanol. Recently, Declau et al. (3) pointed out that this property could be applied to differentiate cartilage from bone in human fetal temporal bones. Indeed, both tissues contain a considerable amount of collagen, but the same authors found that the staining properties of these tissues vary appreciably due to the different physicochemical properties of the collagen types involved. Nevertheless, this so-called specific myelin stain is still being used by several investigators.

Verhoeff presented his staining technique for elastic tissue in 1908 (15). His method makes it possible to differentiate elastin fibers from collagen fibers.

In this study, the techniques mentioned above as well as Masson's Trichrome stain and an immunohistochemical technique were applied to the neurinoma specimens studied.

## Materials and methods

Our material consisted of twelve acoustic neurinomas from a group of 50 specimens that were removed "en bloc". This group is part of a series of 172 acoustic neurinomas that were surgically removed by the senior author (JM) by way of the translabyrinthine technique (7). The specimens were preserved in a 4% formaldehyde solution. They were embedded in paraffin and subsequently cut on a Leitz microtome in sections of 6 microns each. The sections were then mounted on slides precoated with poly-L-lysine.

The Luxol fast blue technique used for staining our tissue sections is a modification of the techniques described by Klüver and Barrera (5) and by Margolis and Pickett (6), as presented by Declau et al. (3). A detailed description of our method is given in Tables 1 and 2. We believe this method to be valuable because of its simplicity and because it facilitates a quick histological evaluation of the specimen. Monoclonal mouse antibodies to human neurofilaments were also applied to separate specimens for peroxidase-antiperoxidase immunohistochemical staining.

## Results

At first, the Luxol fast blue technique as described by Klüver and Barrera (5) was used. Yet, in spite of our efforts, we were not able to obtain a satisfying preparation in which the myelin sheaths of the nerve fibers could be clearly defined. The cellular picture looked overdifferentiated, even when minimal differentiation was performed. Therefore, a decision was made to use the modified staining method described by Declau et al. (3), using a 1% solution of Luxol fast blue MBS. This resulted in a nearly uniform bluish staining of all components. The phenomenon described by Salthouse (12) and Clasen et al. (2) took place, namely that both collagen fibers and myelin stained with this method and even the proliferating Schwann cells remained slightly stained.

The application of Verhoeff's stain, however, eased our recognition of nerve fibers considerably. We found that the tumor mass was stained ochreous and that it was marbleized by red streaks of collagen. The axons appeared grayish or brownish and they were enveloped by a grayish myelin sheath (Fig. 1).

Thus, the detection of nerve fibers is much facilitated because of the contrasting staining of the nerve from that of the tumor mass.

Apart from the myelinated nerve fibers, our specimens contained little myelin. In contrast, collagen fibers were abundantly present. However, the origin of these fibrous long-spacing collagen fibers, or Luse-bodies, remains unclear.

In 9 out of 12 specimens, macroscopically visible adherences between the tumor and the cochlear nerve were found. From these 9 specimens, histological sections were obtained in which both the cochlear nerve and the tumor could be clearly identified. In all of these specimens, there was interpenetration of tumoral tissue in the cochlear nerve and there was no clear cleavage plane between the nerve and the tumor (Figs. 1-3). Correlation of these findings with pre-surgical audiograms showed that these patients had experienced only minimal losses of hearing.

The use of Masson's Trichrome stain results in a red staining of the myelin sheaths. Unfortunately, red blood cells stain red as well, which impedes microscopic interpretation of the tissues being studied. It does, however, allow differentiation of collagen from myelin (Fig. 2).

The immunohistochemical technique used confirmed the presence of the axons by staining them brown (Figs. 3,4).

## Discussion

Recently, myelinization of both the cochlear and vestibular nerve fibers in the more peripheral part of the vestibulocochlear nerve has been confirmed by electron microscopical observations in our department, and will be the subject of a forthcoming report. Our observations concerning tumor involvement of the cochlear nerve are consistent with those of Neely (10) and Ylikoski (16). As for the vestibular nerve, Nager (9) described the peripheral displacement of the vestibular nerve fibers as a thin ribbon that courses over the surface of the neurinoma. These observations are similar to our own. However, we also found vestibular fibers traversing the center of the tumor mass, even in the same specimen. Analogous observations have been published by Urich (14). The ultimate fate of these scattered vestibular fibers is extremely difficult to define. Therefore, we have questioned whether the presence of fibers from the nerve of origin in the center of the tumor versus peripheral displacement of the vestibular fibers should still be applied as a histological criterion in differentiating schwannomas (or neurinomas) from neurofibromas (as in Von Recklinghausen's disease), or could it be that the incidence of Von Recklinghausen's disease is much higher than is generally thought?

On the basis of our results, the following conclusions can be drawn. Histologically in our specimens, the cochlear nerve was at least partially involved in the tumoral process in those cases where adherences were visible. In view of these observations, it is our opinion that the justifiability of attempts to preserve hearing in acoustic neurinoma surgery should be reconsidered, keeping in mind the risk of tumor recurrence (8).

Our findings showed that the Luxol fast blue stain is not specific: both myelin and several collagen types stain equally. It is of little, if any, value when used to stain specimens that contain both collagen and myelin, as is the case with acoustic neurinomas. Hardly any contrasts and considerable background staining are to be expected. Further, Verhoeff's stain does differentiate collagen from myelin and it has the advantage of yielding a clear picture, rich with contrasts. As a consequence, a specific immunohistochemical technique is mandatory when axones are to be identified with absolute certainty.

Our findings indicate that the criteria on which the differentiation between neurofibromas and schwannomas is based may have to be reconsidered, taking into account that a number of solitary neurinomas may belong to the histological entity of neurofibromatosis.

Finally, our present study should be correlated with the functional implications of cochlear nerve involvement in eighth nerve tumors and also include a similar study concerning the involvement of the facial nerve.

It is our hope that our histological studies will assist clinicians in further improving the results of acoustic neurinoma surgery.

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### Staining solutions

Solution A. Make a 1% solution of Luxol fast blue MBS by dissolving 1 g in 100 $cm^3$ ethanol 95%. Add 0.5 $cm^3$ of 10% acetic acid. Filter before using.

Solution B. Make a 0.1% aqueous solution of cresyl violet.

Solution C. Cresyl violet differentiator: add 90 $cm^3$ 95% ethanol to 10 cc chloroform and add 3 drops of acetic acid.

### Method for paraffin sections

1. Deparaffinize.
2. Immerse sections in 95% ethanol for 2 min.
3. Rinse with 95% ethanol.
4. Stain overnight in solution A at 37$^o$C.
5. Immerse in 95% ethanol for 10 s.
6. Rinse in distilled water for 10 s.
7. Begin differentiation with a 0.05% aqueous solution of lithium carbonate for 5 s.
8. Continue differentiation in 70% ethanol for 3 s.
9. Wash thoroughly in distilled water.
10. Stain with solution B for 2 min.
11. Wash briefly in distilled water.
12. Rinse in 70% ethanol.
13. Differentiate with solution C for 2 s.
14. Remove solution C by washing the slides in 95% ethanol.
15. Dehydrate as usual.

*Table 1: staining solutions and method for the modified Luxol fast blue MBS technique*

### Staining solutions

Solution A. Verhoeff's iodine solution: dissolve 2 g iodine and 4 g potassium iodide in 100 cm3 of distilled water. Prepare fresh each time.

Solution B. Working solution: add 8 cm3 of a 10% solution of ferric chloride to 20 cm3 of a 5% alcoholic hematoxylin solution. Add 8 cm3 of solution A. Prepare fresh each time.

Solution C. Van Gieson's counterstain: add 10 cm3 of a 1% acidic fuchsin solution to 100 cm3 of a saturated aqueous solution of picric acid.

### Method for paraffin sections

1. Deparaffinize.
2. Bring sections to water.
3. Rinse in running tap water for 3 min.
4. Stain in Verhoeff's working solution (B) for 10-15 min.
5. Wash briefly in distilled water (10 dips).
6. Differentiate in a 2% aqueous ferric chloride solution, a few dips at a time, until the elastin fibers are clearly visible under the microscope. Rinse in water to remove excess ferric chloride before checking under microscope.
7. Wash in tap water.
8. Rinse in 95% ethanol to remove excess iodine.
9. Wash in tap water for 3 min.
10. Counterstain in Van Gieson's stain (C) for 3 min.
11. Dehydrate as usual.

*Table 2: staining solutions and method for Verhoeff's elastin stain*

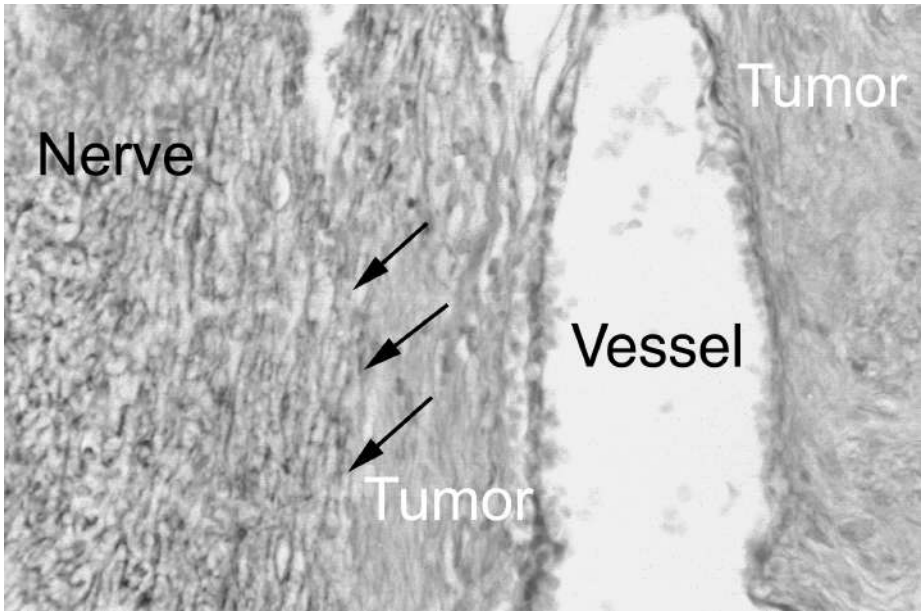


*Fig. 1. Photomicrograph showing the cochlear nerve, cut transversely (left, marked "nerve") and part of the tumor (right, marked "tumor"). Note the interpenetration of tumoral tissue in the cochlear nerve (arrows). Verhoeff's stain, x220*♦

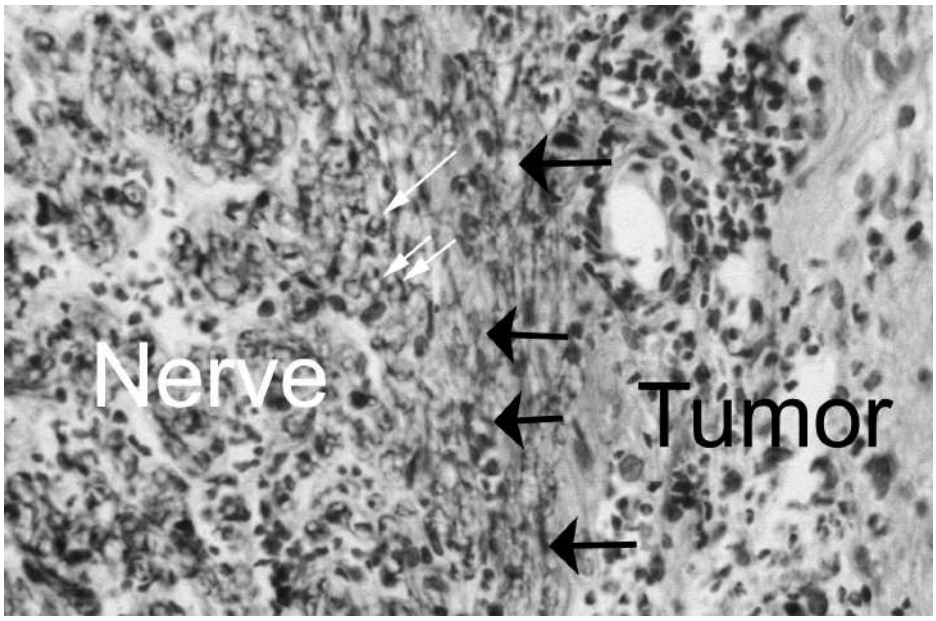


*Fig. 2: Photomicrograph revealing approximately the same site in the specimen as in Fig.1. The large arrows indicate the same as in Fig. 1, while the fine arrows mark the myelin sheaths, which are stained red. Masson's trichrome stain, x270*♦

♦ These pictures can be found in full color in the final section of this book

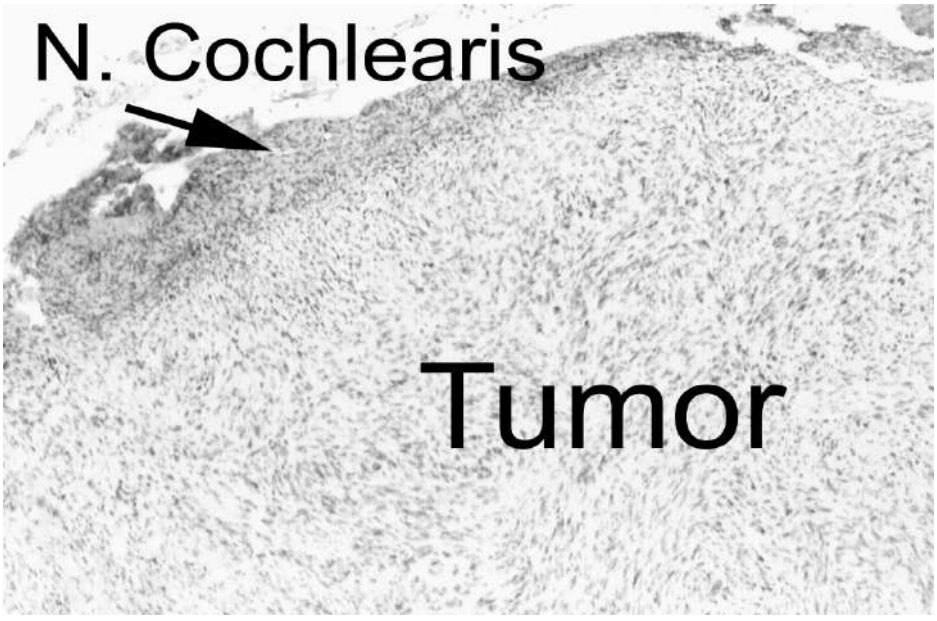


*Fig. 3. Photomicrograph revealing once again approximately the same site as depicted in Fig.1. The axones of the cochlear nerve (marked "nerve") are stained brownish, while the nuclei of the tumoral cells are slightly stained by the hematoxylin counter stain. Immunohistochemical PAP technique with mouse antibodies to human neurofilaments, x166*♦

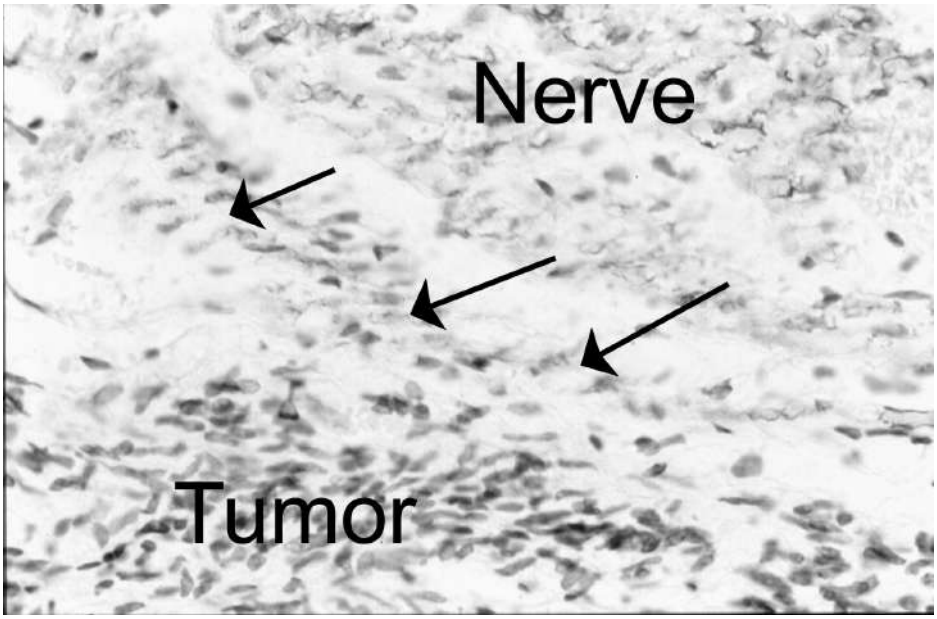


*Fig. 4. Enlargement of the cochlear nerve portion of Fig. 3, clearly showing the darker staining of the axons and the nerve-tumor interface. x 540*♦

♦ These pictures can be found in full color in the final section of this book

## Chapter 2c

# The solitary schwannoma of the eighth cranial nerve:

# An immuno-histochemical study of the cochlear nerve - tumor interface

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Arch Otolaryngol Head Neck Surg 1990;116(9):1023-1025

## Samenvatting

Met behulp van de in het vorige hoofdstuk beschreven kleuringtechnieken, worden tien intacte acousticusneurinomen, waarbij macroscopisch zichtbare vergroeiingen tussen tumor en Nervus Cochlearis bleken te bestaan, bestudeerd. In het bijzonder wordt de grenszone tussen tumor en zenuw in detail bestudeerd. Er blijkt een duidelijke ingroei van tumorale cellen in de zenuw te bestaan. Dit blijkt zowel uit de aanwezigheid van manifeste schwannoomcellen tussen de zenuwvezels, als uit het voorkomen van cochleaire zenuwvezels tot voorbij deze grenszone. In de bespreking wordt opnieuw het concept van gehoorsparende chirurgie in vraag gesteld, al wordt hier reeds gewag gemaakt van een op imaging gebaseerde “wait and see” houding.

## Abstract

Given recent controversy concerning hearing preservation surgery of the acoustic neuroma, an immunohistochemical study was undertaken in order to investigate the cochlear nerve - tumor interface. Ten intact medium-size acoustic neurinomas were studied by means of classical staining procedures, as well as an immunohistochemical technique using monoclonal mouse antibodies to human neurofilaments. Our observations indicate that the cochlear nerve is histologically involved in the tumoral process in those cases where macroscopically visible adherences between the cochlear nerve and the tumor are present. We were not able to discern a clear cleavage plane. In six out of the ten specimens did we objectivate tumoral invasion of the cochlear nerve. In view of these observations and international literature, several therapeutic attitudes are discussed. In conclusion, the principle of hearing preservation surgery is rejected in favor of total tumor removal in every case where surgery is indicated.

## Introduction

Facing the increasing number of papers dedicated to hearing conservation surgery of the acoustic neuroma, we initiated a histopathological study on the interface between the cochlear nerve and the tumor. Indeed, histopathological evidence of cochlear nerve involvement or invasion is, in our opinion, a very serious argument against hearing conservation surgery.

As mentioned by Marquet [1] in 1986, several reflections have to be considered when discussing acoustic neuroma surgery. Recent advances in medical imaging techniques have enabled us to visualize very small acoustic tumors with unprecedented accuracy. The neuro-otologist is therefore offered two options when confronted with a newly diagnosed acoustic neuroma: to operate or not to operate. This attitude is especially indicated with elderly people having a slowly growing tumor, in case of bilateral acoustic neurinomas (as observed in some particular cases and more commonly in neurofibromatosis type II) and in patients with a single hearing ear.

Should the surgeon decide not to perform surgery, a meticulous follow-up stratagem is to be carried out to monitor the growth of the tumor. Fortunately, Gadolinium-pentetic acid enhanced magnetic resonance imaging allows excellent visualization of small intracanalicular tumors. Surgery can thus be postponed and whatever may be left of useful hearing on the affected side be saved until surgery becomes indicated.

