

THE NATURAL HISTORY AND MANAGEMENT OF VESTIBULAR
SCHWANNOMAS

by

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ABSTRACT

Over the past decade (2000-), the management of vestibular schwannomas has been in a state of flux. An increasing availability of magnetic resonance imaging has allowed clinicians to monitor tumour progression and increasingly, it has become recognised that once diagnosed, a significant proportion of lesions do not continue to grow. As a result, a number of neurotological centres have advocated conservative management as appropriate for small-medium sized tumours. Birmingham has been one of these centres, and this thesis presents data gathered over the past fifteen years that reflects this change in management, drawing upon the Birmingham Vestibular Schwannoma Database maintained by the author. The thesis addresses issues pertinent to conservative management: growth rates among observed tumours, risk factors for growth, the evolution of hearing while under observation and proposes a radiological surveillance protocol. More broadly, the thesis examines other themes important in the management of patients with vestibular schwannomas: the role of functional surgery and the possibility of rehabilitation in single-sided deafness. A number of chapters from the thesis have been published in peer-reviewed journals and are presented here in updated or amended form.

DEDICATION

This thesis is dedicated to my parents Jamie and Rosie Martin in gratitude for their love and support over many years.

ACKNOWLEDGEMENTS

This thesis represents work carried out during the course of my registrar training and I have been fortunate enough to have been supported by a large number of colleagues during this time. Several chapters have been published as independent articles, and I am indebted to those colleagues who have collaborated with me in these publications. Dr Roger Holder has clarified countless statistical conundrums over the years. Konstance Tzifa, Caroline Kowalski, Hannah Fox and Eu Chin Ho have all collected data from the database at different times. Swarap Chavda, Latha Senthil, David Proops, Andrew Reid, Huw Cooper and Richard Walsh in particular have all provided advice and support as senior authors. I would like to thank Rachel Lowther for her sterling work in the POCIA testing room. I must also thank Tracey Plant, who has patiently tolerated my frequent residency in her office and disruption of her filing system. My mother, Rosie Martin, has kindly read the proofs.

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INTRODUCTION

Vestibular schwannomas represent 7-10% of intra-cranial neoplasms (Nager, 1993) and their management forms a considerable portion of a neurotologist's clinical workload. The aim of this thesis is to explore issues related to the natural history of tumour growth, to clinical management and to the rehabilitation of patients with a vestibular schwannoma in the light of the world literature and studies performed in the neurotology department of the University Hospital, Birmingham, United Kingdom.

This introduction will consist of the following elements:

- i. An introduction to the pathology, epidemiology and management of vestibular schwannomas.
- ii. A review of published studies addressing the above topics with an identification of weaknesses in the current world literature in the field.
- iii. A description of the data source employed in the studies that form the body of the work.
- iv. A statement of the aims and objectives of the thesis.
- iv. An outline of forthcoming chapters.

Nomenclature

Vestibular schwannomas are commonly described in the United Kingdom as ‘acoustic neuromas’. The term ‘vestibular schwannoma’, reflecting the cell and nerve of origin of the tumour is preferred in this thesis and is recommended by the National Institute of Health Consensus document (Eldridge and Parry, 1992).

Pathology of vestibular schwannomas

Anatomical considerations

Vestibular schwannomas are benign tumours arising from the perineural Schwann cells of the vestibular component of the VIIIth cranial nerve (the vestibulo-cochlear nerve). Figure 1 illustrates the anatomy of the VIIIth cranial nerve as it leaves the brainstem pons, crosses the cistern of the cerebellopontine angle, and enters the internal auditory canal. This anatomical course, in particular the relationship between the VIIIth and VIIth (facial nerve), and the close proximity of the brainstem explain the presenting and later symptomatology described below.

As the nerve leaves the brainstem, it is initially covered by neuroglial cells (astrocytes and oligodendrocytes): Schwann cells sheath the nerve at the neuroglial-Schwann cell junction as the VIIIth nerve emerges from the pia mater some 7 to 13 mm distal to the brainstem (Tarlov, 1937, cited in Nager, 1993). For this reason, tumours most commonly originate in the internal auditory canal, or in the cerebellopontine angle just medial to the medial limit of the internal auditory canal (the ‘poros acusticus’). This tendency to begin growth within the internal auditory canal and emerge into the cerebellopontine angle cistern gives rise to the typical appearance of a moderately large vestibular schwannoma as seen in Figure 2.

Figure 1: Anatomy of brainstem and internal auditory canal (reproduced with permission from Prof. R Jackler)

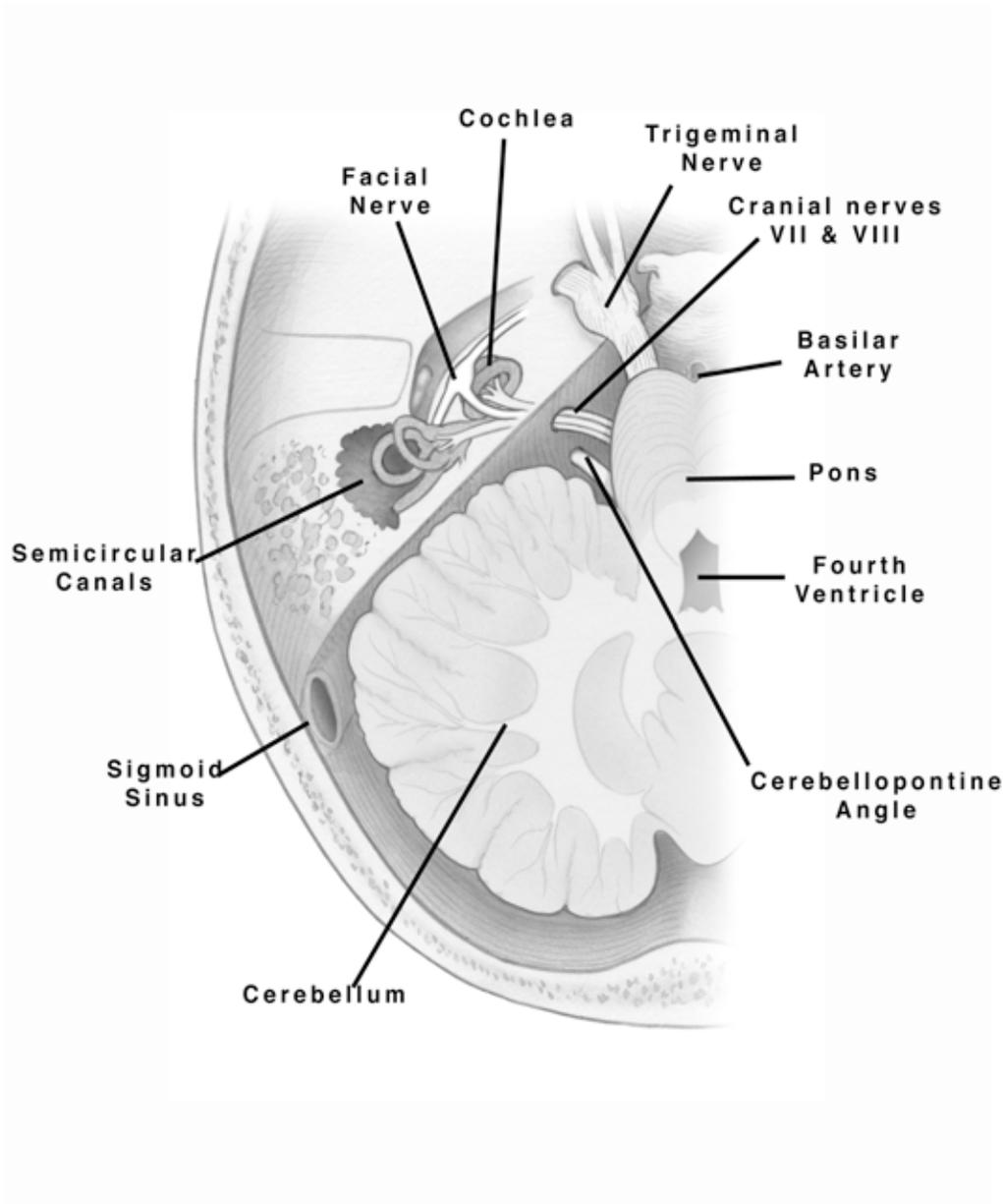
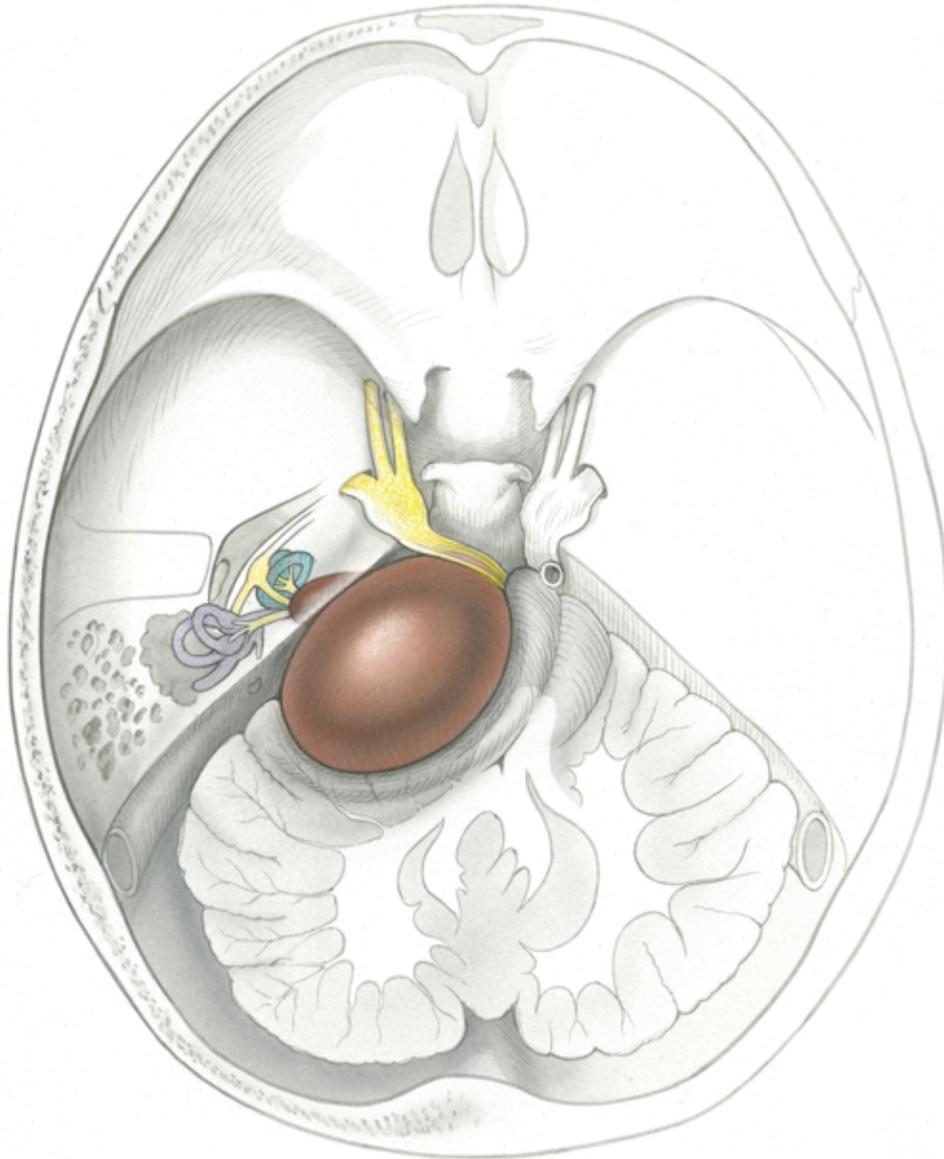