However, should the surgeon decide to operate at once, there are several points worth considering: the surgical inaccessibility of the fundus of the internal auditory meatus by way of the suboccipital approach; the biochemical alterations that occur in the perilymph fluid in the course of tumor development, as demonstrated by Silverstein and Schuknecht [2]; and the vascular lesions that may be caused either by tumor growth or during surgery. House and Hitselberger [3] consider these vascular lesions to be one of the major causes of post-operative deafness, in spite of the anatomical integrity of the cochlear nerve. Also worth considering are the histopathological aspects of acoustic neurinomas in relation to the cochlear nerve. Although benign, the schwannoma, which usually originates from the inferior branch of the vestibular nerve, actually tends to destroy adjacent nerves, first by crushing them and later by invading them. Invasion of the cochlear nerve by the acoustic neurinoma has been described by Neely and associates [4,5], Ylikoski et al. [6,7] and Forton et al. [8]. Even facial nerve involvement has been described by Luetje et al. [9]. Our observations have shown that recurrent acoustic neurinomas have a mean growth rate of 4.2 mm/y in every dimension [1], a fact that is frequently overlooked by several authors. These figures are

comparable with those of Wazen et al. [10], who have found a mean growth rate of 3.8 mm/y. In this study, we are particularly interested in the nerve-tumor interface, in order to establish any cochlear nerve involvement or invasion.

## Materials and methods

We have studied 10 intact medium-sized acoustic neurinomas that have been removed via the translabyrinthine approach. These tumors were removed by the senior authors (J.F.E.M. and F.E.O.) en bloc with the cochlear nerve, allowing not only the identification of all the nervous structures involved, but also the serial sectioning of the specimens. In all 10 cases, macroscopically visible adherences between the cochlear nerve and the tumor were present.

The specimens were fixed in a buffered 4% formaldehyde solution and embedded in paraffin. Subsequently, they were cut on a microtome (Leitz) in 6 µm-thick sections. These were mounted on slides precoated with poly-L-lysine.

Three different staining procedures were performed. First, Masson's trichrome stain was applied, because it is a quick and easy routine stain and because it stains myelin red, which is a useful characteristic. Second, Verhoeff's elastin stain was applied, because it yields a clear picture, rich with contrasts: the characteristic streaks of collagen, which are colored red are readily identifiable in the tumor mass, which is stained ochreous. The nerve fibers, however, are not particularly stained. Only perineural connective tissue is colored red by this method. Thus, any connective tissue septum that might exist between the cochlear nerve and the tumor should be visualised in this manner. Last, we devised an immunohistochemical protocol using monoclonal mouse antibodies to human neurofilament protein (2F11) (Dakopatts M762) as primary antibodies, rabbit immunoglobulins to mouse immunoglobulins (Dakopatts Z109) as secondary antibodies and peroxidase-antiperoxidase monoclonal mouse antibody complexes (Dakopatts P850). A 3,3-diaminobenzidine tetrahydrochloride solution was used as chromogenic agent. Thus, any present bundle of nerve fibers was stained brown. A discrete Harris' hematoxylin stain was used as counterstain. The details of our staining methods are discussed in a previous article [8].

## Results

Rather than searching for tumoral cells invading the cochlear nerve, we decided to look for cochlear nerve fibers past the nerve-tumor interface and to search for connective tissue structures separating the cochlear nerve from the tumor. In none of the 10 specimens were we able to discern any well-defined connective tissue structure separating the cochlear nerve from the tumor, let alone a true septum. There appeared to be only loose and ill-oriented streaks of collagen between them (Figs. 1 through 4).

The immunohistochemical technique, however, revealed the presence of cochlear nerve fibers beyond the nerve-tumor interface in six of the 10 specimens. The axons were surrounded by tumoral and normal Schwann cells (Figs. 5 and 6). Conversely, some specimens showed penetration of tumoral tissue between the cochlear nerve fibers (Fig. 6).

## Conclusions

Our findings indicate that tumor invasion of the cochlear nerve is to be expected in those cases where adherences between the cochlear nerve and the tumor are present. So-called sharp dissection is, in our opinion, not indicated in these cases, since tumoral tissue will inevitably be left behind; eventually this could lead to tumor recurrence.

It is our firm conviction that total tumor removal is of the utmost importance and should remain the primary goal of acoustic neurinoma surgery, even when this implies removal of the cochlear nerve, and in certain cases of the facial nerve as well. Doing exactly so, the senior author has observed only two cases of tumor recurrence in 150 cases from 1974 till 1988. In both cases tumoral tissue had to be left behind for vital reasons.

Our observations indicate that there is no correlation whatsoever between tumor size and the degree of hearing loss, nor between tumor size and tumoral invasion of the cochlear nerve. Total deafness has been observed even with small intracanalicular tumors.

As for the quality of the hearing one would attempt to save, it may be relevant to consider that 95% of all patients having an acoustic neuroma already have poor hearing on the affected side when their tumor is first diagnosed [11]. If good hearing is present on the contralateral side, is it really worth saving non-serviceable hearing and taking the risk of tumor recurrence? On the other hand, if a very small tumor should be found in a patient with excellent bilateral hearing, we are convinced that this particular patient would be far better off if surgery be postponed and meticulous follow-up be carried out.

In conclusion, given the advances that have been made in the field of medical imaging techniques, we feel that the indications for acoustic neuroma surgery may need some reconsidering. Indeed, we advocate that total tumor removal be carried out whenever the decision is taken to operate on an acoustic neuroma. If, for any reason whatsoever, the hearing must be preserved, an expectative attitude is recommended.

Hence, in our opinion, there is no place for hearing preservation surgery.

## Remark anno 2000

This last statement, made in 1990, should be withdrawn. As stated by the editor-in-chief of the Archives in his Editorial Footnote, "*The authors conclude that preservation of hearing cannot and should not be realistic goals in most patients, but they fall short of providing the final answer. We need to know the incidence of tumor recurrence in patients who have had tumor removal with preservation of hearing."* Nowadays, ten years later, we know that answer and we know that tumor recurrence is indeed rare. Therefore, although there actually is ingrowth of schwannoma tissue in the cochlear nerve, we must appreciate this fact in a different light, as was amply discussed in chapter 1.

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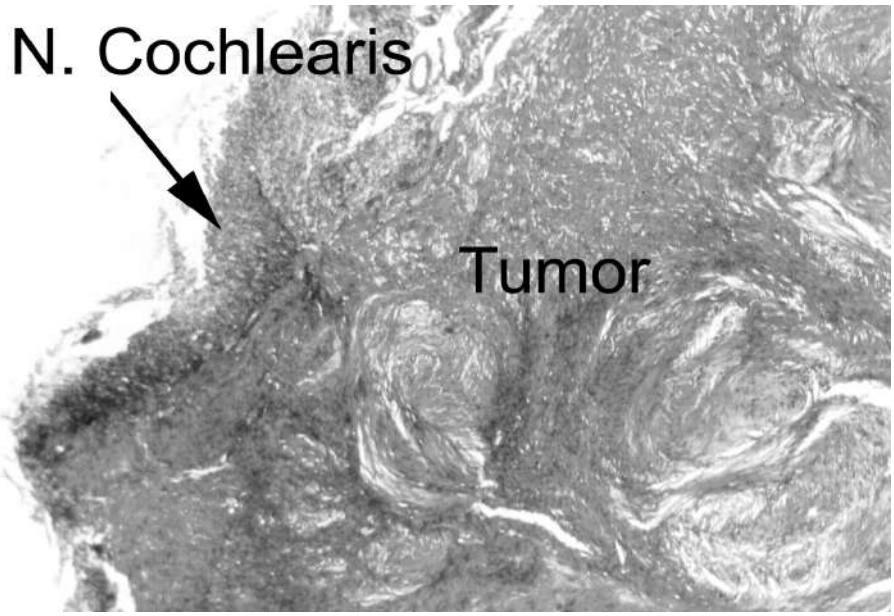



*Fig. 1: The cochlear nerve – tumor interface (Masson trichrome stain, x 166). Note the close relationship that exists between the cochlear nerve and the tumor. A cleavage plane cannot be identified*♦

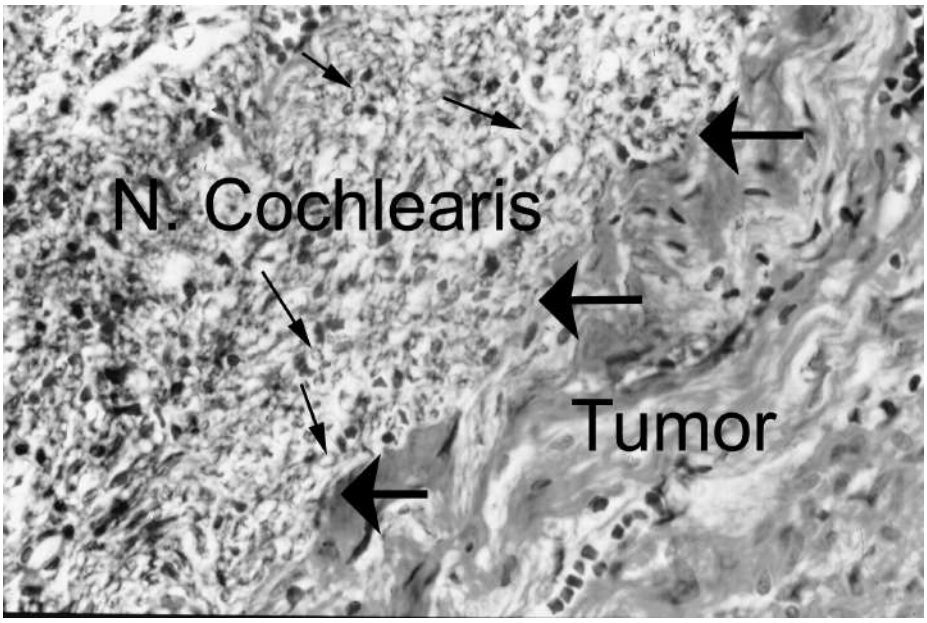



*Fig 2: Detail of the cochlear nerve – tumor interface (Masson trichrome stain, x 646). The tumor mass is stained green, which is partly due to the large amounts of collagen that are present. Note the red myelin sheaths (fine arrows)), surrounded by perineural connective tissue (green). Note, again, the absence of a clear cleavage plane between the nerve and the neuroma*♦

♦ These pictures can be found in full color in the final section of this book

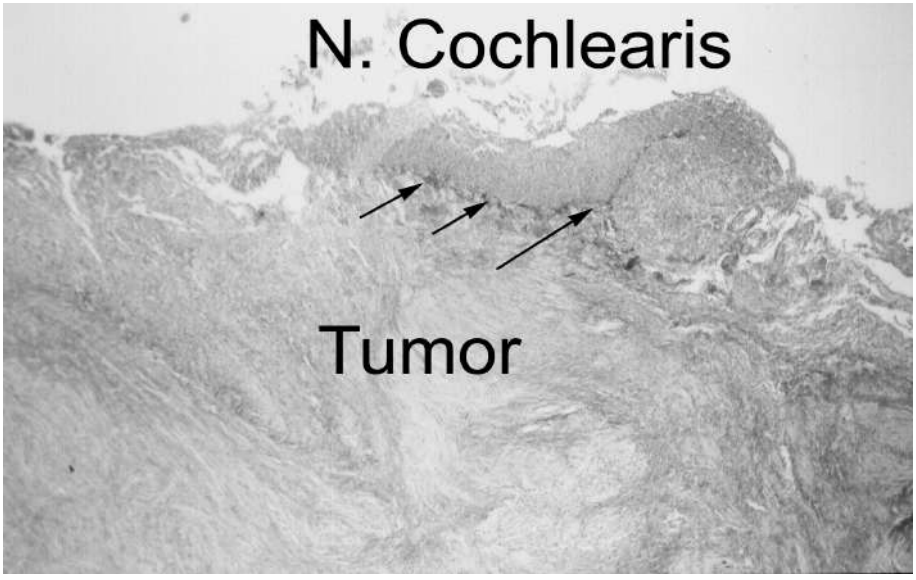



*Fig. 3: The cochlear nerve – tumor interface (Verhoeff's stain, x 66). The tumor mass is stained ochreous, clearly showing red streaks of collagen. The perineural connective tissue is stained red as well and the myelin sheaths show an unspecific gray*♦

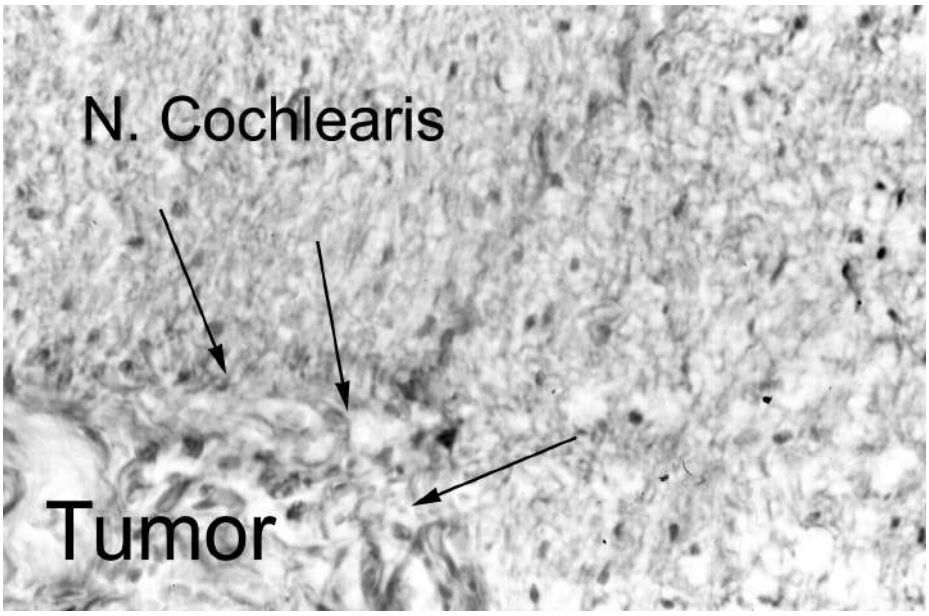



*Fig. 4: Detail of the cochlear nerve – tumor interface (Verhoeff's stain, x 646). Note again the absence of a cleavage plane. The nerve – tumor interface is composed of tumor matrix and poorly organize whirling bands of collagen as well as nerve fibers*♦

♦ These pictures can be found in full color in the final section of this book

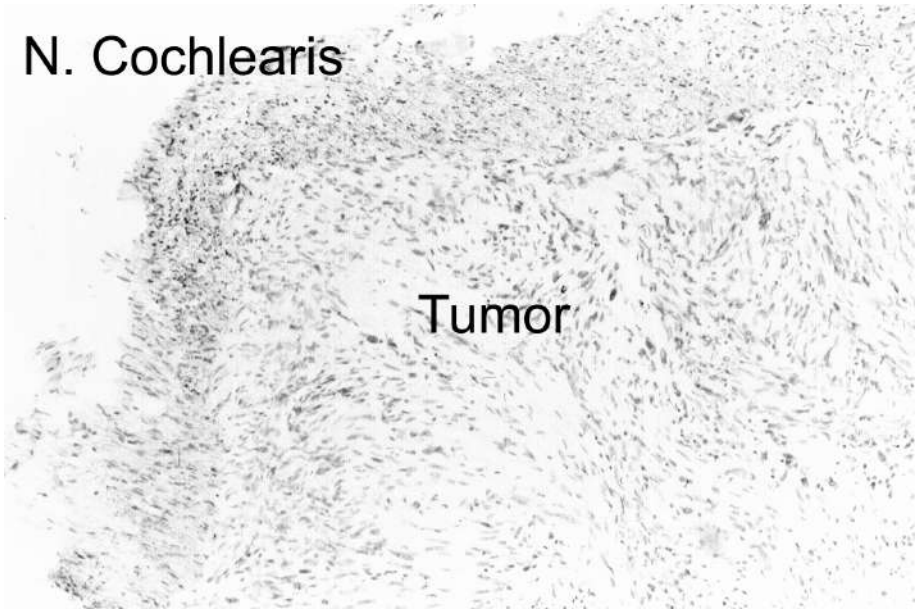



*Fig. 5: Immunohistochemically treated section (Dakopatts M762, Z109 and P850) featuring the cochlear nerve (x 166). The axons are stained brown, indicating the presence of neurofilaments. Nuclei are stained purplish blue*♦

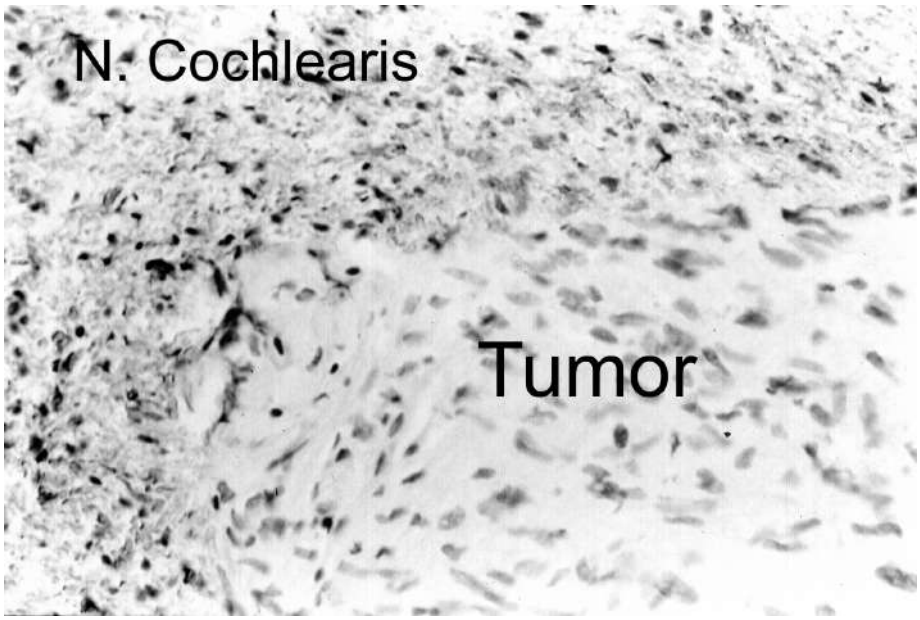



*Fig. 6: Immunohistochemically treated section (Dakopatts M762, Z109 and P850) featuring the cochlear nerve (x 270). Detail of Fig. 1 showing the nerve – tumor interface. Note the absence of a cleavage plane*♦

♦ These pictures can be found in full color in the final section of this book

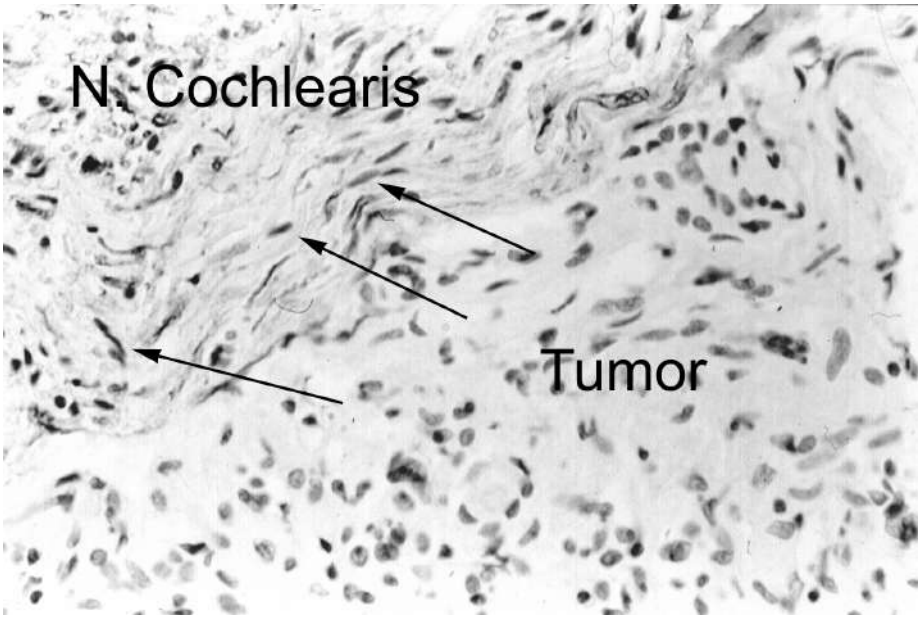
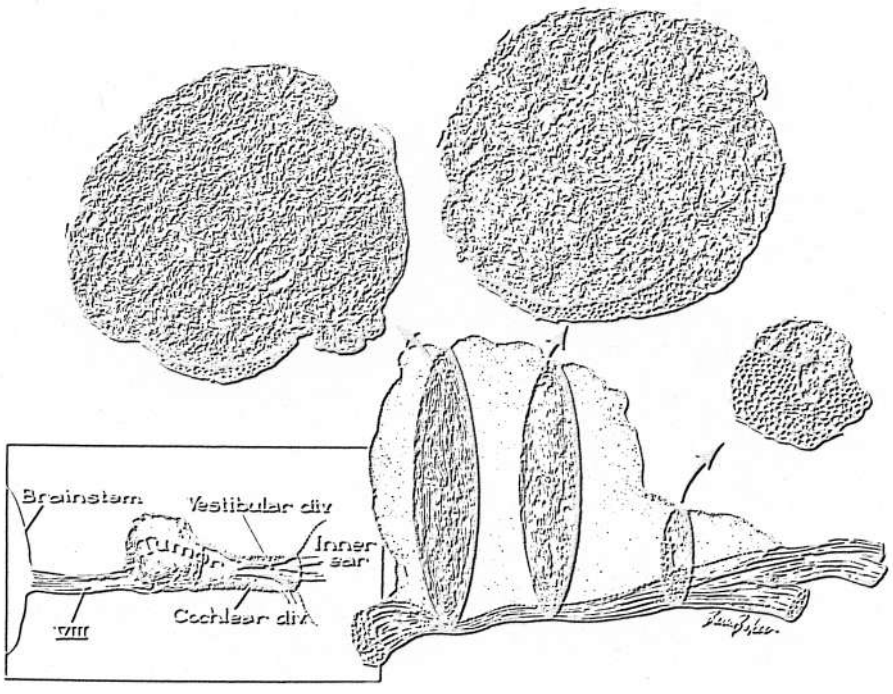



*Fig. 7: Detail of the nerve-tumor interface (peroxidase-antiperoxidase method with monoclonal mouse antibodies to human neurofilaments (Dakopatts M762, Z109 and P850) x 646). Note the presence of polymorphous, elongated nuclei of the proliferating cell population amongst the nerve fibers, inidicating ingrowth of the tumor in the cochlear nerve.*

# Chapter 3

# Clinical Features



# Chapter 3a

# Acoustic neuroma ingrowth in the cochlear nerve:

# An analysis of clinical data

**Glen E.J. Forton**

Submitted for publication

## Samenvatting

In de vorige hoofdstukken werd aangetoond hoe de Nervus Cochlearis histologisch aantoonbaar betrokken is bij het tumorale proces. De afwezigheid van enig duidelijk klievingsvlak werd bewezen. In dit hoofdstuk trachten we te achterhalen of deze histologisch onderzochte neurinomen op enigerlei wijze verschillen van de doorsnee populatie. Met andere woorden: is er in onze groep met bewezen invasie ook een groter aantal zware gehoorverliezen? Tot de onderzochte parameters behoren de tonale audiometrische gegevens, tumorafmetingen zoals bepaald door beeldvorming en B.E.R.A.-gegevens. Deze door de gekozen selectiecriteria beperkte reeks (N = 13) wordt vervolgens getoetst aan enkele grotere gepubliceerde reeksen.