Figure 2: Moderately-large sized vestibular schwannoma compressing neighbouring structures
(reproduced with permission from Prof. R Jackler)



For unknown reasons, the inferior vestibular nerve seems to be more commonly the site of tumour origin than the superior: in a series of 200 consecutive cases Khrais (2007) found that 91% of tumours for which a judgement could be made (76% of the total) arose from the inferior nerve.

Tumour classification

Vestibular schwannomas are classified according to their size in their largest extrameatal diameter, following guidelines produced at the Consensus Meeting on Reporting Systems on Vestibular Schwannoma (Kanzaki, 2003). Prior to this consensus statement, a considerable number of different systems for measurement existed (Tos, 2008), confusing comparison between different studies. The salient feature of this reporting system is that tumours are classified according to their dimensions in the cistern of the cerebello-pontine angle, without measuring tumour within the internal auditory canal. Tumours confined to the internal auditory canal are classified as ‘intrameatal’. Further details (such as whether the tumour is cystic or involves the fundus of the internal auditory canal), may be added to the classification system. The classification is summarised in Table 1.

Table 1. Tokyo Classification System

	Extrameatal size	mm
Grade 1	Small	1-10
Grade 2	Medium	11-20
Grade 3	Moderately large	21-30
Grade 4	Large	31-40
Grade 5	Giant	>41

Histopathology

Vestibular schwannomas are characterised by two distinct tissue types: Antonini types “A” and “B”. Type A tissue is densely packed with cylindrical bipolar cells, arranged in whorls that can lend an ‘onion-skin’ appearance to the tissue. Type B tissue is more loosely packed with cells connected by a finely honeycombed watery matrix prone to microcystic degeneration (Nager, 1993). The importance of cyst formation within tumours is significant to tumour natural history and will be discussed below.

Traditionally, vestibular schwannomas were considered to be encapsulated with connective tissue (Nager, 1993), but more recently, Kuo (1997) has called this into question, observing that a connective tissue layer is present but is microscopically thin (3-5 μm), and that neoplastic cells extend to the macroscopic limit of the tumour. This has clinical relevance when considering sub- and near-total excision of tumour in order to avoid damage to the facial or cochlear nerves (discussed below): a visible remnant of tissue left protecting the surface of the nerve may demonstrate tumour growth at a later stage, whereas a remnant of tumour capsular connective tissue should not.

Molecular genetics

Although this thesis addresses only the management and natural history of sporadic vestibular schwannomas, it is important to recognise that 5% of vestibular schwannomas are associated with the familial disorder neurofibromatosis type 2 (NF-2). NF-2 is a condition characterised by multiple vestibular, spinal and other schwannomas, meningiomas, ependymomas and ophthalmic lesions. The condition is caused by a defect in the tumour suppressor protein

‘merlin’ or ‘schwannomin’, coded by the location 22q12, and originally independently identified by Rouleau (1993) and Trofatter (1993). Prior to this, it had been established that sporadic vestibular schwannomas demonstrated somatic chromosomal deletions of chromosome 22 (Seizinger, 1986 with later addition by Irving 1997), and it would seem clear that merlin plays an important role in the pathogenesis of both NF-2-derived vestibular schwannomas and the sporadic variant.

Merlin appears to have a role in human embryogenesis, in the regulation of growth factors, and in the interaction between the normal Schwann cell and the axon in peripheral nerves (reviewed in Welling, 2009). In the embryo, transgenic studies suggest that merlin is important in the regulation of neural crest cell migration and neural tube closure (Akhmametyeva, 2007): these studies demonstrated particularly high levels of activity at anatomical sites associated with NF-2 disease (the acoustic ganglion, the pigmented retina of the lens and others). Beyond embryogenesis, merlin has been demonstrated to blunt tyrosine kinase receptor-driven proliferation by interacting with intracellular signalling pathways (Chadee, 2006). In a non-functioning form, it is supposed that growth will be inappropriately stimulated. Finally, it has been demonstrated that a loss of merlin-driven suppression of the Rac protein adversely affects the Schwann cell cytoskeletal morphology and function, disrupting Schwann cell-axonal interaction and producing cells morphologically characteristic of schwannomas (Nakai, 2006).

Another field of interest has been the exploration of the significance of angiogenic factors in the development of vestibular schwannomas. In a recent study, Koutsimpelas (2007) examined levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)

expression in a group (n. 17) of sporadic vestibular schwannomas. The group found an association between levels of mRNA and protein expression of these growth factors and tumours that could be described as 'more aggressive': these tumours were larger, more vascular, and had grown to a greater volume during a shorter period of symptoms. Plotkin (2009) also examined levels of VEGF expression in schwannoma tissue, and found high levels, although these were also seen in normal schwann cells.

The aim of the molecular studies briefly described above is both to understand pathogenesis and to identify potential medical treatment. Therapies are likely either to address the underlying genetic abnormality found in NF-2 and sporadic vestibular schwannomas (i.e. the loss of the wild-type NF-2 gene), or to seek to interact with the molecular pathways that merlin is thought to influence. Pursuing the first of these avenues, Messerli (2006) used recombinant viral gene therapy techniques to introduce wild type merlin to a murine NF2 model and achieved a reduction in schwannoma growth without any apparent toxicity.

Targeted chemotherapeutic agents have also been used to effect in animal studies: monoclonal antibodies to ErbB2 (Herceptin) can inhibit vestibular schwannoma growth by interacting with the tyrosine kinase receptor mediated growth pathway (Hansen, 2006). A further avenue is suggested by Nakai in the study described above: restoration of normal Schwann cell: axonal interaction was achieved by administration of a Rac-specific inhibitor with a consequent reduction in schwannoma volumes. In humans, Plotkin (2009) has treated patients with advanced NF2 with beficizumab (an anti-VEGF antibody), and shown evidence of both tumour volume reduction and hearing improvement. Although none of these therapeutic avenues are

currently routinely employed in the management of sporadic vestibular schwannomas, beficizumab is increasingly offered to problematic cases of NF-2 and it may be that this treatment will in time play a part in the management of sporadic tumours.

Risk factors for vestibular schwannomas: radiation exposure due to mobile telephones

Beyond NF-2 abnormalities, there are no well-established risk factors for the development of vestibular schwannomas, although there is a developing literature that suggests an association between the use of mobile telephones and vestibular schwannoma. Hardell (2009) recently reported a series of studies examining an association between mobile telephone usage and neoplasms of the brain. These studies attempt to determine laterality of tumour and (through questionnaires), laterality of mobile or cordless telephone usage. Results are presented according to the age of onset of mobile telephone usage. Interestingly, Hardell reports a significant association between laterality of telephone usage and laterality of vestibular schwannoma (replicated in astrocytoma) in patients with mobile telephone usage beginning before the age of 20 years (OR 6.8, CI 1.4-34). A weaker association (OR 3.0, CI 1.4-6.2) was also found in patients with a later onset of mobile telephone usage.

Hardell's findings are only partly supported by other studies: Shoemaker (2005) found a weak association between usage and ipsilateral vestibular schwannoma development in those patients with an exposure greater than ten years (OR 1.8, CI 1.1-3.1), but no association in overall usage (OR 0.9, CI 0.7-1.1). The confidence intervals in Hardell's data belie the smaller number of patients available for analysis in the high risk group of patients, but the rapid expansion in mobile telephone usage in all age groups and particularly among the young suggests that data

may become more solid in time, and that mobile telephones may prove to be a significant risk factor for vestibular schwannoma development.

Epidemiology

Incidence

The incidence of vestibular schwannomas has been a topic for debate for a number of years and it is generally considered that a rising incidence represents an increasing detection of previously occult tumours (although recent evidence detailed above describing a proposed association between vestibular schwannomas and mobile telephones may cast doubt upon this assertion). Rosenberg (2000) cites a review of 1,400 temporal bones by Shuknecht (1977) that found an prevalence of 570:100,000 vestibular schwannomas at post-mortem (it is unclear whether these were asymptomatic or not). This relatively high prevalence (suggesting an annual incidence of approximately 7:100,000) is contrasted with a clinically significant annual incidence of 1:100,000 reported by the National Institute of Health Consensus Statement (NIH Consensus Statement 1991), and Rosenberg suggests that a ‘true’ incidence is likely to lie somewhere between these two figures. The concept that a significant number of vestibular schwannomas are found at post-mortem without having caused morbidity or mortality is central to the concept of conservative management of tumours that are diagnosed and will be discussed in greater depth below.

In addition to the argument advanced above, strong evidence of a rising incidence of identified vestibular schwannomas has been provided by the Danish group led by Professor Tos. This group is the only medical team serving the Danish population with vestibular schwannoma and

can therefore reasonably claim that any change in referral numbers represents a change in incidence (or at least detection) of vestibular schwannomas nationally. Tos (2004) analyses referral rates over time and calculates incidence based upon a Danish population of 5.2 million people. In consecutive periods (1976-83, 1983-90, 1990-95 and 1996-2001), the calculated incidence rose from 0.8:100,000 in the first period to 0.9, 1.2 and 1.7:100,000 in subsequent years. This increasing incidence is reflected in a trend towards the identification of smaller tumours: in the same time periods detailed above, the median size of extrameatal tumours fell consistently from 28mm in 1976-83 through 25mm, 18mm to 15mm in 1996-2000.

A similar change in incidence as detected by referral patterns is found in the United Kingdom, although the lack of a single referral centre or robust pooled data precludes the analysis described above. In the database detailed in this thesis, annual referrals have increased steadily in number from a level of 28 tumours in 1998 to 124 in 2008 (detailed below). Although an incidence cannot be helpfully calculated from this figure due to the confounding factor of an undoubtedly expanding population base in the context of the relatively fluid referral pattern that exists in the United Kingdom, it would seem reasonable to expect that there is some genuine increase in incidence of detected tumours demonstrated by these figures.

Whether this perceived increase in incidence will continue to rise or has reached a plateau is unclear. It may be that - as argued by Moffat (2004) - incidence will stabilise as facilities for investigation (in particular magnetic resonance imaging (MRI)) are available freely to all clinicians. A contrary view might be that increasingly available healthcare and a more medically aware population lead to presentation of a larger number of patients with milder

symptoms than hitherto. It may be that if this occurs, the clinical incidence of vestibular schwannomas will reflect the post mortem prevalence described by Shuknecht.

Sex distribution

Traditional opinion has maintained that vestibular schwannomas are more common in females than males with a ratio of 2:1 (Zülch, 1986, cited by Nager, 1993). In our experience, there is very little sex difference at presentation: in our database of 730 patients with vestibular schwannoma, 371 (51%) of patients are female, 359 (49%) are male. Other series suggest a very slight tendency towards a female bias, but one less significant than that suggested traditionally: in a series of 1000 surgically managed tumours, Samii (1997) describes a sex distribution of 54% female and 46% male patients; Bakkouri (2009) finds 53:47% F:M ratio in conservatively managed patients; and the Danish group described above reports a 52% female proportion in a total database of 2283 patients (Stangerup, 2009, personal communication).

Age at presentation

In our series, the mean age of presentation is 56 years, with a range 18-88 years. Although presentation in the third decade is rare in our series (3%), presentation is well-distributed over the 4th, 5th, 6th, 7th and 8th decades, with the majority of patients presenting in the 6th and 7th decades (27% and 26% respectively). Vestibular schwannomas in children are very rare, and will usually form part of an NF-2 syndrome.

Clinical features of disease: symptomatology

Traditionally, the symptoms produced by vestibular schwannomas are considered to be either otological or neurosurgical. Patients will often present with a combination of symptoms, and otological symptoms will almost always precede neurosurgical compromise, with the latter rarely found in smaller tumours. The reporting of symptoms in the literature is variable, and it is likely that, particularly in retrospective analyses, the quality of data is questionable. It is unusual that studies will report symptomatology as a primary outcome, and little detail is offered describing definitions or severity. A further confounding factor is whether the symptom reported is seen as the ‘dominant’ symptom within a constellation, or as the only symptom (a rare occurrence in our experience).

Otological symptoms

These are characteristically unilateral, and form the basis for radiological screening guidelines (see below). Samii (1997) reports unilateral hearing loss as occurring in 95% of patients and Glasscock (1997) in 85%, and these figures concord with our experience of 90% of patients presenting with unilateral hearing loss as at least one of their symptoms. Generally, hearing loss is progressive and thought to occur due to a combination of compression of the cochlear nerve by the growing tumour and a degree of ischaemia caused by compromise of the cochlear blood supply (Prasher, 1995). On rare occasions (less than 1% in our database), hearing loss may be sudden in onset. In common with other sensorineural hearing losses and in contrast to conductive hearing loss, the functional hearing loss as measured by speech discrimination thresholds is often more severe than that suggested by pure tone audiometry (Van Dijk, 2000).

Tinnitus is the second most commonly reported symptom and will usually occur in combination with hearing loss. In our database 58% of patients reported tinnitus as a symptom, while in a small but significant number (7%), tinnitus was the sole reported complaint. Glasscock (1997) reports a slightly lower figure (42%) than that found in our database, while Bakkouri (2009) finds 4% with tinnitus alone, and a relatively small group of patients (13%) (in contradiction to our experience) with multiple symptoms.