## Introduction

Given the fact that microscopical evidence as to the involvement of the cochlear nerve has been rendered by several authors including our own research (1, 2), we thought it interesting to assess whether these tumors differ in any way from the mean population of small (1 – 25 mm) to medium-sized (26 – 40 mm) acoustic neuromas. Is there a higher-than-average number of cases with severe hearing loss or deafness in this series? Therefore, we executed a concise statistical analysis on the retrieved data of the microscopically studied cases with proven invasion (such as tumor size, audiometric findings, onset of symptoms) and compared it to some of the large published series.

## Materials and methods

Over the years, we have microscopically studied a fair amount of intact acoustic neuromas in order to evaluate the ingrowth of the tumor in the cochlear nerve. The early cases were operated by the late head of department, Jean Marquet, while the second series was composed of specimens removed by the late Jean Marquet and Erwin Offeciers, both from the Sint-Augistinus Medical Institute of Antwerp (Belgium). The histological findings from both series were published separately (1,2) and are discussed in Chapter 2. A third, more recent, series was provided by Cor W.R.J. Cremers at the University Hospital Nijmegen (The Netherlands).

| Source | Total number of "en bloc" resected specimens | Cochlear and Vestibular Nerves identified on serial sections | Proven invasion of the cochlear nerve | Full clinical data available |
|---|---|---|---|---|
| Marquet | 50 | 12/50 | 9/12 | 6/50 |
| Marquet & Offeciers | 25 | 10/25 | 10/10 | 17/25 |
| Cremers | 10 | 5/10 | 2/5 | 10/10 |
| Totals | 90 | 27/85 | 21/27 | 33/85 |

*Table 1: summary of our clinical and histological data and their respective sources*

Although invasion of the cochlear nerve by the acoustic neuroma has been proven over the years in 21 out of 27 cases where the cochlear and the vestibular could be clearly identified, full clinical data were available in only 33 out of the 85 examined cases. As is often the case in retrospective studies, not all histological slides cases had their clinical data to go with them and vice versa. In order to perform this statistical analysis correctly, we have included only those cases that had histologically proven invasion of the cochlear nerve and full clinical data to go with them. Thus, we have retained only 13 cases out of the original 85 cases studied.

We deliberately have not used the remaining data as a control group without tumoral ingrowth, because in this group we did either not always have representative histological slides, or we did have slides but we were not able to identify the cochlear nerve. In the latter case, invasion might be present but we could not confirm nor deny it. Therefore we have decided not to use these data and keep the aforementioned remaining group of 13 cases.

All tumors have been removed via the (extended) translabyrinthine approach. The staining methods and interpretation of what we determine to be Schwann cell ingrowth or "involvement of the cochlear nerve" have been amply described in previous papers (1, 2, 3). In all of these cases, microscopical evidence of cochlear nerve invasion was present and documented.

We have looked at pure tone audiometry, brainstem evoked response audiometry and the onset of symptoms. Furthermore, we have measured, whenever possible, the two largest diameters of the tumor on contrast enhanced CT and/or MRI images. Most scans were made before three-dimensional or volumetric measurements were routinely possible. In order to get an idea of tumor volume, we had to use a gross simplification. We have used two mathematical models. In a first model, we assumed that the tumor has an ellipsoid shape, thus both diameters a en b (Fig. 1) allowed us to compute the tumor volume using the formula:

$$Volume1 = \left[ \frac{4}{3} \cdot \Pi \cdot \left( \frac{a}{2} \right)^2 \cdot \left( \frac{b}{2} \right) \right]$$

In a second model, we have assumed that the most important volume-effect is caused by the extracanalicular grossly spherical component of the tumor. Volume 2 can therefore be defined as $\frac{4}{3} \cdot \Pi \cdot \left(\frac{a}{2}\right)^3$

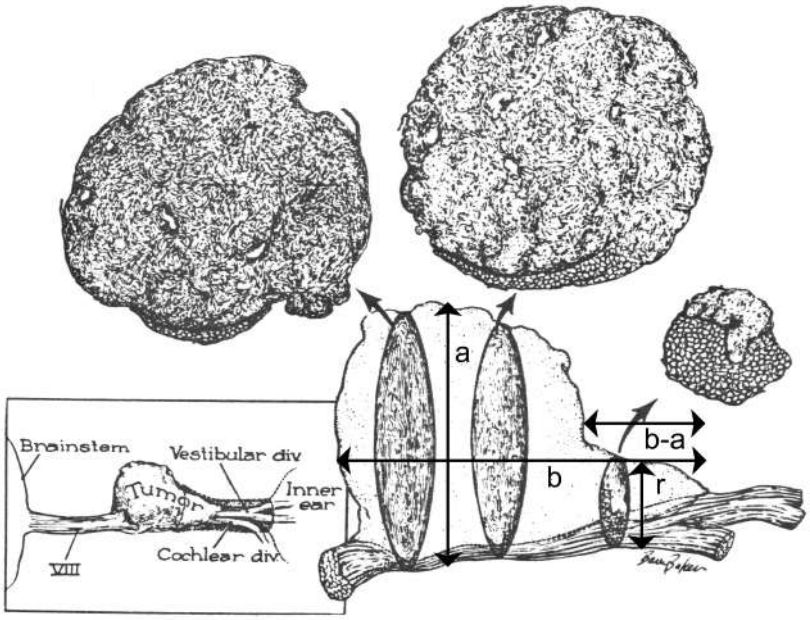



*Fig 1: diameters a, b and r.*

The latest developments in the field of MRI and CT scan imaging now allow on the spot volumetric measurements, which undoubtedly yield more accurate assessment of the size and volume of “police whistle” shaped tumors, such as the acoustic neuroma.

In order to evaluate low frequency, mid-frequency and high frequency hearing loss, we have defined three indices analogous to Fletcher’s index:

$$index1 = \frac{[250Hz] + [500Hz] + [1000Hz]}{3}$$

$$index2 = \frac{[500Hz] + [1000Hz] + [2000Hz]}{3}$$

$$index3 = \frac{[1000Hz] + [2000Hz] + [4000Hz]}{3}$$

Lastly, we measured the interlatency between peaks I and V of the brainstem evoked response audiometry recordings. The onset of symptoms was noted in months and the first symptom that arose was also recorded. Unfortunately, some data were lacking (Table 1).

Nevertheless, we have endeavored to compare the results of our analysis with some of the large published series. We have use a one-sided Spearman correlation coefficient to evaluate correlations.

| Case | Origin | Onset | Sympt. | Diam.A | Diam. B | Vol. 1 | Vol. 2 |
|---|---|---|---|---|---|---|---|
| | | (months) | | (mm) | (mm) | ($mm^3$) | ($mm^3$) |
| 1 | Vest.Inf | 480 | 1 | 6 | 10 | 188 | 113 |
| 2 | Vest.Inf. | 48 | 1 | 10 | 10 | 524 | 524 |
| 3 | Vest.Inf | 12 | 1 | 4 | 8 | 67 | 34 |
| 4 | Vest.Inf | 72 | 1 | 12 | 13 | 980 | 905 |
| 5 | Vest.Inf | 24 | 1 | 22 | 23 | 5.829 | 5.575 |
| 6 | Vest.Inf. | 108 | 1 | 15 | 15 | 1.767 | 1.767 |
| 7 | Vest.Sup. | | 2 | 6 | 13 | 245 | 113 |
| 8 | Vest.Inf | | 1 | 10 | 11 | 576 | 524 |
| 9 | Vest.Inf | | 1 | 10 | 11 | 576 | 524 |
| 10 | Vest.Inf | 8 | 1 | 6 | 10 | 188 | 113 |
| 11 | Vest.Inf | | 3 | 20 | 30 | 6.283 | 4.189 |
| 12 | Vest.Inf | | 1 | 5 | 17 | 223 | 65 |
| 13 | Vest.Inf. | 96 | 1 | 12 | 20 | 1.508 | 905 |

*Table I: subject data concerning tumor origin, onset of symptoms and tumor dimensions*

| Case | 250 Hz | 500 Hz | 1000 Hz | 2000 Hz | 4000 Hz | 8000 Hz | Index 1 | Index 2 | Index 3 | I-V lat. |
|---|---|---|---|---|---|---|---|---|---|---|
| | (dB HTL) | (dB HTL) | (dB HTL) | (dB HTL) | (dB HTL) | (dB HTL) | (dB HTL) | (dB HTL) | (dB HTL) | (msec) |
| 1 | 65 | 75 | 90 | 120 | >120 | >120 | 77 | 95 | N/A | |
| 2 | 15 | 20 | 65 | 85 | 90 | 90 | 33 | 57 | 80 | |
| 3 | 30 | 35 | 50 | 75 | 65 | 75 | 38 | 53 | 63 | 0,68 |
| 4 | 20 | 20 | 30 | 65 | 70 | 80 | 23 | 38 | 55 | 1,63 |
| 5 | 5 | 15 | 35 | 70 | 50 | 55 | 18 | 40 | 52 | |
| 6 | 10 | 10 | 65 | 80 | 120 | 120 | 28 | 52 | 88 | 1,08 |
| 7 | 15 | 15 | 30 | 50 | 30 | 70 | 20 | 32 | 37 | 1,56 |
| 8 | 30 | 40 | 45 | 60 | 60 | 70 | 38 | 48 | 55 | 0,55 |
| 9 | 50 | 50 | 55 | 65 | 65 | 70 | 52 | 57 | 62 | 0,60 |
| 10 | 30 | 30 | 45 | 70 | 80 | 90 | 35 | 48 | 65 | |
| 11 | 30 | 35 | 50 | 55 | 55 | 75 | 38 | 47 | 53 | 4,10 |
| 12 | >120 | >120 | >120 | >120 | >120 | >120 | N/A | N/A | N/A | |
| 13 | 65 | 65 | 110 | >120 | >120 | >120 | 80 | N/A | N/A | |

*Table II: the three indices of hearing loss (dB HTL)*

## Results

The male/female ratio was 6/7 or 0.86. The left/right ratio was 2/11 or 0.15. The youngest patient was 41 years old, the oldest patient 73 years old. The mean age at the time of operation was 59.2 years, the median was 62 years. The standard deviation was 9.3 years. In 9 out of the 13 cases macroscopically visible adherences between the facial nerve and the tumor were mentioned in the surgeon's report.

For 8 out of the 13 subjects, we could retrieve from the charts the time of onset of the first symptom. The duration of symptoms ranged from 8 months to as long as 480 months. The average is 106 months, the median is 60 months. The standard deviation is, of course, high: 156 months. It is conceivable that the high value of 480 months (case 1) distorts these calculations. If we disregard this case, the duration of symptoms would range from 8 months to 108 months. The average would be 53 months and the median 48 months. The standard deviation would drop to 40.4, which is much more acceptable.

In nearly all cases (10 out of 13 or 76.9%) the first symptom was hearing loss, in 1 case it was tinnitus (7.7%) and in one case it was vertigo (7.7%).

The audiometric data were analyzed using the three aforementioned indices 1, 2 and 3. Index 2 is known as the Fletcher-index. Whenever a threshold was exceeding 120 dB, then the corresponding index was not calculated and "N/A" was noted in the table. Subject 12 was, accordingly, completely deaf.

| N=13 | Median | Average | St.dev. | St.error |
|---|---|---|---|---|
| Index 1 | 37 | 40 | 20 | 6 |
| Index 2 | 48 | 52 | 16 | 5 |
| Index 3 | 58 | 61 | 15 | 4 |

*Table III: average, median and standard deviation and standard of the three indices (dB HTL)*

The Fletcher-index mean value in this series is 52 dB HTL. There seems to be a tendency indicating a somewhat more pronounced hearing loss on the high frequencies and somewhat less on the low frequencies. The high standard deviation indicates the heterogeneity of the population.

| N=13 | Median | Average | St.dev. | St. error |
|---|---|---|---|---|
| Diameter A (mm) | 10,0 | 10,6 | 5,6 | 1,6 |
| Diameter B (mm) | 13,0 | 14,7 | 6,3 | 1,8 |
| Volume 1 ($mm^3$) | 580 | 1500 | 2100 | 600 |
| Volume 2 ($mm^3$) | 520 | 1200 | 1700 | 500 |

*Table IV: average, median and standard deviation values of the two diameters and volume*

The average tumor diameter A is 10,6 mm and the average tumor diameter B is 14,7 mm. The mean tumor volume 1 in our series is therefore calculated as 1500 mm³, while mean tumor volume 2 is 1200 mm³. We found no correlation between patient age and tumor size. The correlation was –0,40. Nor did we find a statistically significant correlation between the onset of symptoms and indices 1, 2 and 3, as shown in table V.

| | Index 1 | Index 2 | Index 3 |
|---|---|---|---|
| Onset of symptoms | 0,21 (p=0,3) | 0,32 (p=0,24) | 0,31 (p=0,27) |

*Table V: correlation between the onset of symptoms and indices 1, 2 and 3*

We have also tried to find a statistically significant correlation between tumor volume and hearing loss (Table VI). We were not able to find any in this limited series. The age distribution of these patients is comparable to the data mentioned in the literature.

| Correl | Diameter A | Diameter B | Volume 1 | Volume 2 |
|---|---|---|---|---|
| Index 1 | -0,26 | -0,24 | -0,19 | -0,26 |
| Index 2 | -0,34 | -0,63 | -0,41 | -0,34 |
| Index 3 | -0,21 | -0,52 | -0,28 | -0,21 |

*Table VI: correlation coefficient between hearing loss and tumor size and volume.*

Our calculations clearly indicate that there seems to be no correlation whatsoever between tumor size and hearing loss, be it low frequency, mid frequency or high frequency. We found a borderline significant negative correlation (-0,63) between diameter B and index 2 (p=0.02).

As fig. 2 illustrates, small tumors can indeed cause important hearing loss and vice versa.

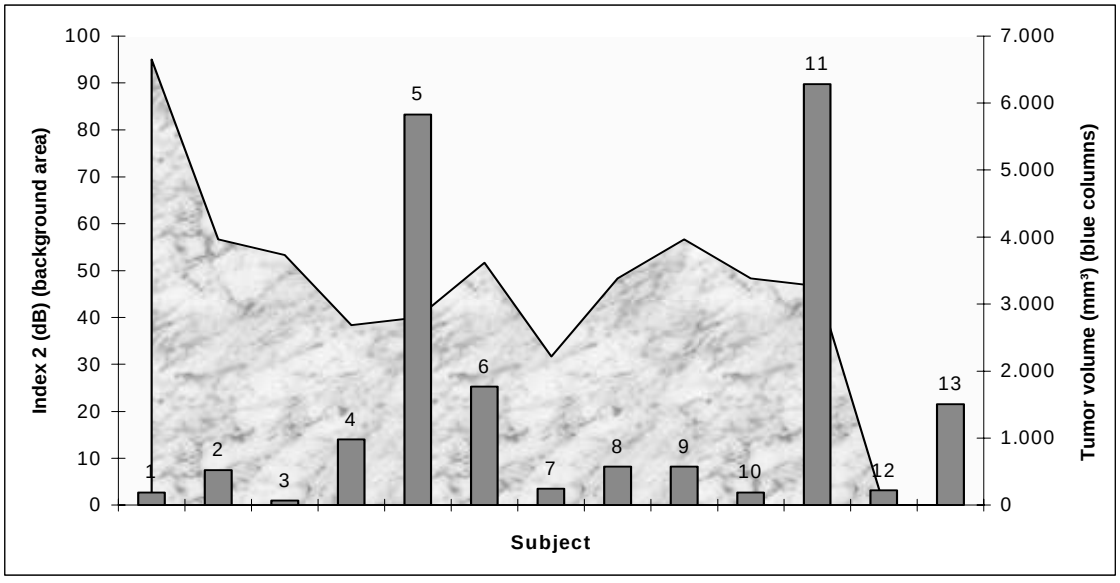



*Fig 2: Tumor size versus hearing loss (subjects 12 and 13 have incalculable index 2).*

Another way of presenting these data is to split them into small (1-25 mm), medium (26-40 mm) and large (> 40 mm) neurinomas and plot the corresponding hearing loss (Table VII).

| Index 2 | 1 - 25 mm (n=10) | 26-40 mm (n=3) | > 40 mm (n=0) |
|---|---|---|---|
| 0 - 20 dB | 0 (0%) | 0 (0%) | 0 |
| 21 - 40 dB | 3 (30%) | 0 (0%) | 0 |
| 41 - 80 dB | 6 (60%) | 1 (33%) | 0 |
| > 80 dB | 1 (10%) | 2 (67%) | 0 |

*Table VII: Tumor size versus Fletcher-index (index 2)*

Correlation was also sought between auditory brainstem response audiometry results and tumor dimensions. We used the wave I – wave V interlatency, measured in milliseconds (Table VIII).

| Subject | I-V Lat.(msec) | Diam.A (mm) | Diam.B (mm) | Volume 1 ($mm^3$) | Volume 2 ($mm^3$) |
|---|---|---|---|---|---|
| 4 | 0,68 | 8 | 4 | 67 | 34 |
| 5 | 1,63 | 13 | 12 | 980 | 905 |
| 7 | 1,08 | 15 | 15 | 1.767 | 1767 |
| 8 | 1,56 | 13 | 6 | 113 | 113 |
| 9 | 0,55 | 11 | 10 | 524 | 524 |
| 10 | 0,6 | 11 | 10 | 524 | 524 |
| 12 | 4,1 | 30 | 20 | 6.283 | 4189 |