Although the tumour derives from the vestibular nerve, patients rarely complain of balance disturbances as their primary symptom. It is generally accepted that this is because of the slow rate of tumour growth allowing the vestibular system to compensate to a gradual loss of function (Driscoll, 2000). Nevertheless, a small proportion of patients present with vertigo alone (1% in our database), and a larger group admit to vertigo or imbalance in combination with other symptoms (30%). Driscoll observes that the symptoms in these patients are probably due to incomplete vestibular compensation, and are rarely significant enough to prompt the patient to seek medical attention. A distinction should be drawn between those patients that present with a small tumour in the internal auditory canal which may cause mild symptoms of imbalance or occasional brief attack of vertigo (as described above), and those that present with ataxia due to a large tumour pressing upon the flocculus of the cerebellum: in the latter case, imbalance will often form part of a constellation of neurosurgical symptoms.

Cranial nerve symptoms

Other cranial nerves, in particular the VIIth (facial) and Vth (trigeminal) are occasionally affected, with the latter more commonly impaired. Despite its location, and in contrast to the

cochlear nerve, the facial nerve appears to particularly resistant to damage: the House Ear Clinic reported a rate of 2% facial nerve impairment (Angeli, 1997), and in our series, we have a lower rate (1.5%). Trigeminal symptoms are more common, and usually a sign of a larger tumour with a significant cerebellopontine angle component involving the under-surface of the trigeminal nerve as it emerges from the pons. Generally, the sensory roots of the nerve are affected with motor branches intact. A rate of 16.5% in a surgical series (Mathies, 1997) compares with a rate of 1% in a conservatively managed series (Bakkouri, 2009), and this is probably reflects the larger tumours found among patients undergoing surgery. In our database, 5% of all patients presented with some form of sensory trigeminal nerve impairment.

Neurosurgical complications

In a number of cases, presentation of the vestibular schwannoma is emergent, usually due to the development of hydrocephalus. Prior to the widespread availability of cross-sectional imaging, a significant proportion of patients presented with neurosurgical symptoms: Cushing (1917, cited by Driscoll, 2000) reported headache as a symptom in all 4 patients. By the latter half of the twentieth century, when cross-sectional imaging was available but limited and investigation was predominantly audiological, this had reduced to 29% (Mathew, 1978) and 38% (Harner, 1981). Currently, in our series, we find a small but significant number of patients presenting with headache or hydrocephalus (23 patients, 3% of the total database).

Interestingly, such low rates of clinical hydrocephalus may underestimate the sub-clinical prevalence. It is traditionally accepted that the hydrocephalus seen in vestibular schwannomas is of an obstructive type caused by compression of the 4th ventricle by large tumours (Driscoll,

2000). In our series, the majority of patients with clinically recognised hydrocephalus have presented with tumours greater than 3cm in size (90%), with the aetiology of the hydrocephalus presumed to be obstructive. A recent publication in the radiological literature, however, describes much higher rates of hydrocephalus in a population with vestibular schwannoma (18% of 157 patients) (Rogg, 2005). In this paper, there is a high rate of communicating hydrocephalus (61%), without a strong correlation with tumour volume (as is seen in non-communicating hydrocephalus). The authors postulate that this sub-clinical hydrocephalus may be related to tumour protein sloughing, but further research is necessary to clarify this.

Asymptomatic patients

A small proportion of patients present without any symptoms, usually following radiological investigations for other pathologies. In our series, 7 patients (1%) have presented in this manner: interestingly, none of these patients have required any management beyond serial monitoring.

Management

The aim is not to comprehensively address issues of management – this will form much of the substance of the thesis – but rather to provide an overview of the investigation and treatment of patients with vestibular schwannoma. Much of the focus of the literature searches that form the second part of this introductory chapter will address issues of management, and these will not be comprehensively addressed in this section.

Investigations

History

Historically, and before the 1980s, the investigation of suspected vestibular schwannomas was focussed upon audio-vestibular investigations supported by plain radiology enhanced with contrast dyes injected into the cerebro-spinal fluid. As detailed above, the most common presenting symptom is a unilateral hearing loss or a unilateral tinnitus. A unilateral hearing loss can be investigated with evoked audiometry (auditory brainstem response) and otoacoustic emissions (a measure of cochlear outer hair cell function) to determine whether a hearing loss is cochlear (the most common form of hearing loss) or retrocochlear (located proximal to the cochlear, and found in vestibular schwannoma). Typically, a vestibular schwannoma demonstrates inter-wave latency (between waves I and V) and inter-aural latency in the auditory brainstem response with otoacoustic emissions better than those expected by the recorded hearing loss.

A recent meta-analysis of studies assessing the sensitivity of auditory brainstem response measurement (Fortnum, 2009) concludes that, while sensitive for large tumours, the technique is less successful for smaller tumours. Pooled results produce sensitivity values of 79%, 95% and 98% for tumours sized at less than 1cm, 1cm-2cm and >2cm respectively. This failure to identify a significant proportion of smaller tumours is indicative of the fact that a positive auditory brainstem response result is dependent upon a mass effect upon the cochlear nerve, and has led to the reservation of the technique as a second-line investigation.

Current investigative strategies

An essential dilemma that has complicated the investigation of patients with a unilateral hearing loss or unilateral tinnitus is the fact that, while the symptoms that are caused by a vestibular schwannoma (unilateral hearing loss, tinnitus or vertigo) are common, the tumour itself is rare (despite the rising apparent incidence discussed above). Harcourt (1999) has demonstrated that 20% of patients attending a general ear, nose and throat clinic have symptoms that could be caused by a lesion at the cerebellopontine angle. This reflects a calculated national prevalence of hearing asymmetry in the United Kingdom of 2.9% (Davis, 1995, cited by Fortnum, 2009).

To address this issue, clinical effectiveness guidelines have been developed by the British Association of Otolaryngologists, Head and Neck Surgeons (now ENT-UK) with the aim (among others) of directing the investigation of patients with symptoms suggestive of a vestibular schwannoma (BAO-HNS, 2002). These guidelines advise investigation of any patient with either hearing asymmetry or unilateral tinnitus. The guidelines also recommend that investigation of patients with facial numbness or imbalance unexplained by another diagnosis should be considered for investigation.

No explicit thresholds for hearing asymmetry are advised in these guidelines, and a variety of protocols exist that offer subtly differing criteria for radiological investigation (see Table 2). These protocols vary in the ‘yield’ of vestibular schwannomas detected, depending upon the audiological criteria imposed. In our series, a significant number of patients have been identified who, for example, fell outwith the Charing Cross guidelines: this issue is discussed below (see Chapter 3).

Table 2. Protocols for the investigation of hearing asymmetry

Protocol and reference	Clinical criteria	Threshold asymmetry	Proportion of positive results
Sunderland (Dawes, 1998)	Unilateral tinnitus, Meniere's disease symptoms	≥ 20 dB in two neighbouring frequencies	0.3%
Charing Cross (Snelling, 2007)	None	≥ 15 dB in any two neighbouring frequencies or ≥ 20 dB if hearing impaired > 30 dB in better hearing ear	4.3%
Oxford (Sheppard, 1996)	Unilateral tinnitus, > 70 years of age	≥ 15 dB mean of frequencies between 0.5 KHz and 4 KHz	0.4%

Further investigation is recommended with MRI in the BAO-HNS guidelines referenced above, and this is supported by Fortnum's recent economic analysis of investigative strategies (Fortnum, 2009). A number of different MRI techniques are available, the most common being 'T1' (longitudinal relaxation time constant) with contrast enhancement (gadolinium), and 'T2' (transverse relaxation time constant) without contrast. Within T2 are a number of subtly differing techniques that can all be used to image vestibular schwannomas ('Constructive interface steady state' (CISS), 'Fast imaging employing steady state acquisition' (FIESTA)). The gold standard test is generally considered to be T1 weighting enhanced with gadolinium but

increasingly, T2 techniques are found to have comparable sensitivity: Fortnum's meta-analysis of studies produced a pooled sensitivity of 98% (Fortnum, 2009). There are considerable cost benefits in employing T2 in preference to gadolinium-enhanced T1 imaging, both in terms of reduced cost of materials, reduced time, and in particular because patients undergoing imaging without contrast enhancement do not require the supervision of a medically trained radiologist.