*Table VIII: I-V interlatency data versus tumor size and volume*

We found a significant correlation of 0.76 (p=0.023) between tumor diameter B and the I-V interlatency. The correlation between the I-V interlatency and diameter A and the tumor volume was not as significant (table IX).

| Corr. | I-V lat. (msec) | p |
|---|---|---|
| Diam. A | 0,52 | 0,11 |
| Diam. B | 0,76 | 0,023 |
| Volume 1 | 0,52 | 0,11 |
| Volume 2 | 0,52 | 0,11 |

*Table IX: correlation between I-V latency and tumor diameter A en B and tumor volume*

## Discussion

We have compared our data to the Nijmegen series (4), the Copenhagen series (5) and a recent report from the House Ear Insitute (6) (Table X). Unfortunately, the authors do not mention mean values or standard deviation of their data. Therefore, we could not test whether there is a statistically significant difference between our data and theirs.

| | Nijmegen | House Ear Institute* | Copenhagen | Our series |
|---|---|---|---|---|
| **Nr of patients** | 164 | 333 | 300 | 13 |
| Patient age | 17 – 79 (49) | 10 – 72 (46) | 14-78 (51) | 41-73 (60) |
| M/F | 76/88 (0.86) | 191/142 (1.34) | 129/171 (0.75) | 6/7 (0.86) |
| First symptom: Hearing loss | 93% | N/A | 75% | 76.9 % |
| Tumor size | 8 – 72 mm<br>(26.5 mm) | Class 1 – 20 mm:<br>275 (92 %)<br>Class > 20 mm: 23 (8 %)<br>(*data available in 298 of the 333 cases)* | Class 1–25 mm: 97 (32%)<br>Class 26–40 mm: 85 (28%)<br>Class > 40 mm: 118 (39%) | Class 1-25 mm: 12 (92%)<br>Class 25-40 mm: 1 (8%) |
| Hearing<br>0-20 dB<br>21-40 dB<br>41-80 dB<br>> 80 dB | <26 mm 26-40mm >40mm<br>6 (7%) 2 (3%) 3 (18%)<br>25 (29%) 13 (22%) 4 (24%)<br>46 (53%) 30 (50%) 7 (40%)<br>10 (11%) 9 (15%) 3 (18%) | Class A*: 199 (60%)<br>Class B*: 101 (30%)<br>Class C*: 14 (4 %)<br>Class D*: 19 (6%) | <26 mm 26-40mm >40mm<br>5 % 3 % 1 %<br>13 % 21 % 14 %<br>59 % 49 % 34 %<br>23 % 27 % 51 % | <26mm 26-40mm >40mm<br>0 0 0<br>3 (30%) 0 0<br>6 (60%) 1 (33 %) 0<br>1 (10%) 2 (67 %) 0 |

*Table X: comparison between the Nijmegen, House Ear Institute and the Copenhagen series (* hearing assessment according to the American Association of Otolaryngology, Head and Neck Surgery: Class A: PTA ≤ 30dB and SDS ≥ 70%; Class B: PTA >30 dB, ≤50dB and SDS ≥50%; Class C: PTA >50dB and SDS ≥50%; Class D: any level and SDS <50%)*

Although it would be quite natural and logical to expect that large tumors would cause more functional damage to the adjacent nerves and would be more prone to crush, stretch or invade these nervous structures, we were not able to demonstrate such behaviour. We found no correlation whatsoever between tumor size or volume and hearing loss. This is in agreement with Thierney et al. (7), who found no statistically significant difference between the incidence of dead ears between a group of small tumors and a group of large tumors. Neither did they find a correlation between tumor size and frequency selectivity of the hearing loss. This supports the consensus that a simple pressure effect on the cochlear nerve is not the only cause of the hearing loss. As discussed in chapter 1, a number of other mechanisms may contribute to the progressive hearing loss that invitably occurs.

We did demonstrate, however, a significant correlation between tumor size (diameter B) and ABR measurement of the I – V interlatency. As stated by van Leeuwen (8) , acoustic neuromas can indeed arise at any age, but the mean age seems to lie between 40 and 60 years of age (54 years in our series). The rate of growth seems to vary greatly, as reported by Wazen et al. (9). In our series, we were not confronted with this tendency of larger tumors in older patients. This would be the case if the growth rate were constant. Apparantly, it is not. In their volumetric radiological study, Niemczyk et al. (10) were able to demonstrate that in 17 out of their 27 cases (63%) significant growth could be demonstrated; As the authors themselves point out, the mean observation time was only 6.3 months. If the observation time were longer, a higher growth rate would probably be found, as is the case in the series presented by Thomsen et al (11) and Charabi et al. (12). Notwithstanding these

observations, correlations with either age or onset of symptoms were not reported by these authors.

The majority of our patients presented with hearing loss, although two presented themselves with tinnitus or vertigo. We were not, however, able to confirm van Leeuwen's observation that impaired hearing as the main symptom decreases as tumor size increases (8). Neither could we confirm a correlation between tumor size and time of onset of symptoms. This is in contrast to Thomsen and Tos' Copenhagen study (13). We could not demonstrate a relation between tumor size and hearing loss, we nor did we find a relation between hearing loss and onset of symptoms. Stipkovits (14) did find significant correlations between duration of symptoms and pure tone thresholds. The average tumor size, however, was significantly larger than in our series. Stipkovits did not find significant correlations between tumor size and pure tone thresholds either (14).

Although our series is small (N = 13) and composed of selected cases, there is no clear difference between our series and the quoted Nijmegen and Copenhagen series, as far as the small (1-25 mm) and medium size (16 – 40 mm) acoustic tumors are concerned. We do see a small difference with the House Ear Institute series, which could be explained by their selection criteria. As they are discussing prognostic factors for hearing preservation surgery by way of the middle fossa approach, their series is mainly composed of small tumors with serviceable hearing.

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## Chapter 3b

# Acoustic Schwannoma: MR Findings in 84 Tumors

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## Samenvatting

Beeldvorming door middel van magnetische resonantie (M.R.I.) is hét diagnostisch instrument bij uitstek om een acousticus neurinoma aan te tonen en dit wegens de hoge sensitiviteit van dit onderzoek, in het bijzonder na injectie van paramagnetische contraststof. Deze tekst behandelt de M.R.I. eigenschappen van het acousticus neurinoma, zoals vastgesteld in een reeks van 84 tumoren. Bijzondere aandacht wordt geschonken aan de differentieel diagnostische kenmerken met andere brughoektumoren.

## Summary

MR imaging is the study of choice for the examination of patients with suspected acoustic schwannoma, because of its high sensitivity, especially after the use of contrast material. This essay illustrates the common MR features of acoustic schwannomas as seen in a study of 84 tumors. We pay special attention to the role of MR imaging in the distinction between acoustic schwannoma and meningioma.

## Materials and Methods

The study group comprised 81 patients with 84 acoustic tumors; three patients had bilateral tumors. The 36 male and 45 female patients were 10-83 years old (average age, 54 years). They were studied with a 0.5-T superconductive MR unit (Magnetom, Siemens, Erlangen, Germany). MR images were obtained with spin-echo short-TR (T1-weighted) and long-TR (proton density- and T2-weighted) sequences, and 5-mm-thick, contiguous slices were used. Ninety of the 105 reviewed examinations were performed before and after IV administration of paramagnetic contrast material, either gadopentetate dimeglumine (Magnevist, Schering AG, Berlin, Germany) or gadolinium tetra-azacyclododecane tetraacetic acid (Gd-DOTA, Laboratoire Guerbet, Aulnay-sous-Bois, France). Fifty patients underwent surgery with anatomopathologic diagnosis of 52 acoustic schwannomas. Thirteen patients were followed up with repeated MR examinations, two patients underwent stereotaxic radiotherapy, nine older patients did not have surgery for medical reasons, and no clinical follow-up is available for seven patients.

## Results

Acoustic schwannomas were small (<15 mm) in 29 patients (36%), intermediate-sized (15-30 mm) in 36 patients (44%), and large (>30 mm) in 12 patients (15%). Tumor size varied from 2 x 2 mm to 50 x 50 mm in diameter.

On the unenhanced MR images, 35% of the acoustic schwannomas had a signal intensity equal to that of adjacent brain tissue (pons), 63% of them were (slightly) hypointense, and 2% (two tumors) were undetectable (Figs. 1 and 2).

After contrast administration, all tumors showed intense enhancement, except for one small intracanalicular tumor, which did not enhance (Fig. 3).

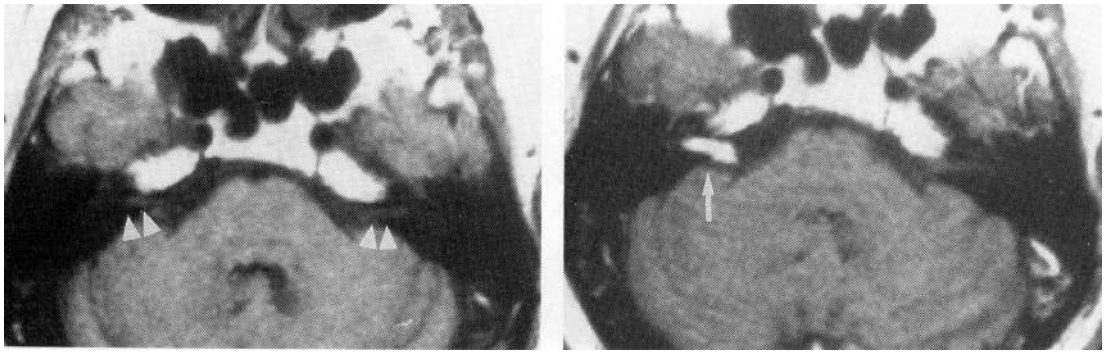
The enhancement pattern was homogeneous in 67% (Fig. 4), (slightly) inhomogeneous in 10% (Fig. 5), and heterogeneous with areas of cystic degeneration in 22% (Fig. 6).

Tumor shape was mostly round (29%) or oval (36%) and was polylobular in 14%. Five percent of all masses had irregular margins. The intracanalicular tumors were usually fusiform. Of the 84 lesions, 14 (17%) were purely intracanalicular, eight (10%) were purely extracanalicular, and 62 (74%) occupied both the internal auditory canal and the cerebellopontine angle-cistern (74%).

On 13 (37%) of the 35 T2-weighted images, mild to moderate peritumoral edema was visible (Fig. 7). Six acoustic schwannomas (7%), all measuring at least 25 mm in diameter, were associated with arachnoid cysts around the tumor (Fig. 7).

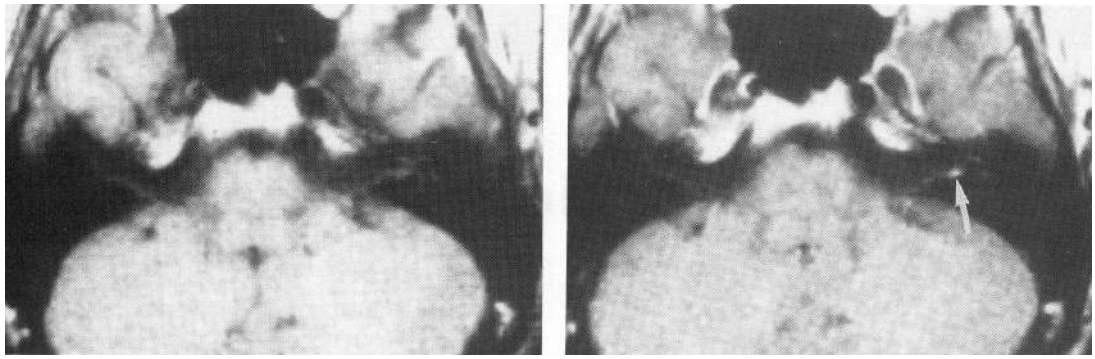
Of the tumors with a component in the cerebellopontine angle-cistern, 85% were centered at the level of the meatus of the internal auditory canal. The angle formed between the tumor border and the petrous bone was acute in 81%. The fourth ventricle was compressed in 18% and displaced contralaterally by tumor compression in14%.

Six patients had contrast-enhanced MR imaging postoperatively. An enhancing nodular mass, suggestive of residual or recurrent tumor, was identified in two of them. (Fig. 8). None of the patients had the “dural tail” sign (1).



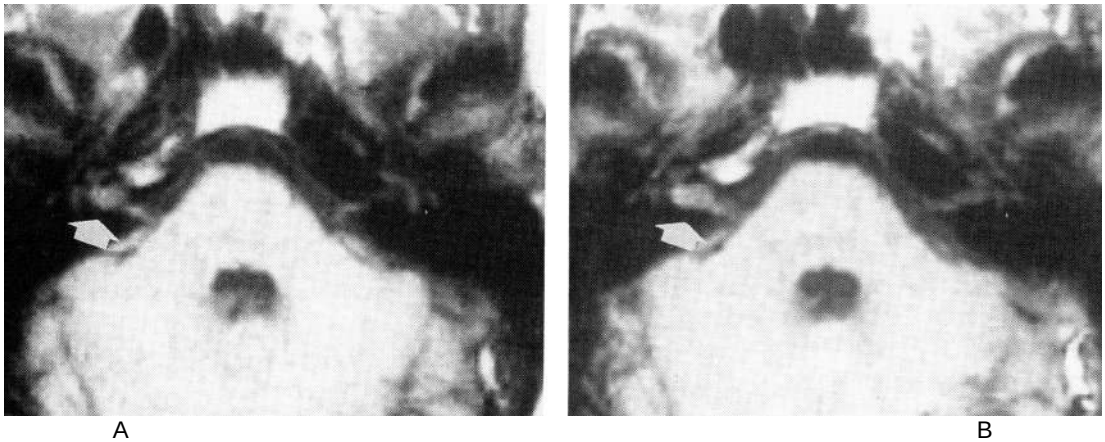
A B

*Fig. 1: Axial T1-weighted (550/30) MR images show the value of contrast administration in detection of small acoustic tumors. A: Non-contrast enhanced image through internal auditory canals (arrowheads) shows no convincing evidence of tumor. B: After IV injection of Gd-DOTA, an elongated, uniformly enhancing tumor (arrow) is shown within right auditory canal, with a component protruding into cerebellopontine angle.*



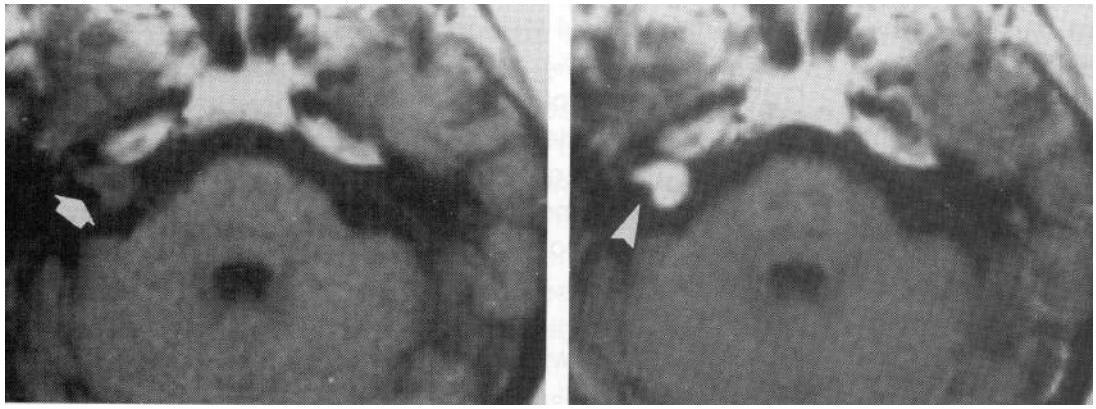
A B

*Fig. 2: Axial T1-weighted (500/30) MR images of 61-year-old man with recent onset of left-sided sensorineural hearing loss. A: Before contrast administration, no abnormality is apparent in left cerebellopontine angle or internal auditory canal. B: Only after administration of gadopentetate dimeglumine is a very small, punctiform enhancing lesion (arrow) seen along intrameatal nerve bundle.*



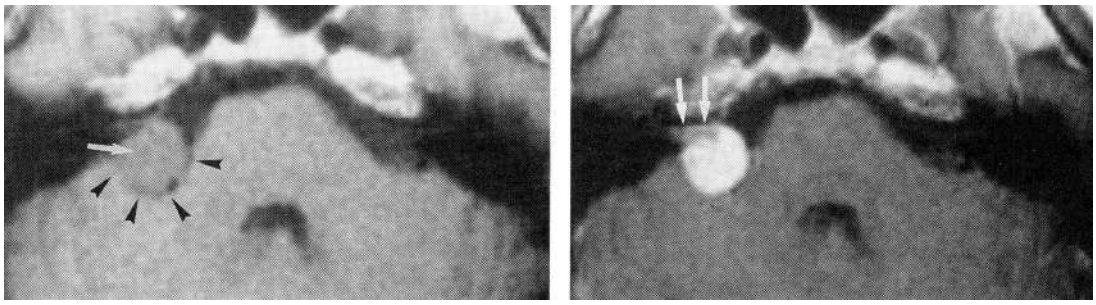
A B

*Fig. 3: Small acoustic schwannoma, without contrast enhancement. This young man had progressive right-sided hearing loss and vertigo. A: Axial T1-weighted (500/30) MR image shows a slightly hypointense nodular lesion (arrow) in right internal auditory canal. B: MR image after administration of gadopentetate dimeglumine shows no obvious enhancement of tumor (arrow). Because of further hearing loss, patient underwent surgery 1 year later, during which a small (3 x 4 mm diameter) acoustic schwannoma was found.*



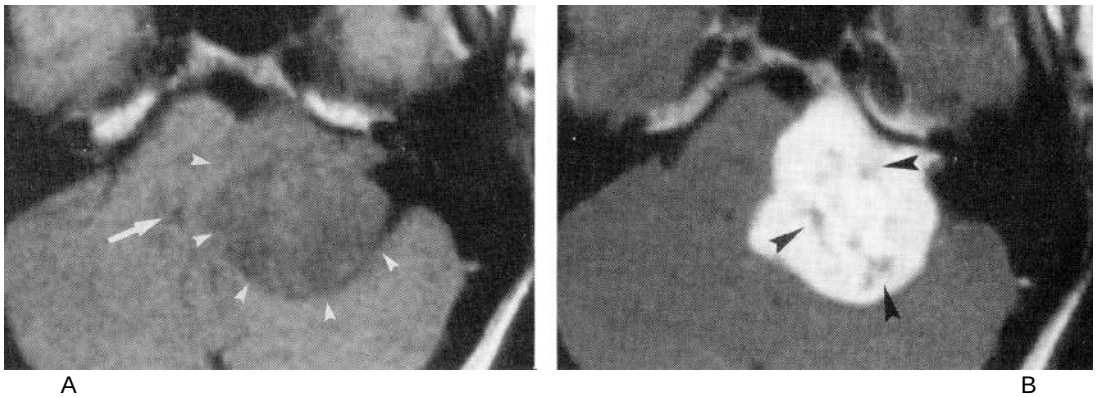
A B

*Fig. 4: Axial T1-weighted (550/30) MR images of a typical example of a small acoustic schwannoma. A: Non-contrast enhanced image shows round tumor mass (arrow) in right cerebellopontine angle with funnel-shaped extension into internal auditory canal. Lesion is slightly hypointense relative to brainstem. B: After gadopentetate dimeglumine injection, intense and homogenous enhancement (arrowhead) is visible.*



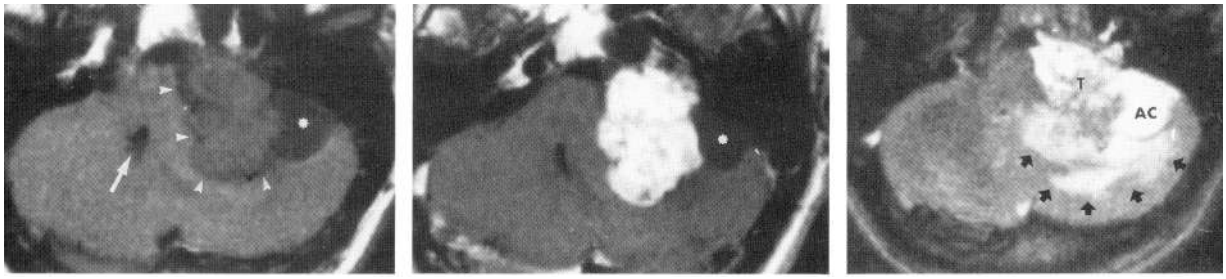
A B

*Fig. 5: Acoustic schwannoma with a slightly inhomogeneous pattern of signal intensity. A: Axial T1-weighted (500/30) MR image at level of internal auditory canal shows an intermediate-sized rounded cisternal mass (arrowheads), nearly isointense with respect to adjacent pons. Central region of tumor (arrow) has same small hypointense areas. B: Contrast-enhanced axial T1-weighted (500/30) MR image shows intense enhancement of tumor, with a slightly inhomogeneous aspect. A small band of enhancing tissue (arrows) is inside internal auditory canal.*



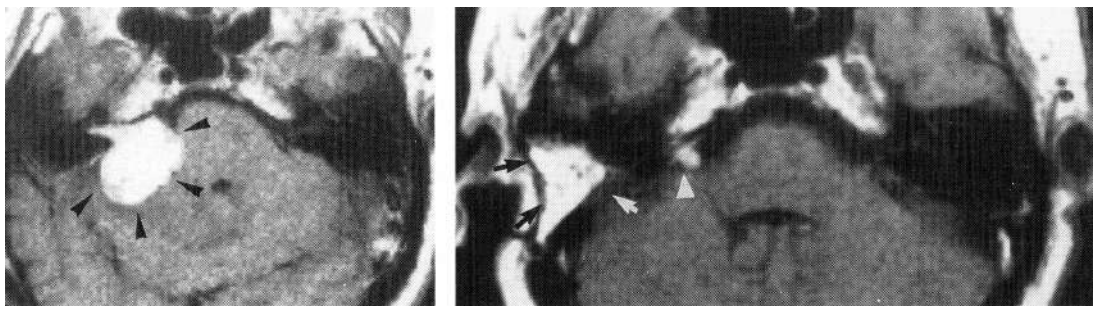
A B

*Fig. 6: Large polyglobular acoustic schwannoma in left cerebellopontine angle with obvious extension into internal auditory canal. A: Axial T1-weighted (550/30) MR image shows slightly hypointense and inhomogeneous mass (arrowheads), causing compression of brainstem and fourth ventricle, which is displaced contralaterally and barely visible (arrow). B: Axial T1-weighted (550/30) weighted MR image after administration of gadopentetate dimeglumine shows clearer demarcation between tumor border and brainstem and better visualization of multiple intratumoral cystic areas (arrowheads).*



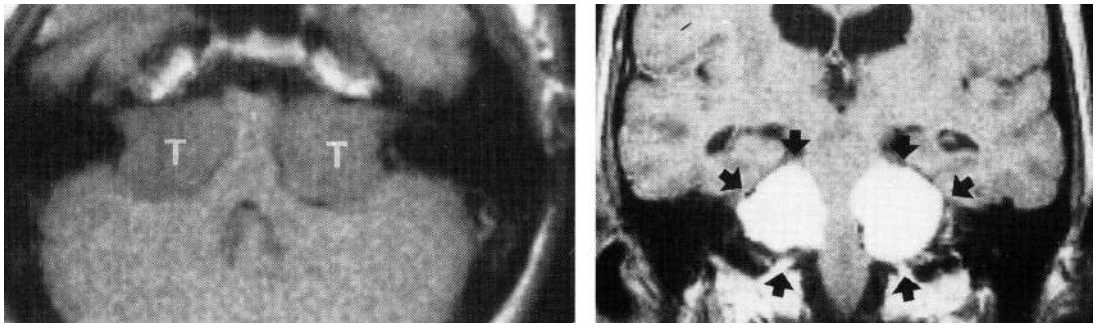

A B C

*Fig. 7: Large acoustic schwannoma with associated arachnoid cyst. A: unenhanced axial T1-weighted (500/30) MR image shows large mass in cerebellopontine angle on left side (arrowheads), which causes compression of brainstem and fourth ventricle (arrow) and associated arachnoid cyst (asterisk). B: After administration of gadopentetate dimeglumine, presence of a hypointense arachnoid cyst (asterisk) between lateral border of tumor and petrous bone is even more clearly depicted on axial T1-weighted (500/30) MR image. C: Only T2-weighted (2500/120) MR image shows presence of peritumoral edema, as hyperintense areas (arrows) in left cerebellar hemisphere. T = acoustic tumor; AC = arachnoid cyst.*



A B

*Fig. 8: 49-year-old man who was completely deaf on right side. A: Contrast-enhanced axial T1-weighted MR image shows large acoustic schwannoma (arrowheads). B: 16 months after surgery, contrast-enhanced T1-weighted (550/30) MR image shows small enhancing nodular mass in right cerebellopontine angle (arrowhead). Although postoperative enhancing scar tissue cannot be excluded, this finding is suggestive of residual or recurrent tumor. Mastoidectomy cavity is filled with hyperintense fat (arrows).*




A B

*Fig. 9: T1-weighted (500/30) MR images of 21-year-old man with neurofibromatosis type 2. A: Axial view shows bilateral large acoustic schwannomas (T) causing extreme compression of brainstem.*
*B: Coronal view shows intense and homogeneous enhancement of schwannomas (arrows) after administration of Gd-DOTA.*

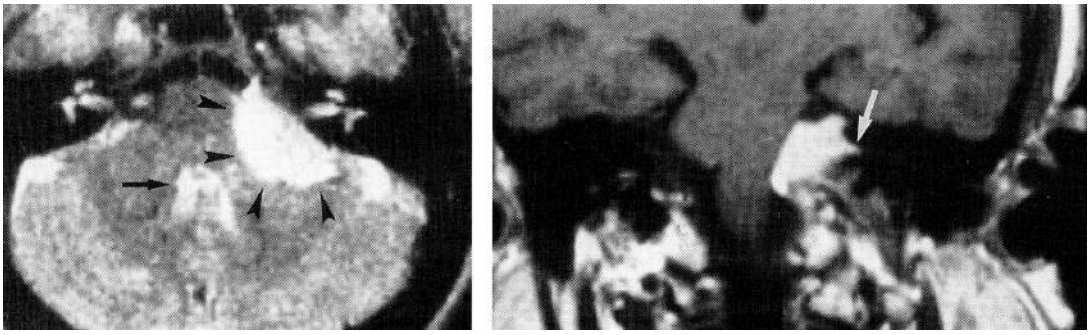


*Fig. 10: Meningioma in cerebellopontine angle with intracanalicular extension. A: Axial T2-weighted (2000/100) MR image shows oval mass (arrowheads) in cerebellopontine angle on left side, with broad- based attachment to petrous bone. Signal intensity is similar to that of CSF in fourth ventricle (arrow). Note symmetric aspect of both seventh and eighth nerve bundles, with no apparent difference in dimensions of canal and no abnormal change in signal intensity. B: After contrast administration, this coronal T1-weighted (500/30) MR image shows intense and homogeneous enhancement of meningioma, with enhancing tissue in internal auditory canal (arrow). At surgery, meningiomatous extension along seventh and eighth nerve sheaths were found.*

## Discussion

Acoustic schwannomas are benign tumors that arise from the nerve sheath of the eighth cranial nerve, most frequently the vestibular portion (2). They constitute approximately 7-8% of all primary intracranial neoplasms and approximately 90% of the cerebellopontine angle tumors (2). The presence of bilateral acoustic tumors implies the diagnosis of neurofibromatosis, type 2 (2) (Fig. 9).

MR imaging has rapidly supplanted other imaging techniques in the diagnosis of these tumors, especially after the development of paramagnetic contrast agents. MR imaging shows a greater level of soft-tissue contrast even without the use of contrast material and can show either the normal seventh and eighth nerves or acoustic tumor (2).

The use of contrast material improves the sensitivity of MR imaging by selectively increasing the level of contrast enhancement in all acoustic schwannomas (3). The capillaries of these extra-axial tumors do not exhibit a blood-brain barrier, and their degree of enhancement is greater (average, 300%) than that of any other intracranial tumor (3). The absence of enhancement after contrast administration in a pathologically proved acoustic schwannoma in one of our patients is therefore very unusual and has, as far as we know, never been reported before.

When contrast material is administered, clearer demarcation and more precise anatomic delineation of the tumor, with improved diagnostic information, can be achieved (2, 3). In our series, the small tumors were mostly round or oval and were of homogeneous signal intensity both before and after contrast administration. Larger acoustic schwannomas were

more polylobular or irregular in shape and showed more heterogeneous signal intensity, with cystic areas and/or peritumoral arachnoid cysts. These features are important in distinguishing acoustic schwannoma from meningioma especially, since differentiation on the basis of signal-intensity differences is not reliable (2, 3).

The presence of a homogeneous, small or intermediate-sized tumor in the cerebellopontine angle-cistern, with a tumor component in the internal auditory canal that enhances homogeneously or slightly inhomogeneously after contrast administration strongly suggests the diagnosis of acoustic schwannoma. However, contrast enhancement in the internal auditory canal has been described in some cases of meningioma also (2, 4) (Fig. 10). This may be caused by direct tumor invasion, meningeal hyperemia, or both. The visualization of the normal seventh and eighth nerve bundles favors the diagnosis of a meningioma.

Larger acoustic schwannomas tend to be more heterogeneous in morphology and signal intensity, owing to the presence of intratumoral cysts, areas of different cellular histology (Antoni type A or type B tissue), calcifications, or regions of hemorrhage (2). This significant heterogeneity on MR images is more characteristic of acoustic schwannoma than of meningioma (2).

Other signs are important in the differential diagnosis: a tumor centered at the meatus of the internal auditory canal and/or with an “acute angle” with the petrous bone is more likely to be an acoustic schwannoma, whereas a broad-based, “obtuse-angled” tumor in contact with the tentorium or with a dural tail sign is more likely to be a meningioma. The dural tail sign is highly suggestive of meningioma, but it is not specific and has recently been described in a case of acoustic schwannoma (1).

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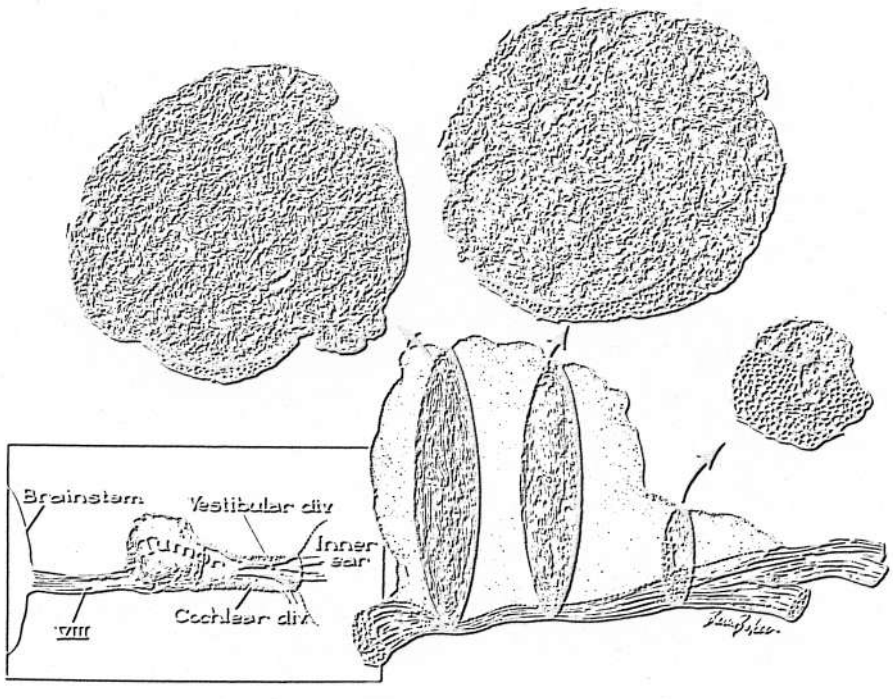
# Chapter 4

# Atypical manifestations of the neuroma in the petrous bone and other pitfalls



## Chapter 4a

# Facial Nerve Neuroma: Report of Two Cases Including Histologic and Radiological Imaging Studies

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## Samenvatting

In tegenstelling tot het acousticusneurinoma is het neurinoma van de Nervus Facialis een vrij zeldzame vondst, zelfs in tertiaire centra. Wij presenteren twee gevallen met daarbij bijzondere aandacht voor de typische beeldvorming en de histologische kleuringstechnieken zoals deze in de twee vorige hoofdstukken werden beschreven. De heelkundige behandeling wordt besproken en getoetst aan de literatuur.

## Summary

Unlike the acoustic neuroma, the facial nerve neuroma is an uncommon finding, even in referral clinical centers. Two cases of facial nerve neuromas are presented, with special focus on the importance of adequate radiological imaging techniques and on the histological characteristics of tumor specimens. Surgical modalities regarding tumor removal as well as facial nerve repair are discussed and the current world literature reviewed.

## Introduction

Unlike the acoustic neuroma, a neuroma of the facial nerve is an uncommon clinical finding, even in referral medical centers. The world literature indicates that only about 180 cases have been reported. In the review of Shambaugh and Clemis [31] neoplastic involvement of the facial nerve accounted for no more than 5% of all lower motor neuron palsies. Most frequently, in these cases, the mastoid segment is involved (58.1% of all cases according to Isamat et al. [13]). In 23.4% of all cases, the tumor originates from the labyrinthine segment, while the tympanic portion of the nerve is involved in only 10.3% of all cases.

Nine percent of all facial nerve neuromas are located extracranially and they usually appear as asymptomatic parotid tumors [2]. Even more rare, facial nerve neuromas can present as middle fossa or pontocerebellar angle tumors [3, 5, 9, 16, 17, 20, 24, 25, 27, 30, 34]

Malignant facial nerve neuromas are even less common. To our knowledge, only six cases have been published [4, 10, 15, 23], one of them being a tumor localized in the parotid gland of an 8-year old child [33]. To the best of our knowledge, bilateral facial nerve tumors have only been described in central neurofibromatosis (type II) [1, 17].

About 50% of all facial nerve neuromas present as a lower motor neuron paralysis and are frequently misdiagnosed as being an idiopathic Bell's palsy. Indeed, the clinical symptoms of

a facial nerve neuroma are subtle, depending on the site of origin, and are usually slowly progressive.

We present our experiences with two patients having neuromas originating from the facial nerve. Radiological characteristics and histological features are discussed.

## Case reports

Patient 1:

A 62-year old white female was referred to our department because of a left Bell's palsy that failed to respond to a treatment with prednisolone. Her medical history revealed the occurrence of a sudden left lower motor neuron paralysis without accompanying signs or symptoms. Her family doctor first referred the patient to a local ENT specialist, who initiated a corticosteroid (prednisolone) treatment. No further investigations were carried out. When the facial palsy failed to resolve after 3 weeks of therapy and another 3 weeks of contemplation, the family doctor referred her to our department.

Upon first physical examination the left facial palsy was still present and, according to the patient's own judgment, had not improved or worsened. Micro-otoscopy revealed normal eardrums bilaterally, with normal aeration of the middle ear cavity. Using the facial nerve grading system of House & Brackmann [12], the facial paralysis was estimated to be a grade V dysfunction. Electromyography and electroneuronography revealed an axonotmesis stage of the lesion. Denervation potentials of the facial musculature were present and hardly any blink reflex of the left eye could be induced, with latency being very significantly increased.

Pure-tone audiometry indicated a mild bilateral sensorineural hearing loss of approximately 20 dB HTL, suggesting mild presbycusis. There was no air-bone gap. Impedance audiometry showed the stapedius reflex to be absent in the left ear, while a normal reflex pattern was present on the opposite side. There was no stapedius reflex on the left side after contralateral stimulation. Clinically, there were no signs of vestibular disorders. The blood analysis was unremarkable.

Contrast-enhanced CT of the petrous bone and the posterior fossa revealed significant widening of the mastoidal portion of the fallopian canal, starting a few millimeters proximal to the stylomastoid foramen and extending up to the geniculate ganglion (Fig. 1). The geniculate ganglion itself seemed not to be involved. There appeared to be considerable

thinning of the otic capsule over the lateral semicircular canal, indicating erosive properties of a tumor. This lesion appeared moderately enhanced after intravenous contrast administration.

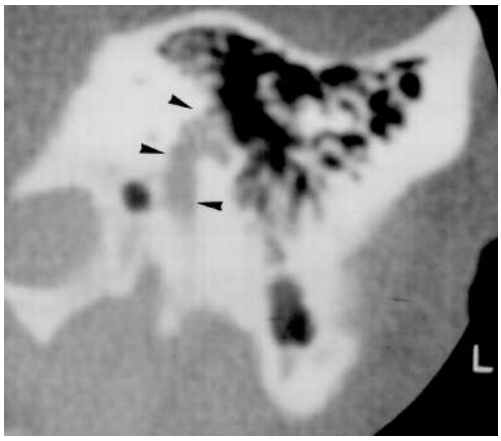



*Fig 1. Coronal CT scan (patient 1): demonstrating the widened Fallopian canal*

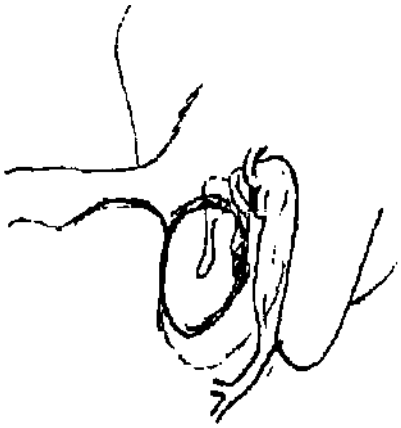


*Fig. 2: Artist's drawing of tumor extent*

A diagnosis of a facial nerve neuroma was made and surgical intervention was performed by the late Prof. Jean Marquet.

At surgery, a large atticomastoidectomy was performed, after which tumor could be readily discerned. The entire tympanic segment and at least two-thirds of the mastoidal portion were involved macroscopically (Fig. 2)

After denuding the most distal part of the facial nerve down to the stylomastoid foramen and exposing the geniculate ganglion, the affected portion was entirely removed (Fig. 3). This had a "string-of-pearls"-like appearance, with two fairly large "pearls".

Subsequently, anastomosis of the distal facial nerve with the proximal hypoglossal nerve was performed, as there was not enough facial nerve trunk left to carry out a rerouting operation and a primary VII-VII anastomosis. The ossicular chain and the inner ear were anatomically preserved throughout the operation, although there appeared to be an erosion of the bone covering the lateral semicircular canal.

In the immediate postoperative period, hearing proved to be unaltered and only a few episodes of mild vertigo occurred during the first days following surgery. However, during the next weeks, hearing on the operated side deteriorated progressively and a total deafness ensued. Presumably, a perilymph fistula existed at the site of the labyrinthine dehiscence.