Treatment

History

For the majority of the 20th century, the mainstay of treatment of vestibular schwannomas was surgical, usually involving the excision of large tumours presenting with neurosurgical symptoms. Cushing (1917, cited by Driscoll, 2000), credits Thomas Annandale, a surgeon in Edinburgh, with the first successful removal of a vestibular schwannoma from a pregnant patient, who later successfully gave birth to a healthy child. Subsequent attempts in the early 20th century were characterised by high mortality rates of over 50%, although Cushing himself was able to achieve a rate of 21% (Cushing, 1917, cited by Driscoll, 2000). Driscoll observes that Cushing's relative success could be attributed to his surgical skill and (Cushing's own words), a 'celerity of execution'. As the century progressed, a second neurosurgical pioneer, Dandy, was able to reduce the mortality rate further (to 11%) with improved technique as more sophisticated anaesthetic and haemostatic techniques allowed for a longer operative time (Dandy, 1941, cited by Driscoll, 2000).

Incremental developments in technique were substantially enhanced by the introduction of the operating microscope in 1961 by House and Doyle (Driscoll, 2000). The operating microscope,

combined with high-speed drills, microsurgical instruments and the concept of a team surgical approach between neurotologist and neurosurgeon, has led to a situation currently where mortality is rare, and the surgical goals have become focussed upon the preservation of neural function (facial and auditory). The complications and results of surgical treatment are discussed below in the literature search.

Table 3: Outline of management strategies for tumours of differing size and hearing status at Queen Elizabeth Medical Centre, Birmingham

Tumour size and hearing function	Management	Caveats
Intracranial, non-hearing	Conservative, radiosurgery if tumour growing	Some may advocate primary treatment, either surgery or radiotherapy
Intracranial, hearing	Conservative, radiosurgery if tumour growing	Many would advocate hearing-preserving surgery
0-2cm in cerebellopontine angle (hearing or non-hearing)	Conservative, radiosurgery if tumour growing	Many would argue an upper limit of 2cm for conservative management too large, similar debate as above re. hearing preservation surgery
>2cm, <3cm in cerebellopontine angle	Either radiotherapy or surgery, depending upon patient choice	Many would offer only surgery
>3cm in cerebellopontine angle	Surgery (translabyrinthine or retrosigmoid)	Non controversial

Current practice

Current practice consists of three treatment modalities: surgery, radiotherapy, and conservative (sometimes called ‘watch and scan’) management. The aim of this introduction is not to discuss in depth the merits of each individual technique – this will be addressed in literature searches that follow and the substance of the text – but rather to give a broad overview of current techniques in order to provide a context for subsequent discussions.

Management varies considerably in different medical jurisdictions and in different neurotological centres, influenced in part by available expertise and equipment and in part by medical philosophy, an understanding of the medical literature and healthcare economics. There is therefore limited consensus about the ‘correct’ way to manage vestibular schwannomas. In Table 3, management in our centre is outlined, with caveats to indicate areas of controversy, and recognition that management of the individual patient is dependent upon an informed discussion between clinician and patient, rather than dictated by medically devised protocols.

Surgical approaches

Three surgical approaches are commonly used to extirpate vestibular schwannomas: the translabyrinthine, middle fossa, and retrosigmoid. The choice of approach will depend upon tumour factors (size, location and hearing status), and upon surgeon factors (personal preference and experience). Table 4 outlines some of the advantages and disadvantages of each approach. The post-operative results of different surgical techniques, and results in our own series of surgically treated patients will be discussed in greater detail below.

Table 4: Summary of advantages and disadvantages of different surgical approaches (after Driscoll, 2000)

Approach	Advantages	Disadvantages
Translabyrinthine	<p>Good access to tumours of any size</p> <p>Early lateral identification of facial nerve with good rates of preservation</p> <p>Low rates of post-operative cerebro-spinal fluid (CSF) leak and headache</p>	<p>Inability to preserve hearing</p>
Retrosigmoid	<p>Ability to preserve hearing</p> <p>Can remove larger tumours than middle fossa approach</p> <p>Approach familiar to neurosurgeons</p>	<p>Poor access to fundus (lateral limit) of internal auditory canal</p> <p>Higher risk of post-operative headache and CSF leak.</p>
Middle fossa	<p>Better results for hearing preservation than retrosigmoid</p> <p>Good exposure of lateral IAC tumours</p> <p>Low risk of post-operative CSF leak and headache</p>	<p>Limited to small tumours of the IAC</p> <p>Risk of post-operative epilepsy</p> <p>Difficult to preserve facial nerve</p>

Although mortality is rare in the modern era (in our series, <0.5%), even an uncomplicated procedure represents a significant trauma for the patient. Pritchard (2003) reported that one-third of patients were unable to work following surgery for at least six months and calculated that the mean loss of income to patients undergoing surgery for vestibular schwannomas was

£11,220. 40% of patients were depressed post-operatively, and 75% expressed anxiety that they 'would ever be the same again'. The majority of patients who are treated surgically will lose residual hearing, and among those for whom hearing preservation is attempted, this is successful in only 50% (see below). A degree of facial nerve impairment is found in most cases, even if only temporarily, with results reflecting the size of the tumour (Mamikoglu, 2002). Other complications include cerebrospinal fluid leak, imbalance, headache and facial numbness (Driscoll, 2000).

Radiosurgery

Radiosurgical techniques were first introduced in the 1950s (Leksell, 1951, cited by Driscoll, 2000), and over the past two decades have become increasingly popular in the management of vestibular schwannomas. The principle of radiosurgery is to deliver a single fraction of high-dose radiation to the tumour with the aim of arresting tumour growth. The patient's head is fixed in a stereotactic frame that allows the accurate planning of the delivery of ionising radiation in multiple doses to conform to the contours of the tumour (Rowe, 2008). In general, the tumour undergoes a period of oedematous swelling after the delivery of the radiosurgery, and then subsequently either reduces in volume or remains static. Two forms of radiosurgical treatment are commonly used: gamma-knife - which employs gamma radiation - and linear accelerator (LINAC) - which uses x-rays. Details of tumour control rates, complications and controversies will be discussed below.

Conservative management

Over the course of the past 3 decades, conservative management has become an increasingly popular management option for treating vestibular schwannomas measuring less than 2cm in the cerebellopontine angle. The practice depends upon serial monitoring of the tumour, with definitive intervention - or in some cases, continued observation - in those cases that demonstrate growth. Initially proposed as a treatment modality to manage those patients who are unsuitable for definitive treatment due to old age or medical co-morbidities (Wazen, 1985, Nedzelski, 1986), a period of observation to prove active tumour growth has become standard practice in almost all small and many medium-sized tumours. A detailed discussion of the literature pertaining to the conservative management of vestibular schwannomas follows.

Literature search

The aim of this literature search is to carry out a systematic review of the literature pertinent to topics raised in this thesis. Situating this literature search in the introduction to the thesis will allow the reader to refer back to this section while reading forthcoming chapters, and avoid repetition of material.

There are two main topics addressed in this literature search:

- the natural history of tumour growth (a review of published series of conservatively managed vestibular schwannomas).
- the status of hearing in vestibular schwannomas treated by the three modalities most commonly used (observation, radiosurgery and microsurgery).

Search strategy

A Pubmed search was carried out using the MeSH terms ‘vestibular schwannoma, acoustic neuroma and acoustic neurinoma’ for titles containing the words: ‘watch’, ‘conservative’, ‘wait’, ‘growth’, ‘surveillance’, ‘hearing preservation’, ‘radiosurgery’ and ‘microsurgery’. All articles identified were case series, representing level 3 evidence, and none were excluded for reasons of methodological quality. Series that contained less than 50 patients were excluded in most cases, as were those written in a language other than English. Due to the heterogeneity of the studies and the lack of randomised, controlled trials, formal meta-analyses were not attempted.