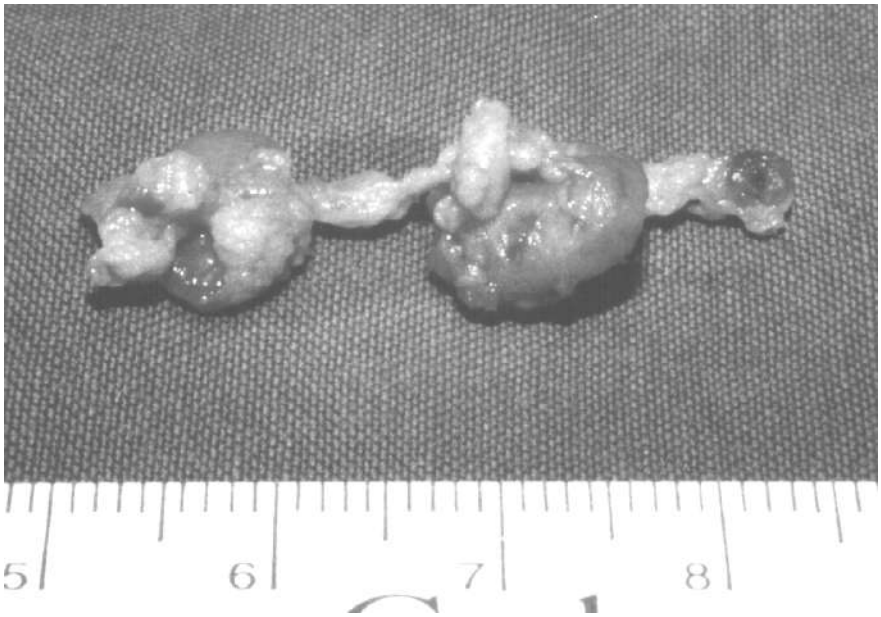


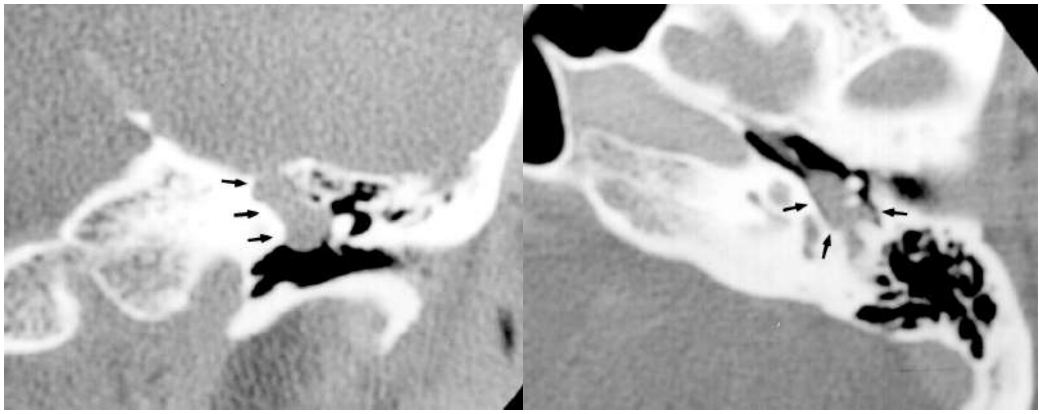

*Fig. 3: Photograph of excised surgical specimen from patient 1 (measured in cm)*

Patient 2:

A 70-year-old white male was referred because of a slowly developing left facial palsy, gait disturbances and a bilateral hearing loss. Physical examination revealed a House-Brackmann [12] grade II left facial paresis and gait disturbances with lateral deviation to the left. Right micro-otoscopy was unremarkable, while a red-bluish mass was visible in the cavum tympani through a normal left eardrum.

Pure tone audiometry showed a right sensorineural hearing loss up to 80-90 dB HTL, while the left ear had mixed hearing loss with moderate presbycusis and an air-bone gap of 40-50 dB HTL (Fletcher index 90 dB). Speech audiometry revealed a significant right-sided rollover phenomenon ($PB_{max=60\%}$ : 80 dB HTL). The stapes tendon reflexes were present on the right side, but absent on the left. ABR patterns were aberrant on both sides and no discernible third or fifth waves could be seen. CT demonstrated a large facial nerve neuroma in the left ear (Figs. 4 and 5). This lesion extended from the intracanalicular portion of the nerve up to the tympanic segment. There was marked displacement of the ossicular chain.

Furthermore, a small right intracanalicular tumor was also found and was believed to be consistent with either an acoustic neuroma or a facial nerve neuroma. Both tumors were demonstrated clearly by means of contrast-enhanced MRI techniques (Fig. 6).



*Figs. 4 and 5: Contrast enhanced CT scan images of patient 2: demonstrating the neoplasm*

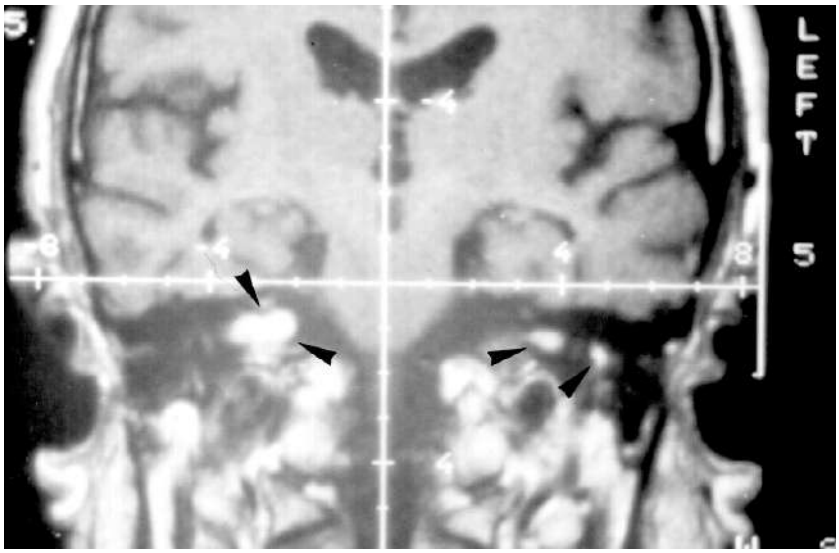



*Fig. 6: Coronal Gd-DTPA enhanced MRI-image (frontal view), illustrating the right intracanalicular tumor (arrows) and the left facial nerve neuroma (arrows).*

Given these findings, central neurofibromatosis (type II) was suspected, but no other stigmata were found.

A decision was made to remove the facial neuroma first in order to preserve hearing on the left side.

This lesion was removed by the senior author (F.E.O.) via a large atticomastoidectomy. There were in fact three separate neuromas: one on the mastoid segment of the facial nerve at the site of emergence of the chorda tympani nerve, one arising from the second genu of the facial nerve and one extending from the geniculate ganglion into the internal acoustic meatus. The incus was removed and subsequently, the mastoid and tympanic portions of the tumor were easily removed. Although bony erosion over the lateral and posterior semicircular

canals existed, there appeared to be no fistulas. The facial nerve was further skeletonized and the fundus of the internal acoustic meatus was opened from above, anteriorly to the superior semicircular canal. Thus, the most central portion of the tumor was also removed via the atticomastoidectomy without opening of the labyrinth. The distal facial nerve stump was the anastomized with the hypoglossal nerve and the ossicular chain was reconstructed using the remodeled original incus.

There were no postoperative complications. Contrast-enhanced CT scan 1 week after the operation and 6 months after surgery showed no residual tumor. A pure-tone audiogram 2 months after surgery revealed a marked improvement in hearing with complete closure of the air-bone gap (Fletcher-index 50 dB HTL).

## Histological features of the neuromas

Immediately after removal, both specimens were fixed in a buffered 4% formaldehyde solution and later on embedded in paraffin. Subsequently, 6 µm serial sectioning was performed on a Leitz microtome. The sections were mounted on glass slides precoated with poly-L-lysine.

Three different staining methods were performed: Masson's trichrome stain, Verhoeff's stain and an immunohistochemical technique using monoclonal mouse antibodies to human neurofilaments. The latter technique enabled identification of any nerve fiber within the tumor mass. The staining methods have been amply described in previous papers [8, 21].

The fascicles of the compromised facial nerve are easily recognized in Fig. 7 using Masson's Trichrome stain. In this section, the tumor mass is stained green, while the myelin sheath stains red. Both tumors were typical Antoni A-type schwannomas: the nuclei were polymorphous, ranging from round, to oval or even fusiform shapes. There was a moderate degree of hyperchromatosis. Both specimens showed palisading of the nuclei, which is a rather typical characteristic. The facial nerve fibers were completely surrounded by neoplastic tissue and there also was a marked infiltration by the tumor cells. There were no signs of malignancy.

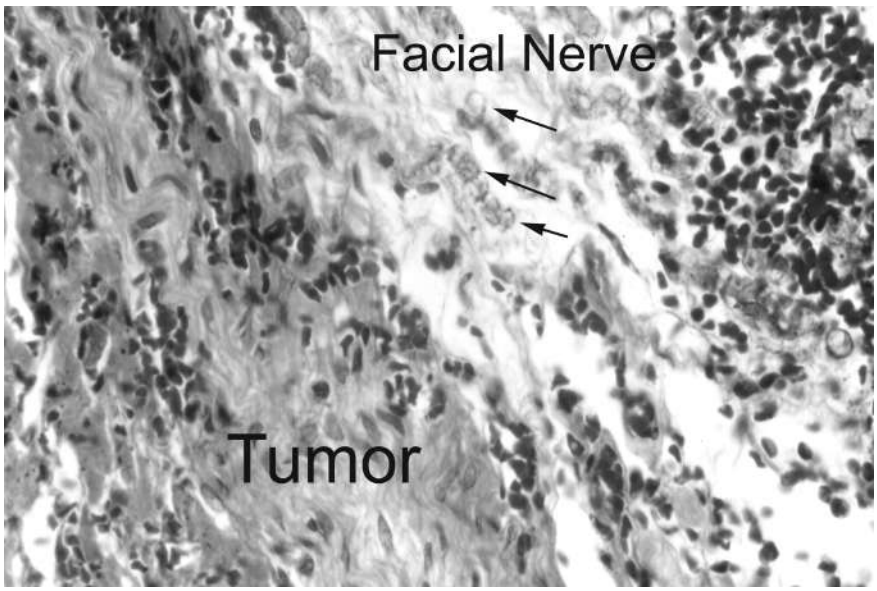



*Fig. 7: Masson's Trichrome stain (270x): mark the red myelin sheaths surrounding the facial nerve fibers within the tumor (arrows)*

Figure 8 is a more detailed picture using Verhoeff's elastin stain and shows typical fibro-cellular whorls. The tumor mass is stained ochreous, while the collagen bundles stain reddish. Although neither of our patients had general stigmata of Von Recklinghausen's neurofibromatosis, remnants of the facial nerve were found within the tumor (as in neurofibromatosis) and were not spread over its surface, as is usually the cases with schwannomas.

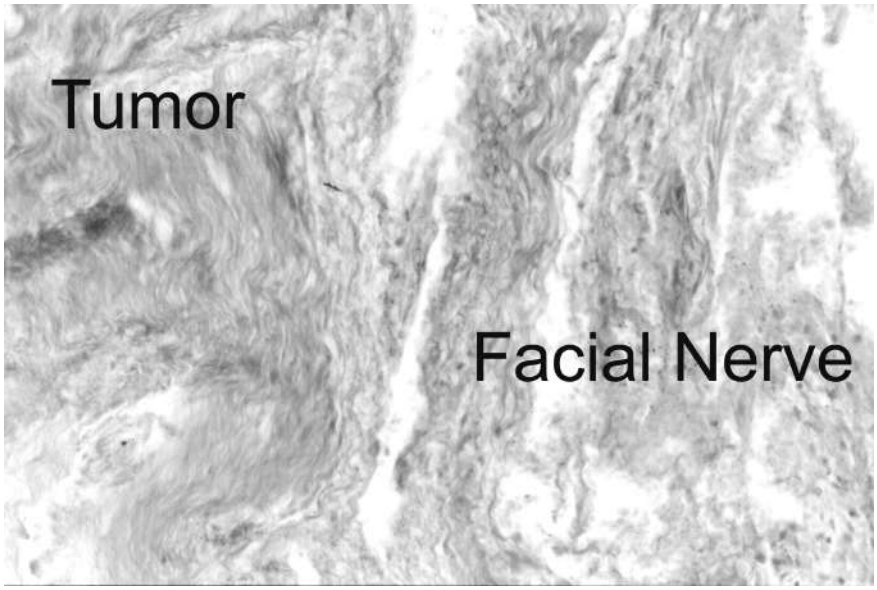



*Fig. 8: Verhoeff's elastin stain (270x): demonstrating typical fibrocellular whorls (arrows)*

Figure 9 shows the immunohistochemical stain identifying residual facial nerve fibers within the tumor mass. The neurofilaments are stained brown, while the nuclei are stained purplish. The presence of oval or fusiform-shaped tumor nuclei surrounding nerve fibers, indicates invasion and dispersion of the nerve fibers.

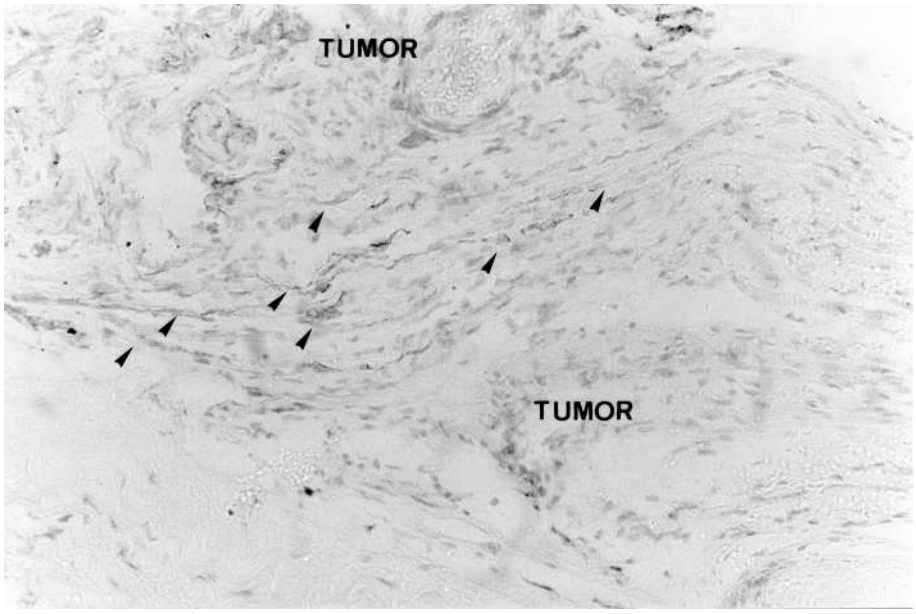



*Fig. 9: immunohistochemical stain using monoclonal mouse antibodies to human neurofilaments (520x). The axones are clearly visible (brown, arrows) throughout the tumor mass*[♦]

## Discussion

We present two cases of a facial nerve neuroma, in which diagnosis was established pre-operatively in both cases by high-quality imaging techniques. Indeed, high-resolution CT and MRI techniques are of paramount importance in order to gauge tumor extent and to choose the most appropriate surgical approach for tumor removal (suboccipital, translabyrinthine, middle fossa or combined approaches). Diagnostic pitfalls do exist: proximal facial neuromas enlarging the internal acoustic meatus are readily mistaken for acoustic neuromas. Latack et al. [18] have indicated that two radiographic signs can help to differentiate between such lesions: first, erosion of the anterior superior margin of the internal acoustic meatus and, second, erosion in the area of the geniculate ganglion. Indeed, the geniculate ganglion area is considered to be a site of predilection [7, 11]. Although CT-scan typically demonstrates a well-delineated enhancing soft-tissue mass with sharply marginated erosion of the surrounding bone, atypical hypodense facial neuromas do exist [22].

♦ These pictures can be found in full color in the final part of this book

Recent work emphasizes the need for MRI in patients with facial nerve palsy. Even with non-enhanced MRI, detection of an intracanalicular tumor is feasible in most cases, although small intracanalicular facial nerve neuromas can be inconspicuous [6]. Also, non-homogeneous signals of uncertain origin and without peroperative surgical correlative can render interpretation cumbersome [6]. Contrast-enhanced MRI, however, dramatically improves sensitivity and allows significant accuracy for detecting small acoustic or facial nerve tumors. Even in cases of genuine Bell's palsy, Ramsey-Hunt syndrome and radiation-induced facial palsy, diffuse homogeneous enhancement of the facial nerve can be observed [32]. The true nature of this enhancement is still not fully understood.

Martin et al. [22] have described MRI findings in four facial nerve neuromas. All tumors were slightly heterogeneous lesions isointense to brain on T1 as well as T2-weighted images. Martin's group also stressed the superiority of MRI over CT in detecting and delineating extensions of intrapetrous lesions. These qualities are improved even more after intravenous injection of gadolinium-DTPA or gadopentetate-dimeglumine, since facial nerve neuromas typically present as distinct, intensely enhanced masses. However, Lidov et al. [19] have described a facial nerve neuroma that clinically and radiographically mimicked a cystic posterior skull base lesion, which extrinsically compressed the facial nerve. Even detailed contrast-enhanced MRI studies were not able to discover preoperatively the true nature of this peculiar neuroma. Only after transmastoid exploration and frozen section examination was a final diagnosis established.

In general, neuromas and hemangiomas of the facial nerve customarily occur near or in the geniculate ganglion and typically result in enlargement of the nerve with adjacent bone erosion [14]. Our first patient, however, did not present any evidence for geniculate ganglion involvement, while our second patient had apparent multicentric neuromas, including geniculate ganglion involvement. Neoplastic bridging of these lobulations has been demonstrated elsewhere, contradicting the multicentric origin hypothesis [7, 11]. Our findings agree with these observations, since we were able to demonstrate tumor cells penetrating nerve fascicles and thus pursuing the natural course of the facial nerve. Such a growth pattern readily explains the classical "dumbbell tumor".

Both of our cases illustrate the need for thorough investigation of all so-called "Bell's palsies" that do not resolve spontaneously within 6 weeks. Facial nerve neuromas can indeed appear in several forms, including vague pain without facial paralysis, simulating acoustic tumors, appearing as parotid masses with or without paralysis, and causing sudden onset of facial paralysis to simulate Bell's palsy [26]. In these latter cases, electrical excitability can be

maintained (as in neuropraxia) or it can recover clinically or electromyographically. A slowly progressive facial palsy is, of course, very suggestive of neoplasm.

In our opinion, adequate removal of facial neuromas not extending medially beyond the fundus of the internal acoustic meatus, can be performed via a large atticomastoidectomy and with extensive denuding of the facial nerve. Whenever necessary, a middle fossa approach ensures complete removal of those tumors that extend more medially. An immediate reapproximation of nerve ends with primary end-to-end anastomosis should be accomplished whenever feasible. Unfortunately, the nerve segment that needs to be removed is often too large to allow such anastomosis to be done. Whenever this is the case, we prefer a primary anastomosis with the hypoglossal nerve. Interpositional (sural) nerve grafting is also a reliable method if and when the proximal stump is readily accessible. Both methods will in time provide acceptable facial tone and allow voluntary facial movement in most cases.

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# Chapter 4b

# Preoperatively diagnosed utricular neuroma treated by selective partial labyrinthectomy

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## Samenvatting

In tegenstelling tot het acousticusneurinoma dat doorgaans de inwendige gehoorgang opvult en zich vervolgens in de brughoek uitstrekt, is het échte intralabyrinthaire neurinoma een zeldzaamheid. De meerderheid der beschreven gevallen werden ofwel aangetroffen bij autopsie, ofwel toevallig ontdekt ter gelegenheid van een destructieve labyrinthectomie voor een medicamenteus oncontroleerbare ziekte van Ménière. Voor zover wij konden achterhalen, is dit het kleinste tot op heden gepubliceerde intra-utriculaire neurinoma waarbij reeds pre-operatief deze diagnose bekend was. Gedetailleerde MRI beelden lieten ons toe deze kleine tumor van slechts 3,5 mm diameter te detecteren. De tumor werd via een ruime atticomastoïdectomie en een partiële labyrinthectomie verwijderd. De diagnostische oppuntstelling, radiologische kenmerken en de heelkundige behandeling worden besproken en getoetst aan de literatuur.

## Summary

Unlike the acoustic neuroma that occupies the internal acoustic meatus and extends into the cerebellopontine angle, the true intralabyrinthine neuroma is an extremely uncommon finding. The majority of the published cases were found at autopsy or during destructive labyrinthectomy for uncontrollable Ménière's syndrome. To the best of our knowledge, we present the smallest exclusively intrautricular neuroma that has ever been diagnosed preoperatively. Detailed magnetic resonance imaging studies allowed the detection of this tumor, measuring only 3.5 mm in diameter. The tumor was removed via atticomastoidectomy and partial labyrinthectomy. The diagnostic workup, radiographic characteristics and surgical treatment are discussed, together with a review of the literature.

## Introduction

Acoustic neuromas are benign tumors that originate from the Schwann cell portion of the acoustic nerve, with a predilection for the vestibular nerve in the internal acoustic meatus. Acoustic neuromas penetrating the cribrose area and thus penetrating into the labyrinth have been described several times since Henschen (1) first reported on this topic in 1923. True intralabyrinthine neuromas are very rare: to the best of our knowledge, only 35 cases have been reported in the English-language world literature. Twenty of these tumors (2-18) were primary intracochlear neuromas. Several of these cases, among them the first case ever described (2), were associated with von Recklinghausen's disease. The intracochlear neuroma seems to have a predilection for the modiolus and the scala tympani of the basal turn of the cochlea.

The other cases are vestibular schwannomas, arising from the macula utriculi (19-28) or, even more rarely, from the crista of the ampulla of one of the semicircular canals (29-31). Among these is a peculiar case worth mentioning: Hallpike (19) described in 1963 a case of neurofibromatosis (NF-1) with an intralabyrinthine schwannoma that impinged on the stapes footplate, thus causing conductive deafness.

The majority of all described intralabyrinthine neuromas presented as "Ménière-like" syndromes with severe sensorineural hearing loss and poor discrimination, and there was no prominent fluctuation in 83 % of all cases (31). Spells of vertigo or unsteadiness are the second most important symptom (57% of all cases [31]). Tinnitus is reported in 45 % (31). The mean age at the time of diagnosis is 61 years. In contrast to the "classic" acoustic neuroma, vertigo seems to persist or even worsen during the natural course of the disease. The destruction of the vestibular neurons by the intracanalicular neuroma is a progressive but slow process that allows for central vestibular compensation. Therefore, the vestibular function is usually significantly diminished before auditory deficits are noted (23). Intralabyrinthine tumors are probably capable of eliciting inappropriate activity of the residual vestibular sensory epithelium. These abnormal discharges are then transmitted via the intact vestibular neurons (23,31). Stewart et al (29), indeed, describe a temporal bone harboring a neuroma originating from the utricular macula with intact vestibular sense organs and only a slight loss of superior vestibular nerve fibers. Several theories exist as to the Ménière-like sensorineural hearing loss. DeLozier et al (23) and Miyamoto et al (24) suggest that 1) release of proteins or potassium ions by the tumor, 2) compression of the organ of Corti by extension of the tumor into the basal turn of the cochlea, and 3) endolymphatic hydrops secondary to tumor compression of the ductus reuniens and sacculus may be responsible for

the hearing loss. The third possibility might explain the sometimes fluctuating hearing threshold mimicking true Ménière's disease.

All but 4 tumors were discovered during destructive labyrinthectomy for Ménière's disease with in tractable vertigo or at postmortem temporal bone study. Only 3 vestibular neuromas were discovered preoperatively: 1 by conventional polytomograms (21) and 2 by means of the combination of computed tomography and magnetic resonance imaging (MRI) (27). All 3 tumors were protruding from the vestibule into the middle ear cavity. One large intracochlear neuroma was discovered radiographically before the intervention took place (15). The latter tumor partially filed the middle ear cavity and was even visible through the tympanic membrane. Only 1 small intracochlear schwannoma has been of MRI (32).

These facts illustrate the devious symptomatology of these tumors, for they usually grow slowly and inconspicuously. Frequently, these cases are misdiagnosed as "uncontrollable" Ménière's disease. Only recent MRI techniques seem to be a helpful tool in discovering such small lesions.

We present a very small intrautricular schwannoma that was discovered preoperatively by means of detailed, high –resolution MRI studies.

A 49-years-old woman was referred to our department because of a progressive left-sided hearing loss with short episodes of tinnitus. Over a period of only 18 months, the hearing loss deteriorated until total deafness ensued. There never was any vertigo. The patient was an experienced diver and most positively denied having had any trouble with equilibrium. Otoscopic examination yielded no remarkable findings. There were no neurologic signs. Pure tone audiometry revealed normal hearing on the right side (Fletcher-index, 10 dB hearing threshold level) and a left-sided deafness.

When the hearing started to worse rapidly, contrast-enhanced computed tomography of the petrous bone and the posterior fossa was performed elsewhere. There were no enhancing lesions to be found in the internal acoustic meatus, nor in the labyrinth.

Given the fact that eventually deafness supervened, an MRI study of the brain was performed at the Department of Radiology of the University Hospitals of the Catholic University of Louvain. The examination was done on a Magnetom SP (Siemens, Erlangen, Germany), operating at 1 T, using the standard head coil as an antenna. Axial T2- weighted images, proton-density images, and frontal T1 weighted sequences were obtained before and after intravenous administration of gadolinium. These showed normal brain parenchyma and brain stem. Both internal acoustic meati were quite symmetric and free from disease. In the labyrinth, however, a small enhancing focus was noted. Subsequently, axial 3-mm-thick

slices using a T1-weighted spinecho sequence (Fig 1) and axial 1-mm-thick slices using a 3 DFT-CISS (three-dimensional Fourier transformation-constructive interference in steady state) sequence (Fig 2) were obtained. The enhancing spot was located in the vestibulum, and the diagnosis of a small intravestibular tumor was made.

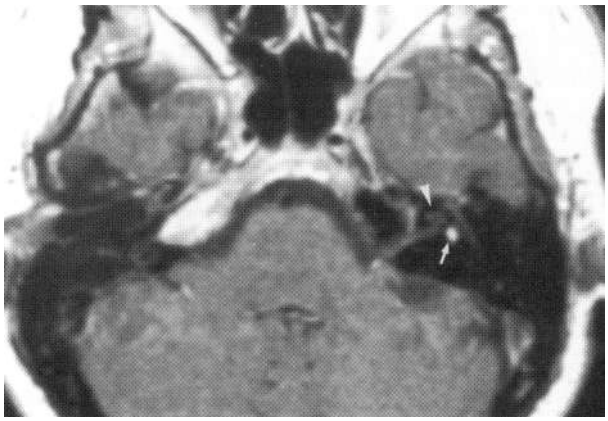

*Fig. 1: Enhanced axial T1-weighted spin echo image. Note focal zone of high contrast uptake in left vestibulum (fine arrow) and the non-enhancing cochlea (solid arrowhead)*

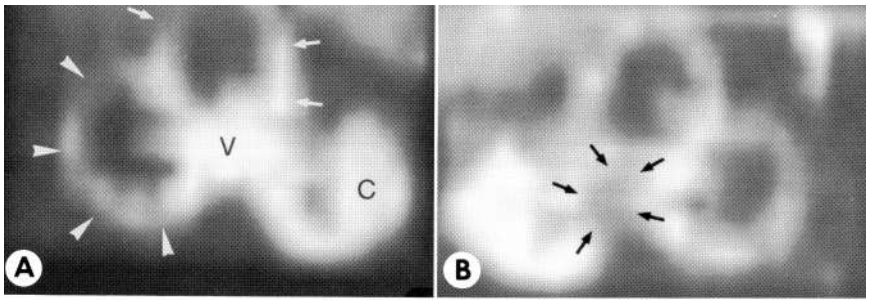


*Fig. 2: Maximum-intensity projection of axial 3DFT-CISS, rendering 3-D images of labyrinthine structures. Inner ear fluids appear bright. A) Normal right ear. Note cochlea (C), vestibulum (V), superior semicircular canal (fine arrows) and posterior semicircular canal (solid arrowheads). B) Pathological left ear: a lacunar defect in the vestibulum (arrows) proves the presence of a mass lesion that replaces normal intravestibular fluid (compare with opposite side).*

The tumor was removed via a large atticomastoidectomy. After opening the lateral semicircular canal, the ampulla of the lateral semicircular canal appeared to be partially filled with a soft, pale pink tumor that clearly originated from the utricle (Fig. 3A). The utricle was completely opened and inspected after total tumor removal. There was no extension toward the cochlea. The cavity was obliterated by means of a fascia flap. The patient recovered quickly and the postoperative period was uneventful. After some training to enhance central vestibular compensation, the patient resumed diving after 3 months without problems.


*Fig. 3: Photographs of tumor: left: demonstrating opened vestibulum and tumor (arrows); right: tumor size*

The tumor measured only 3 x 3.5 x 4 mm (Fig. 3B) and was composed of bundles of spindle cells with nuclear palisading. Streaks of collagen were noted, and the rather elongated nuclei were slightly irregular. The spindle cells were clearly stained after application of immunohistochemical techniques using monoclonal antibodies to S-100 protein and vimentin. There was no staining with antibodies to desmin or glial fibrillary acidic protein. These findings confirm the diagnosis of schwannoma.

## Discussion

Intralabyrinthine neuromas are very uncommon findings, even in a tertiary referral center. The majority of the cases that have been published were erroneously taken for Ménière's disease with intractable vertigo. Either the tumor was discovered during destructive labyrinthectomy, or else postmortem examination revealed the true cause. Few of these tumors were found before one or both events took place, for obviously, the indispensable, sophisticated and highly sensitive imaging tools that allow detection of such small intrapetrous lesions have only recently become available.

Although the tumor we found originated from the utricular macula and did not extend into the basal turn of the cochlea, its only clinical manifestation was a progressive sensorineural hearing loss. Never was there any vertigo or unsteadiness. This rules out the theory of cochlear invasion, but possibly there could have been a blockage of the ductus labyrinth,

causing a secondary endolymphatic hydrops. It should be noted however, that the hearing threshold did not fluctuate, but deteriorated progressively.

In conclusion, the intralabyrinthine schwannoma is a rare pathologic entity that is capable of mimicking atypical Ménière's disease. A thorough diagnostic workup, supplemented with detailed MRI studies, is mandatory in order to expose such small lesions. The tumors can be relatively safely and adequately be removed by simple labyrinthectomy – if need be with opening of the fundus. Technology has allowed us to surpass the era of "unexpected" or "unsuspected" intralabyrinthine tumors.

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♦ These picturs can be found in full color in the final section of this book

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## Chapter 4c

# Problems with flute playing: an otological problem? Case report of a peculiar cerebellar astrocytoma

# Problematisch dwarsfluitspel: een otologisch probleem? Case report van een bijzonder cerebellair astrocytoma

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## Summary

A rare case of cerebellar astrocytoma presenting as a cerebellopontine angle tumour is discussed. A 35-year old woman noticed a bizarre twitching and fatigability of the left upper lip while playing the flute. There was also a mild hearing loss on the left side and she sometimes felt unsure of herself when walking. A thorough examination by means of speech audiometry, electronystagmography, ABR, CT-scan and MRI revealed a large, partly calcified mass occupying the cerebellopontine angle. Only the histological examination of the surgical specimen revealed the true nature of the tumor. The special characteristics of this tumor and the unusual clinical course are discussed. The importance of a good histological diagnosis is stressed.

## Samenvatting

Een zeldzame casus van een cerebellair astrocytoma, dat zich presenteerde als een brughoektumor wordt besproken. Een 35-jarige dame kreeg progressief last van een abnormale vermoeibaarheid en trillen van de linker bovenlip tijdens het dwarsfluit spleen. Er bestond ook een gering gehoorverlies links en een transiënte instabiliteit bij het stappen. Een grondige oppuntstelling met behulp van tonale en spraakaudiometrie, elektronystagmografie, BERA, CT-scan en MRI wezen op een grote, gedeeltelijk gecalcificeerde brughoektumor links. Enkel na histologisch onderzoek kwam de ware aard van deze tumor aan het licht. De bijzondere kenmerken en het ongewone klinisch verloop worden besproken, met nadruk op een adequaat histologisch onderzoek.

## Gevalstudie

### Ziektegeschiedenis

Een 35-jarige patiënte bood zich aan op de raadpleging wegens trekkingen van de linker bovenliphelft, gepaard gaande met krachtverlies van deze linker bovenliphelft en dit na een tiental minuten dwarsfluit spelen. Dit probleem bestond reeds enkele weken. Bij verdere anamnese bleek dat patiënte sinds haar kinderjaren aan de linkerkant minder scherp hoorde, echter zonder tinnitus. Intermittent vertoonde zij de neiging naar links af te wijken. Tenslotte werd er nog melding gemaakt van frequente, drukkende bifrontale hoofdpijn.

## Klinisch onderzoek

Het klinisch N.K.O.-onderzoek is volkomen normaal. De beweeglijkheid van het aangezicht is absoluut normaal te noemen. De proef van Dix & Hallpike is negatief en ook in de Rosenposities treedt er geen nystagmus of vertigo op.Er zijn geen tekens van dysdiadochokinesis. De proef van Romberg en de proef van Unterberger vallen normaal uit, terwijl patiënte bij de proef van Babínski-Weil wat afwijkt naar links. Ook bij de koorddansersgang neigt patiënte naar links.

## Technische onderzoeken

**Audiometrie**

Het tonaal liminair audiogram (fig. 1) toont links een discreet perceptief verlies. Het spraakaudiogram (fig. 1) toont links echter een duidelijke afname van de spraakverstaanbaarheid met roll-over effect.

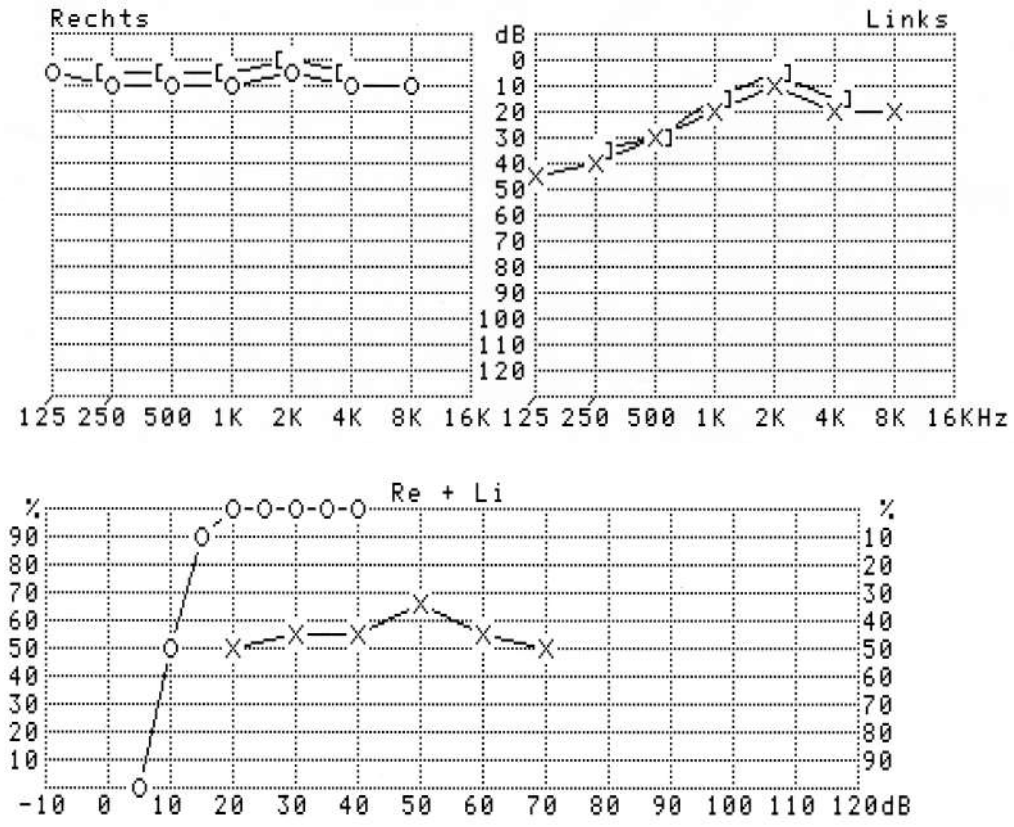


*Fig 1: tonaal audiogram en spraakaudiogram.*

Het *tympanogram* toont bilateraal een normale curve, dwz. type A volgens Jerger, geregistreerd. Links kan er na ipsilaterale stimulatie geen stapediusreflex worden opgewekt. Na contralaterale stimulatie lukt dit wel. Er is geen pathologische reflex-decay. Rechts is de

stapediusreflex na ipsilaterale stimulatie normaal aanwezig, doch hij is afwezig na contralaterale stimulatie. Het gaat hier dus om een zogenaamd diagonaal reflexpatroon.

**B.E.R.A.-onderzoek**

Rechts kan een normaal representatief tracé geregistreerd worden met een normale I-V latentietijd van 3.81 msec op 80 dB nHL stimulatieniveau. Links daarentegen wordt een morfologisch abnormaal patroon geregistreerd: de pieken zijn stomp en minder hoog. De eerste golf komt op 2.97 msec, de derde op 5.34 msec en de vijfde golf op 8.49 msec. Dit betekent dat zowel de I-III (2.37 msec), als de III-V latentietijden (3.15 msec) pathologisch verlengd zijn. De I-V latentietijd bedraagt dus 5.52 msec.

*Elektronystagmografie*: er is geen spontane nystagmus, noch een pathologische blikrichtingsnystagmus aanwezig. De saccadeproef en de optokinetische proef vallen volkomen normaal uit. Ook de vlotte oogvolgbewegingen zijn normaal. Bij de pendelproef bestaat er een duidelijk uitgesproken directionele preponderantie naar rechts. De calorisatieproef bevestigt een areflexie van het linker labyrinth.

**Medische beeldvorming**

*C.T.-scan van de rotsbeenderen en de fossa posterior*

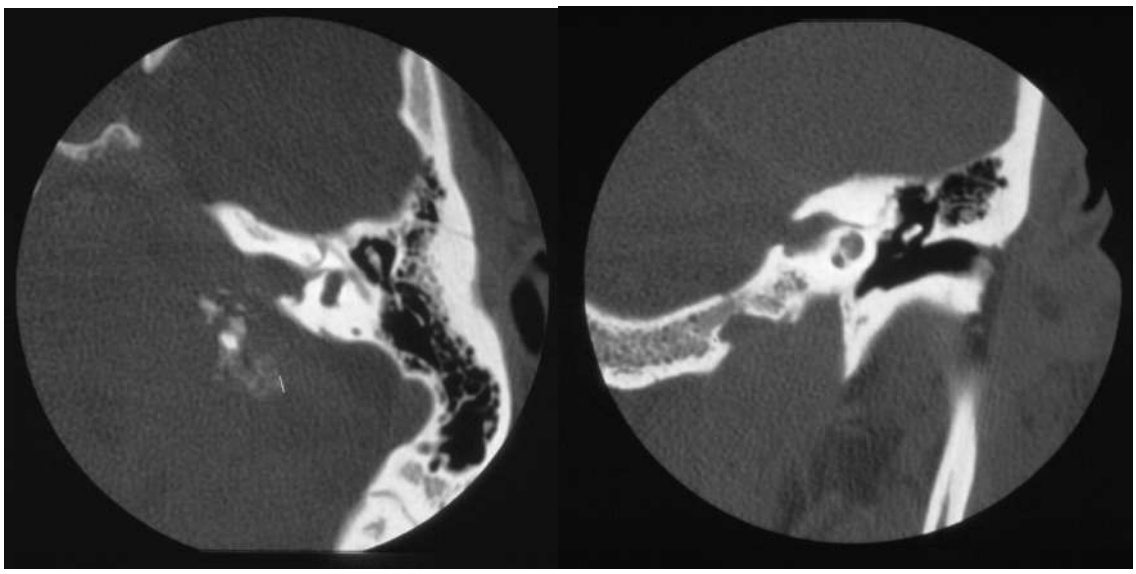

*Fig. 2: CT-scan van het linker rotsbeen na IV contrastinjectie (axiaal zicht links, coronaal zicht rechts).*

Een eerste C.T.-scan bracht een volumineuze, verkalkte tumorale vorming aan het licht ter hoogte van de pontocerebellaire hoek links (zie fig. 2). Uit de afdrukken met botvenster blijkt een duidelijke, onregelmatige verbreding van de meatus acousticus internus met erosie van

de crista falciformis. De tumor is ietwat posterior van de meatus gecentreerd. De lokalisatie van de tumor en de aanwezigheid van calcificaties doen in eerste instantie denken aan een meningeoom. Anderzijds is de verbreding van de meatus acousticus internus en de erosie van de crista een argument dat wijst in de richting van een acousticusneurinoma. Tegen beide hypothesen pleit dan weer de eerder povere aanverving van de tumor na contrastinjectie. Aanvullende investigatie met M.R.I. is dus alleszins geïndiceerd!