Table 5: Summary of published series of conservatively managed patients with vestibular schwannomas

Reference	Centre	Period of data collection	N	Mean age	Follow-up (months, (range))	Percentage growth	Growth rate	Factors predictive of growth	Loss to follow-up	Tumour measurement technique
Malhotra, 2009	Philadelphia, USA	1997-2007	202	60	2.5 (1-192)	9.4% failed	No details	Larger tumours, disequilibrium	10% (time of presentation to most recent treatment)	Largest linear dimension of tumour in any direction
El-Bakkouri, 2009	Paris, France	1990-2005	386	58	Range 12-108 (no mean given)	24% failed, 8% had growth >3mm per year	1.15 mean, 10% growth rate >3mm per year	Short duration of symptoms	16% lost to follow-up at 1 year	Largest diameter outside the IAC
Hajihoff, 2008	Toronto, Canada	1987-98	72	61	121	35% failed	1 mm overall	Larger tumours	3%	Square root of product of maximum AP and ML dimensions (axial scan)
Ferri, 2008	Bologna, Italy	1981-2006	123	61	56	35.5% growth	1.2mm in growing tumours, 0.3mm overall	Short duration of symptoms, CPA tumours and tinnitus	2% (but no definition)	Tumours measured along 3 axes, and recorded as greatest dimension: IAC included
Al Sanosi, 2006	Sydney, Australia	1989-2005	205	61	41	34% growth	No rate given	None	4% excluded because follow-up less than 12 months	No details of measurement technique given
Battaglia, 2006	San Diego, USA	1986-2004	111	71	38	51% growth	0.7mm overall	Larger tumours more likely to grow than IAC tumours	No details but patients excluded if less than 1 year of follow-up recorded	Square root of product of maximum AP and ML dimensions (axial scan)
Grayeli, 2005	Clichy, France	1991-2002	111	59	33	47% growth	1.1mm overall, but gives full break-down	None	17%	Greatest diameter on axial scan including IAC component
Flint, 2005	Auckland, New Zealand	1992-2003	100	61	26	36% growth (80% in 1st year)	2.7mm, with breakdown of cases	None	No details	Largest measured diameter in CPA, IAC excluded
Hoistad, 2001	Chicago, Illinois, USA	1982-99	102	64	29	44% growth	2.2mm (growing tumours only)	None	4 patients with growing tumours lost to follow-up.	Largest diameter on a single image (usually from the porous acousticus to the brainstem)
Shin, 2000	Toulouse, France	1989-98	87	63	31	53% growth	1.5mm all patients	None	20%. Good follow-up defined as at least 2 MRI scans	Mean of sum of largest AP and ML dimensions (axial scan), including IAC

Table 5 (cont'd): Summary of published series of conservatively managed patients with vestibular schwannomas.

Reference	Centre	Period of data collection	N	Mean age	Follow-up (months, (range))	Percentage growth	Growth rate	Factors predictive of growth	Loss to follow-up	Tumour measurement technique
Tschudi, 2000	Zurich, Switzerland	1989-94	74	53	35	31% growth	2.7mm mean in growing tumours, max growth 7.7mm	None	7% with inadequate follow-up excluded	Greatest axial dimension along long axis of the IAC
Deen, 1996	Arizona, USA	1983-92	68	67	41	29% growth, 15% requiring treatment	3.0mm in tumours requiring treatment, 0.72mm in overall group	No details	32% did not attend after first presentation	Not given
Strasnick, 1994	Norfolk, Virginia, USA	1979-1992	51	68	30	24% failed surveillance	1mm overall, 3.5mm in tumours failing surveillance	No details		Mean of greatest AP and ML diameter (IAC inclusion not specified)
Stangerup, 2006	Copenhagen, Denmark	1975-2005	729	59	43	24% growth	Growing tumours: high (10mm intra- and 5mm extra- if grew in first year, less if discovered later	More common in larger tumours (ie extra-meatal)	Not recorded	Largest extrameatal dimension
Fucci, 1999	Fort Myers, Florida, USA	1988-1996	119	65	30	30% growth, 18.5% underwent treatment	1.2 mm overall, growing tumours, 3.5mm	Larger tumours (>20mm more likely to grow	No details, but excluded some patients with inadequate data prior to analysis	Longest dimensions on a film (including IAC)
Mohyuddin, 2003	Manchester, UK	No details	50	NA	17	41% definite growth, a further 38% probable growth	3mm in growing tumours	None	Some lost to follow-up, but no details given	Volumetric measurements, also maximal tumour diameter (no further details)

The natural history of tumour growth

The studies identified by the literature search are summarised in Table 5 above. A number of issues related to the quality of data are instructive and these are discussed here, followed by a presentation of the salient findings from the literature search.

Critique of existing literature

Population selection bias

Perhaps the ideal study to explore the natural history of vestibular schwannoma growth would be a cohort study. In such a study, all patients with tumours of a certain size would be entered into the study and then monitored using a standardised imaging protocol. In most of the studies identified in the literature search, however, there is a bias towards monitoring patients who are either elderly or medically unfit, and hence not thought to be ‘good’ surgical candidates.

Interestingly, this bias is perhaps not as marked as might be expected: although the majority of authors cite old age as an important indication for conservative management, the mean age of patients in the series presented in Table 5 (61 years) is only 5 years older than the mean age of all patients presenting to our service (56 years). The cause for this discrepancy is not clear: it may be that authors rationalise their use of conservative management as a treatment for the elderly, while the reality is that it has become a standard treatment for the majority of small to medium-sized tumours. This is clearly demonstrated in Grayeli’s paper (2005):

“Conservative management was chosen in patients aged >60 years or in those for whom surgery was contraindicated or refused. This group comprised 49 males and 62 females... with a mean age of 59 years (range 19-87)...”

As will be described below, one strength of the database presented in this thesis is a lack of population bias in the selection of patients for conservative management, although as seen by the above quotation, the apparent population bias in the literature as a whole may not be as genuine as that suggested at first sight.

Follow-up

Effective follow-up is an essential element of conservative management, and an important part of the consultation with a patient considering conservative management is emphasising the importance of compliance with serial imaging and clinical review. It could be argued that the mark of an effective conservative management regime is the integrity of its follow-up: patients should be monitored regularly until the clinician is confident the tumour is not growing and then less frequently, but few would argue that any but the most elderly patients with stable tumours should be discharged. Unfortunately, there are considerable defects in the existing literature in terms of accurate and clear description of the definition of follow-up, and in the reporting of compliance.

Loss to follow-up is not consistently defined. In a number of series (Fucci, 1999, Tschudi, 2000, Battaglia, 2006), patients with inadequate serial follow-up are excluded prior to

analysis, thus preventing a calculation of a loss to follow-up rate. In those series that do admit to a loss to follow-up, the definition of ‘loss’ would seem to be very generous: an inclusion criterion often mentioned is that of having undergone at least two MRI scans; those that do not fulfil this criteria are then considered ‘lost’ (Shin, 2000, Al Sanosi, 2006, El Bakkouri, 2009). While it is true that these patients with at least two MRI scans have been seen more than once, it is difficult to argue that a patient seen in (for example) 1998 for the first time and then reviewed in 1999, is not ‘lost’ if the series is reported in 2005. Such a patient could quite easily have a very slow growing tumour that was not detected in 1999, but was falsely reassured and is now at some risk.

The effect of the loose definitions applied to follow-up in the series reporting conservative management is to give reasonably positive figures for loss to follow-up (see Table 5), but the true nature of follow-up in these series is belied by the duration reported. Although rarely explicitly defined, it is implied that ‘follow-up’ is calculated by measuring the time between the first MRI scan (i.e. at presentation), and the most recent scan reviewed. The duration of follow-up often sits oddly with the study recruitment period: thus Ferri (2008) reports a series of patients recruited over 25 years with a mean follow-up of only 56 months. Even assuming that a disproportionately large proportion of the patients studied were recruited in latter years, this short duration of follow-up suggests a considerable number of patients are not being followed-up routinely and that the loss to follow-up rate of 2% has been generously calculated.

'Front-loading' of series

While the detailing of a lack of follow-up has safety issues as outlined above, there are also important confounding factors that may confuse an appreciation of the natural history of vestibular schwannomas. It is well-recognised that the growth of a significant number of tumours is very slow: the mean calculated rate for all tumours is described in most series as in the region of 1mm annually (see Table 5). For this reason, a number of tumours only reveal themselves as 'growing' tumours after a number of serial MRI scans. If series report large numbers of patients with a short period of follow-up, there is a risk that a considerable proportion of tumours that are slow-growing are registered as 'not-growing'.

A close examination of El Bakkouri's data (2009) reveals the extent to which patient numbers are often concentrated in the early years of follow-up:

- initial number of patients (and publication 'headline') = 386
- number of patients following exclusion of those without at least 2 scans = 325
- number of patients with 3 scans = 160
- number of patients with 4 scans = 56
- number of patients with 5 scans = 21
- number of patients with 6 scans = 8

The stated surveillance regimen for this study is as follows:

- initial scan at presentation
- a first follow-up scan at 1 year
- a further scan at 1 year if the tumour demonstrated slow growth, scan at two

years if growth not seen

- further scans every two years if no growth seen

Given this surveillance regime, and the fact that the study recruited between 1990 and 2005, it is surprising that only 8 patients underwent 6 MRI scans.