*M.R.I.-onderzoek van de fossa posterior*

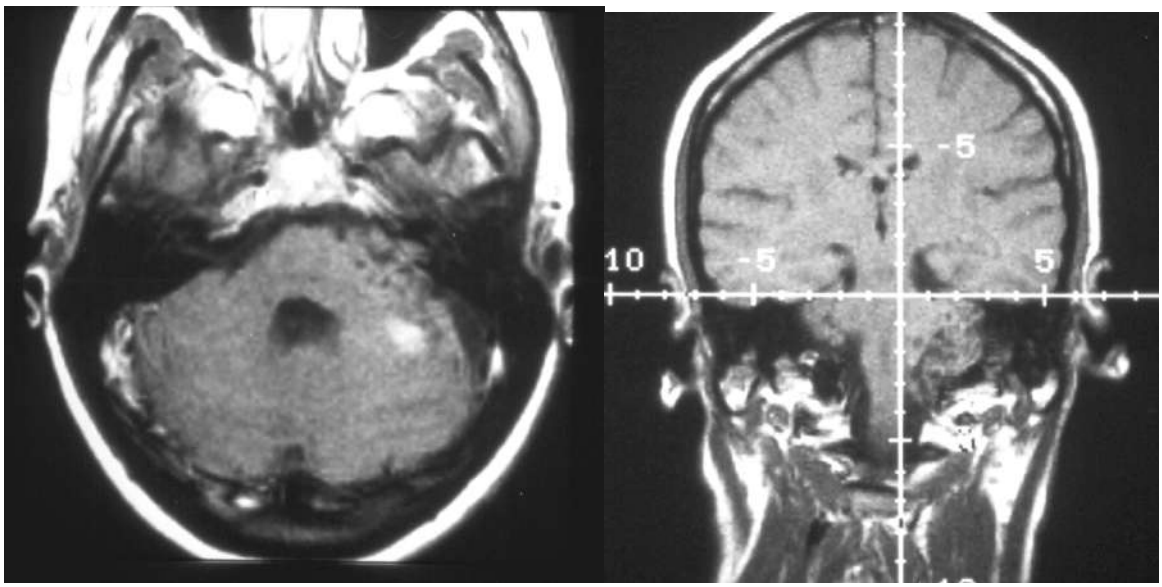


*Fig. 3: T1-gewogen M.R.I.-beelden na IV Gd-DTPA injectie (axiaal zicht links, coronaal rechts)*

Een eerste M.R.I. van de brughoekregio werd uitgevoerd, zowel zonder als met intraveneuze toediening van Gd-DTPA. Dit onderzoek bevestigt de aanwezigheid van een vrij groot ruimte-innemend proces in de linker brughoek (zie fig. 3), dat gekenmerkt wordt door heterogene signaalintensiteiten, zowel op de T1- als op de T2-gewogen opnamen. Deze zones met lage signaalintensiteit corresponderen met de inliggende calcificaties. De tumor reikt tot aan de middellijn in de prepontiene cisterna en is moeilijk aflijnbaar ten opzichte van de linker cerebellaire hemisfeer. De tumor ligt eveneens in nauw contact met de hersenstam, doch hier is een scheidingsvlak merkbaar. Caudaalwaarts reikt de tumor tot aan het foramen magnum. Na intraveneuze injectie van Gd-DTPA is er een discrete aanverving van deze massa, wat een sterk argument is tegen de acousticusneurinoma-hypothese. Ook in het geval van een partieel verkalkt meningeoom zou men een sterke contrastcaptatie verwachten. Er is doorbraak van de bloed-hersenbarrière ter hoogte van het cerebellum. De mogelijkheid van een epidermoïdtumor wordt geopperd, gezien de toch wel vrij hoge signaalintensiteit op de sterk T2-gewogen sequenties. Ook een hamartoma of een teratoma

kunnen worden opgenomen in de differentiële diagnose. De middellijnstructuren blijven alleszins gerespecteerd en er is geen uitzetting van het ventriculair systeem.

## Evolutie

Gezien de eerder geringe subjectieve last en het vrij goede gehoor enerzijds, en gezien de majeure implicaties van een chirurgische interventie anderzijds, werd geopteerd voorlopig een afwachtende houding aan te nemen en de evolutie nauwlettend te volgen.

Bij een controle 6 en 9 maanden na de eerste raadpleging bleken de klachten subjectief ongewijzigd te zijn gebleven en toonden noch het zuivere toonaudiogram, noch het spraakaudiogram enige noemenswaardige evolutie. Bij een volgende raadpleging 1 maand later waren de klachten toegenomen: de valneiging naar links was meer uitgesproken, terwijl de tics en de vermoeibaarheid van de linker bovenliphelft waren toegenomen. Klinisch was er geen facialisparese merkbaar. Patiënte vertoonde echter wel tekenen van cerebellaire ataxie, vooral dan ter hoogte van de linker arm. Er werd ook melding gemaakt van een discrete dysarthrie bij vermoeidheid. Het zuivere toonaudiogram was ongewijzigd, doch het spraakaudiogram toonde een duidelijke achteruitgang van de spraakdiscriminatie. Een tweede M.R.I.-onderzoek van de fossa posterior toonde geen noemenswaardige toename van de tumorale vorming ten opzichte van de vorige opnamen. Er waren echter wel tekens van cerebellair oedeem. De vierde ventrikel was nog steeds gerespecteerd.

Gezien de ongunstige klinische evolutie werd door het multidisciplinair otoneurochirurgisch team een fossa posterior benadering van de tumor gepland. Een in het kader van de pre-operatieve oppuntstelling uitgevoerde angiografie van het linker vertebrobasilair systeem toonde een discrete nodulaire blush in de pontocerebellaire hoek zonder duidelijke pathologische bloedvaten.

## Ingreep

Na spinale drainage werd een retrosigmoïdale fossa posterior benadering uitgevoerd. Na ecarteren van het cerebellum werd de zeer heterogeen uitziende tumor in het licht gesteld. De tumor bleek sterk verkleefd te zijn met het cerebellum. De Nn. VII en VIII waren nog moeilijk te identificeren en dienden als verloren te worden beschouwd. De andere omliggende craniale zenuwen, in het bijzonder de Nn. V, VI, X en XII waren verdrongen en dun uitgewaaierd. Zij bleven echter macroscopisch gespaard. Na debulking kon dan de tumor vrijgedisseceerd worden van de hersenstam en kon een macroscopisch volledige

resectie worden verricht. Omwille van het vreemde aspect van de tumor werd een vriescoupe uitgevoerd. De eerste anatomopathologische diagnose luidde: schwannoma.

## Definitief anatomopathologisch protocol

De cresylviolet kernkleuring (zie fig. 4) toont licht onregelmatige, ovale tot spoelvormige celkernen met doorgaans een fijne chromattinekorreling of soms ook een nucleolus. Sommige kernen vertonen een hyperchromasie. Er is bijgevolg een zekere graad van kernatypie aanwezig. Er worden geen mitosen gezien. De cellen vertonen slechts een smalle boord eosinofiel cytoplasma, dat zeer fijne uitlopers vertoont. De cellen zijn overwegend in lange bundels gerangschikt. De tumor is diffuus hypercellulair met een achtergrond die bestaat uit een fijn fibrillair netwerk. De tumor is weinig gevasculariseerd. Hyaline verbreding van de vaatwand komt voor, evenals talrijke calcificaties. De reticulinekleuring toont de afwezigheid van reticulinevezels aan tussen de tumorcellen. De GFAP-kleuring (glial fibrillary acidic protein) toont aan dat de meerderheid der cellen sterk immunoreactief is (zie fig. 5), wat bevestigt dat het om een glioma, in casu een astrocytoma gaat. Deze beschrijving is compatibel met een fibrillair astrocytoma graad II, zowel volgens Bailey & Cushing (1), als volgens de indeling van Daumas-Duport et al. (2).

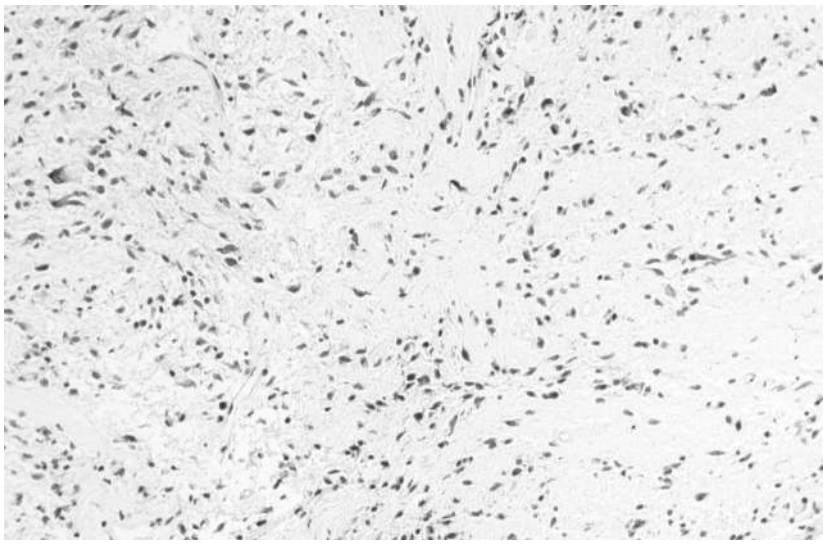

*Fig. 4: histologische coupe: cre*sylviolet kernkleuring (646 x)♦

♦ This picture can be found in full color in the final section of this book

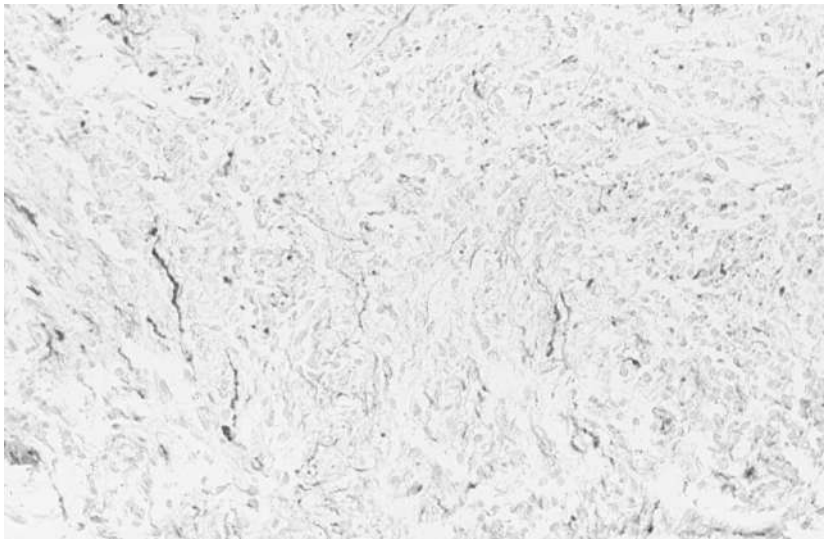

Fig. 5: *GFAP immunohistochemische kleuring (646 x)*♦

## Bespreking

Cerebellaire astrocytomen zijn essentieel pediatrische tumoren: na de medulloblastomen zijn zij de meest frequente fossa posterior tumoren bij kinderen (3). Naast deze groep van juveniele astrocytomen, vertoont de incidentie der astrocytomen ook een piek in de vierde levensdecade (4). Het gaat in die groep meestal om cerebrale astrocytomen, terwijl het bij kinderen doorgaans om cerebellaire astrocytomen gaat. Primaire centraal zenuwstelseltumoren die zich manifesteren als een brughoektumor zijn een zeldzaamheid: in hun overzicht van 1354 gevallen van brughoektumoren beschrijven Brackmann en Bartels (5) 118 niet-acousticusneurinomen. Slechts twee van deze gevallen waren astrocytomen. House en Burt (6) beschrijven één geval van een cerebellair fibrillair astrocytoom graad II bij een volwassene, dat zich eveneens presenteerde als een brughoektumor.

De ontwikkeling van de tumor kan soms lange tijd insidieus verlopen, terwijl de eerste manifeste klinische tekens soms lang onopgemerkt blijven Kepes et al. (7) rapporteren drie gevallen van oudere patiënten met een cerebellair astrocytoma, waarbij -retrospectief bekeken- de eerste klinische tekens reeds meer dan dertig jaar lang bestonden! Ook onze patiënte, die nu 35 jaar oud is, verklaarde van kindsaf aan minder scherp te horen links, dit wil zeggen toch reeds een 20-tal jaren lang!

Een recente studie van Daumas-Duport et al. (2) bevestigde de gekende correlatie die er bestaat tussen de histopathologische gradering van de tumor en de overlevingsduur na

♦ This picture can be found in full color in the final section of this book

heelkunde als monotherapie. Zij stelden meteen ook een vereenvoudigde indeling voor (zie tabel 1). De auteurs deelden de in hun studie opgenomen astrocytomen in in vier graden aan de hand van vier duidelijke histologische criteria: de aanwezigheid van kernatypieën, de aanwezigheid van mitosen, het optreden van necrose en het optreden van endotheliale proliferatie met zogenaamde rozetvorming.

| Gradering | Aantal criteria voldaan | Procentueel aandeel in totaal aantal astrocytomen | Overlevingsduur post-operatief |
|---|---|---|---|
| Graad I | 0 | 4.1 % | > 11 jaar |
| Graad II | 1 | 23.4 % | Gemiddeld 4 jaar |
| Graad III | 2 | 15.7 % | Gemiddeld 1.6 jaar |
| Graad IV | 3 of alle 4 | 56.8 % | Gemiddeld 0.7 jaar |

*Tabel 1: gradering van astrocytomen volgens Daumas – Duport et al. (2)*

Totale radicale exerese van de tumor is de alom geaccepteerde voorkeursbehandeling voor cerebellaire astrocytomen (8, 9, 10). Volgens Ilgren (8) lukt dit slechts bij ongeveer 60% van de gevallen. Van deze groep is 95% vrij van recidieven gedurende 25 jaar. Van de groep met onvolledige tumorresectie heeft amper 35% een recidiefvrije periode van vijf jaar. Astrocytomen staan inderdaad bekend om hun onvoorspelbaar gedrag: er worden drie recidiefpatronen beschreven (8):

- een vroegtijdig recidief, meestal binnen de vijf jaar post-operatief, en dit vooral bij jongere patiënten.
- een laattijdige, onvoorspelbare vorm, waarbij het recidief histologisch niet noodzakelijk gerelateerd is met de primaire tumor.
- een zeldzame laattijdige vorm: het maligne gedegenereerd astrocytoom.

Zeer laattijdige recidieven worden eveneens beschreven: Pagni et al. (10) signaleren een recidief van een volledig verwijderd pilocytair astrocytoom van het cerebellum 36 jaar na de ingreep! Bovendien bestaat er ook, zoals hoger gezegd, een geringe kans op een dedifferentiatie in het recidief, met een meer hooggradige tumor als gevolg. Schwartz (11) rapporteert een geval van een patiënt waarbij op vierjarige leeftijd een laaggradig cerebellair astrocytoom onvolledig verwijderd werd en die na een symptoomvrije periode van 28 jaar een hooggradig recidief ontwikkelde: in casu een glioblastoma multiforme (graad IV).

Een controversieel onderwerp is dan ook het nut van radiotherapie na onvolledige verwijdering van een astrocytoma of van radiotherapie als monotherapie. Volgens Ilgren & Stiller (8) is radiotherapie niet geïndiceerd, zelfs niet in het geval van onvolledige resectie. Deze auteurs stellen dat post-operatieve radiotherapie de overlevingsduur na onvolledige

resectie niet verlengt, noch het aantal recidieven doet afnemen. Niettemin geven deze auteurs toe dat radiotherapie het risico op locale tumorspreiding via de subarachnoïdale ruimte zou doen afnemen. Andere auteurs, zoals Garcia et al (11), Fazekas (12) en Leibel et al. (13) poneren daarentegen dat post-operatieve radiotherapie wel degelijk nuttig is, zowel voor wat de overleviungsduur betreft, als voor wat de recidiefkans betreft. Er werd dan ook besloten onze patiënte 56 Gy toe te dienen ter hoogte van de ponto-cerebellaire hoek.

## Besluit

Deze case report benadrukt de noodzaak van een grondige investigatie van elk asymmetrisch perceptieverlies en van elk geval van Nervus Facialisprikkeling of -parese. Vooral indien er een combinatie van beiden bestaat, dient de brughoekregio aan een grondige oppuntstelling onderworpen. Alhoewel zeldzaam, kunnen andere tumoren dan acousticusneurinomen, meningeomen of epidermoïdtumoren zich als een klassieke brughoektumor presenteren. Een grondig histopathologisch onderzoek van het specimen kan in dergelijke gevallen in belangrijke mate mede bepalend zijn voor het verdere beleid en de prognose.

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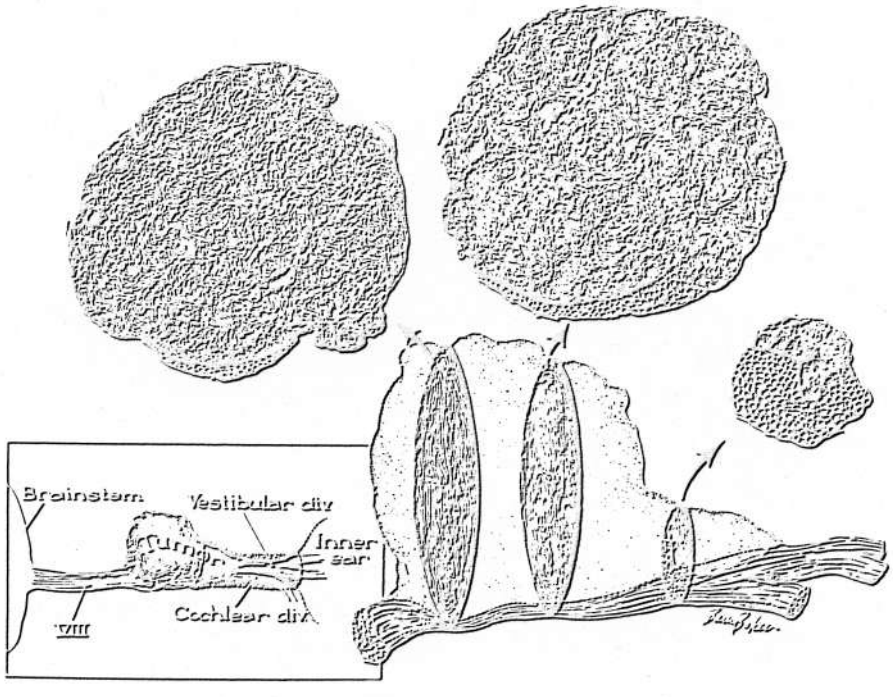
# Chapter 5

# Summary and Conclusions



Over the last decennia, the diagnostic regimen and treatment of the acoustic neuroma has changed dramatically. As always during a period of changes, questions arise that need be answered on a sound scientific basis. We have tried to formulate and answer to some of these questions in this thesis.

In chapter 1, we provide a historical overview regarding important advances in diagnostics and treatment of the acoustic neuroma. One of the most dramatic diagnostic acquirements is undoubtedly the fast evolution of magnetic resonance imaging. New techniques allow for long-term follow-up of acoustic tumors, which already yields new insights on the natural course of the acoustic neuroma. A wait-and-see policy has therefore become a valid alternative for immediate surgery when the acoustic neuroma still is in an early stage. MRI also enables us to study the changes in the inner ear fluids that are quite possibly linked to inner ear deterioration and thus allows in a timely fashion to choose the best moment for surgery and the suitable surgical access to the cerebellopontine angle.

Another most important feature of MRI is early detection and follow-up of tumor recurrence and/or monitoring of residual tumor. Since we have provided irrefutable histological evidence of tumor ingrowth in the cochlear nerve in chapter 2, it is quite thinkable that more than once tumor remnants that are indeed invisible to the surgeon at the time of surgery, but nonetheless present on the microscopical level, are left behind after successful removal of the tumor. MRI provides us and will continue to provide us the necessary data as to the fate and growing potentials of these remnants. The same logic holds true for the facial nerve, which is almost always preserved.

Up till now, CT and MRI follow-up studies do not indicate that sharp dissection of the facial nerve, in order to maximize nerve function preservation, yields a higher risk of tumor recurrence due to tumor remnants that are inevitably left behind.

In chapter 3, the clinical data of 13 selected cases are presented. In all of these cases, the cochlear nerve was positively identified in the microscopical specimen and tumor ingrowth was established. Moreover, all required clinical data of these subjects could be retrieved from the patient files. Comparison of these data with other series in contemporary literature teaches us that there is no significant difference between these selected cases and similar cases in the literature.

As MRI was introduced in the clinic and was rapidly recognized as a very powerful diagnostic tool, more data were required as to the sensitivity and specificity of MRI in the differential diagnosis of cerebellopontine angle tumors. In the second part of chapter 3, a pictorial essay on the characteristics of the acoustic neuroma is presented. Meanwhile, daily practice has