Assuming a change in practice shifting towards conservative management over time, it might be expected that less patients might be allocated to surveillance in the period 1990-1995 than in 2000-2005, but if it is assumed that only 50 patients were recruited during this period (13% of the total number of patients included in the study), it would be reasonable to expect all of these individuals (unless diverted to definitive treatment) to have undergone at least 6 scans. The fact that only 8 patients are reported in this group suggests a significant loss of patients to follow-up, and hence a potentially confoundingly low estimation of the risk of tumour growth.

Definition of tumour growth

There is considerable heterogeneity seen in the definition of tumour growth in the series presented in Table 5. In some cases, the primary outcome measure is ‘failure of conservative therapy’, in others ‘tumour growth’. It is important to recognise that these two terms are not synonymous: patients may elect to have definitive treatment in the absence of tumour growth due to other symptoms, or in many cases, the clinician and patient will tolerate very slow growth and elect to continue monitoring the tumour.

Recording of growth rates

The definition of tumour growth is variable in the series examined. In many series, a helpful distinction is drawn between ‘growing tumours’ and ‘static tumours’, while in others, a mean growth rate for all tumours is produced (see Table 5). This has been discussed in the literature previously (Martin, 2005), and has led to the under-estimation of growth in meta-analyses (Smouha, 2005). A concentration upon mean growth rates is perhaps less helpful clinically than a recognition of the range of potential rates of growth - in our series, we have seen rates of growth of almost 20mm annually in a very small number of conservatively managed patients – a recognition that a number of tumours show an aggressive biology is more beneficial than a calculation of mean growth rates when a considerable proportion of the calculation involves tumours that do not grow at all.

Tumour measurement technique

A number of different techniques are used to determine tumour size. The most common (but only appearing in two series) is that recommended by the 1995 guidelines produced by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)(AAO-HNS, 1995). In these guidelines, the tumour dimension is calculated as the reciprocal of the product of the maximal anteroposterior and mediolateral dimensions on axial scan ($\sqrt{(AP)(ML)}$). There are many other techniques employed with subtle variation, as demonstrated in Table 5.

Although consistency may aid a confident estimation of tumour growth rates, probably more important is the quality of measurements carried out, and unfortunately none of the described studies employ a quality-controlled measurement system such as independent calculations made by two individual assessors.

Long time period covered by studies

It is noticeable that a number of the studies report periods of data collection extending over a number of years. Stangerup (2006) reports over 30 years, Ferri (2008) over 28 years; the majority of groups report series with a recruitment period of 10-15 years (see Table 5). Such long periods of time carry risks for confounding factors. It is noticeable, for example, that a number of studies (especially those recruiting before the mid-1980s) employ both computed tomography (CT) studies and MRI in assessment of tumour size and location. There is also a probability of considerable clinician heterogeneity during such an extended time period, leading to likely inconsistency in tumour measurement techniques or recording of symptoms. It is one of the strengths of the series reported in this thesis that a large population has been recruited over a relatively short period of time, allowing predominantly homogenous data collection.

Conclusions from reviewed publications

With the above reservations noted, it is possible to draw a number of tentative conclusions from the published data assessing tumour growth rates and risk factors for tumour growth.

Tumour growth

As is seen in Table 5, there is a range of rates offered between 10 and 55% for either ‘tumour growth’ or ‘failure’ of conservative management, with a coalescence around a figure of approximately 30-35%. As noted above, however, questions of data quality, in particular questions of follow-up, call a number of series’ results into question. One series that offers sound follow-up data is that reported by Hajihoff (2008): this series (although relatively small), is collected prospectively and offers a mean follow-up (121 months) that is both consistent with

the period of data collection and significantly has a range that begins at 80 months, thus avoiding the confounding effect of ‘front-loading’ described above. A further strength of this series is a relatively low rate of loss-to-follow-up of 6%, although a weakness is that this is not explicitly defined.

In Hajihoff’s series, the overall rate for ‘failure’ of conservative management is 40% (this includes those lost to follow-up, the rate would be 35% without this group). Interestingly, the reported rate of tumour growth is higher: 40% are reported as demonstrating ‘significant growth’ of >1 mm per year, suggesting that a small number of patients with growing tumours are being managed conservatively. 38% are described as demonstrating growth of <1mm per year, and this is described as ‘non-significant’. A further 22% have negative growth rates of <0mm per year. This growth rate is higher than that reported by the largest series reported to date in the literature (Stangerup, 2006) (24%), but this may be explained by the relatively low rate of follow-up in the latter study (43 months in a study collecting tumours over 30 years).

Factors predictive of growth or failure of conservative management

This issue is one that is important for advising patients considering conservative management and valuable for clinicians debating conservative or definitive treatment in ‘borderline’ cases. In those series that address the issue, two consistent factors seem to suggest growth: tumour size and a short duration of symptoms are predictive of growth in a number of papers (see Table 5).

Tumour growth rates

As discussed above, a consistent definition of tumour growth is difficult to obtain. Series that break tumours into groups of 'growing' tumours to calculate a mean growth rate suggest a mean of 3mm annually in most cases. Those that consider all tumours together will provide a mean growth rate of 1mm.

The status of hearing in managed vestibular schwannomas (a review of hearing outcomes with different treatment modalities).

The management of the hearing patient with a small-medium-sized vestibular schwannoma is perhaps the most controversial area of management, and hence one where there is considerable diversity of practise among clinicians. The aim of this literature search is to review the evidence for the natural history of hearing progression in watched vestibular schwannomas.

Hearing preservation in conservatively managed patients

In common with those papers discussed above addressing the natural history of tumour growth (many are the same series, and often the same studies), much of the data pertaining to hearing status is problematic, and this section will begin with a discussion of methodology in the various studies summarised below. In many papers, clarity is compromised because hearing data is included with other data pertaining to tumour growth, often with a different sub-set of patients considered, and rarely a separate discussion of, for example, follow-up within the group of patients in whom hearing is addressed.

Hearing Classification

The majority of studies use the classification system proposed by the American Academy of Otolaryngology-Head and Neck Surgery (1995) to determine whether hearing is ‘serviceable’ or not. This system employs both pure tone audiometry (PTA) and speech discrimination studies (SDS), and is summarised in Table 6 below. A further classification system is the Gardner-Robertson (1988), a system that emphasises speech discrimination and in which there are four

grades (I-IV, corresponding to A-D in the AAO-HNS classification). This latter classification is used more frequently in the literature relating to radiosurgery.

Table 6: American Academy of Otolaryngology – Head and Neck Surgery Classification of Hearing (1995)

Class	Pure-Tone Thresholds (Average of 0.5, 1, 2, 3 kHz)	Speech Discrimination (%)
A	30dB or less and	70 or greater
B	30dB or less and	50-69
B	30-50dB and	50 or greater
C	>50dB and	50 or greater
D	Any level	Less than 50

Follow-up

As found in the discussion of the natural history of tumour growth, the importance of the duration of follow-up and its documentation is central to a critical appraisal of the studies described. Unfortunately, as outlined above, many of the studies that appear in Table 7 and discuss hearing preservation also appear in Table 5. In these studies, hearing preservation is often reported as a secondary outcome, and it is often difficult to calculate duration of follow-up of hearing results distinct from follow-up of tumour surveillance. In Table 7, an attempt has been made to clarify these questions.

Table 7: Summary of hearing outcomes in published series of conservatively managed vestibular schwannomas

Reference	Centre	N	Mean age	Follow-up (months, (range))	Classification of hearing	Patients (%) with serviceable hearing at presentation	Evolution of hearing over period of observation	Patients with inadequate data for assessment (%)	Factors predictive of hearing loss
Malhotra, 2009	Philadelphia, USA	202	60	2.5 (1-192)	Mean pure-tone audiometry levels only given	No classification, mean pure-tone audiometry levels only given	Deterioration of existing hearing: 20%	6% either had no post-diagnostic MRI or no post-diagnostic audiogram	Tumour growth
El-Bakkouri, 2009	Paris, France	386	58	Range 12-108 (no mean given)	AAO-HNS	Class A: 34% Class B: 17	Deterioration in hearing of those with Class A or B hearing at presentation: 3 years: 14% 5 years: 15% (these figures not cumulative)	56% without initial diagnostic audiogram. Follow-up data available at 3 years for 140 patients (88%), at 5 years for 47 (84%) patients.	No association with tumour growth
Ferri, 2008	Bologna, Italy	123	61	54 (no range)	AAO-HNS	Class A or B: 46%	Maintaining Class A or B (percentage of group initially presenting): 73%	All patients included	No association between growth and hearing loss seen
Stangerup, 2008	Copenhagen, Denmark	636	58	47 (4-126)	AAO-HNS, Meyer word recognition scoring system	Class A: 20% Class B: 29%	Maintaining Class A (as a percentage of those presenting with Class A hearing): 48% Maintaining A or B (as a percentage of those presenting with Class A or B hearing): 49% Patients dropping at least 1 AAO-HNS Class: 35%	14% with no post-diagnostic audiogram.	100% speech discrimination score at presentation predictive of greater rates of hearing preservation. No association with hearing loss and tumour size. Tumour growth (low frequencies).

Table 7 (cont'd): Summary of hearing outcomes in published series of conservatively managed vestibular schwannomas.

Reference	Centre	N	Mean age	Follow-up (months, (range))	Classification of hearing	Patients (%) with serviceable hearing at presentation	Evolution of hearing over period of observation.	Patients with inadequate data for assessment (%)	Factors predictive of hearing loss
Hajioff, 2008	Toronto	72	-	121 (median, range 80-272)	Mean change in PTA	-	Mean change in hearing from baseline 35.6 dB	18%	Growth
Grayeli, 2005	Clichy, France	105	59	33 (6-111)	AAO-HNS	Class A: 23% Class B: 18% Class C or D: 58%	Maintaining Class A or B as a percentage of group at last follow-up visit: 8%	17%	Tumour growth
Flint, 2005	Auckland, New Zealand	79	No details	No details	AAO-HNS	Class A: 28%	Maintaining Class A (as a proportion of those presenting with good hearing): 66%	32% (of those with good hearing)	No details
Tschudi, 2000	Zurich, Switzerland	70	53	No details	AAO-HNS	Class A: 21% Class B: 27%	Maintaining Class A: 67% Maintaining A or B: 65% Percentages refer to a percentage of those with initially good hearing.	5% of total	

Hearing loss in observed vestibular schwannomas

As is indicated by Table 7, there is a general trend towards a decline in hearing in patients managed conservatively over time: of the 50% of patients that present with ‘serviceable’ hearing, a significant proportion will lose this over the relatively short period of follow-up described in the series presented. Thus, Stangerup (2008) reports that approximately 50% of patients with serviceable hearing maintain this. Tschudi (2000) reports that a proportion of 65% approximately maintain hearing that is useful over the period studied. Unfortunately, neither author details follow-up within each group: hearing preservation may simply be a reflection of shorter follow-up.

Other studies suggest that this may indeed be the case. Grayeli (2005) details hearing results at serial visits: thus at the first visit, 41% of 105 patients tested have useful hearing (Class A or B), but by the 6th visit, only 8% of 13 patients have been able to preserve this level of hearing. Ferri’s paper suggests a similar phenomenon: patients with preservation of hearing have a mean follow-up period of 44 months, whereas those with deterioration have a mean follow-up of 80 months. Useful data to be made available would be the proportion of patients within each group that maintain static hearing, but this is rarely offered.

Risk Factors for Hearing Loss

Predicting whether a patient is likely to lose their hearing is obviously of interest to clinicians. In most series, tumour growth is associated with an increased risk of hearing loss, but this is not universally the case, and often hearing loss can occur in the absence of growth. A further indicator, suggested by Stangerup (2008) is the significance of perfect speech discrimination at

presentation: thus while in the series as a whole, Class A hearing was preserved in 48%; in those with perfect speech discrimination, this level was maintained in 80%.

Stangerup's observation, further supported by a later publication (Stangerup, 2009) recording further data from the same series, is of interest and can possibly inform the wider debate about the most appropriate management for the sub-group of patients that present with normal or near-normal hearing. The cause for this finding is not clear - and its validity is debateable (see Chapter 3 below) - but it is possible to speculate that if the process that leads to hearing loss has not begun at the time of presentation, it is unlikely to develop during a period of observation, particularly in the absence of tumour growth. The argument is sometimes made that clinicians should expedite definitive treatment of patients with good hearing to prevent further deterioration in auditory function (Meyer, 2006): this argument is undermined if, as this evidence suggests, this group of patients are the least likely to demonstrate a deterioration in hearing when observed.

Hearing preservation in surgically treated patients

Table 8 summarises a number of recent series that address outcomes in surgical treatment of vestibular schwannomas when hearing preservation is attempted. Although the series are heterogenous (in particular with reference to inclusion criteria), a number of tentative conclusions are possible:

Table 8: Surgical series detailing hearing preservation results

Reference	Centre	N	Mean age	Surgical approach	Hearing at presentation	Hearing preservation (percentages refer to total group, unless otherwise stated)	Factors influencing outcome
Yamakami, 2009	Chiba, Japan	22	51	Retrosigmoid	Class A: 50% Class B: 32% Total A or B: 82%	Class A: 9% Class B: 55% Total A or B: 64%	Nil (series of small tumours)
Samii, 2006	Hannover, Germany	200		Retrosigmoid		51% functional preservation	
Arts, 2006	Ann Arbor, USA	74	No details	Middle cranial fossa	Class A: 46% Class B: 38% Total A or B: 84%	Class A: 29% Class B: 33% Total A or B: 62%	Nil (series of small tumours)
Meyer, 2006	Iowa City, USA	162	49	Middle cranial fossa	Class A: 62% Class B: 16% Total A or B: 78%	Class A: 28% Class B: 18% Total A or B: 46%	Tumour size (larger tumours give worse outcomes) Introduction of near-field cochlear nerve action potential monitoring improved outcomes
Mangham, 2004	Seattle, USA	72	No details	Retrosigmoid	Class A: 31% Class B: 38%	Class A: 22% Class B: 26% Total A or B: 48%	Analysed results from other institutions to conclude that hearing preservation more successful with middle fossa approach than retrosigmoid
Yates, 2003	San Francisco, USA	64	45	Retrosigmoid	All tumours class A or B, no breakdown given	Class A: 0% Class B: 6% Total A or B: 6%	All tumours large (>15mm in CPA). 'Best results' with (relatively) smaller tumours
Gjuic, 2001	Erlangen, Germany	735	51	Middle cranial fossa (enlarged)	Class A: 51% Class B: 27%	Class A: 18% Class B: 14%	Strong correlation between tumour size and hearing preservation
Kaylie, 2001	Portland, USA	97	N/A	Suboccipital	Class A or B: 45%	Class A or B: 29%	Nil (small sample)
Brackmann, 2000	Los Angeles, USA	333		Middle cranial fossa		Class A: 33% Class B: 26% Total A or B: 50%	Outcomes significantly improved if pre-operative hearing better, if tumour originating from the superior vestibular nerve and if characteristic ABR findings present
Irving, 1998	San Francisco, USA	98		Retrosigmoid and middle cranial fossa		Class A or B (MCF): 52% Class A or B (RS): 17%	Comparison between two techniques found middle cranial fossa approach superior, significant association between results and tumour size
Gormley, 1997	Pittsburgh, USA	197	47	Retrosigmoid	Gardner-Robertson I or II: 39%	Gardner-Robertson I or II preserved in 48% of those in which preservation attempted	Strong correlation between tumour size and hearing outcomes

Hearing preservation rates

In most of the above series, initial pre-operative hearing is considered suitable for attempted hearing preservation (usually considered either Class A or B) in approximately 50% of cases. An excellent hearing outcome (preservation of Class A hearing in a patient presenting with this hearing level), is achieved in between 30-60% of patients. A good outcome (preservation of Class A or B) can equally be achieved in between 30-60% of individuals.

Factors determining outcomes

Two factors would seem to influence outcome in these series: tumour size and surgical approach. The most important is tumour size, with all those series including tumours of different sizes reporting a strong correlation. In Yates' series, where all tumours are of a size that would be considered an upper limit for tumour resection with attempted hearing preservation, outcomes are notably poor. A further correlation is seen between surgical approach: in a direct comparison between the retrosigmoid and middle cranial fossa approaches, both Irving (1998) and Staecker (2001) found the latter to be more likely to give a successful result, and this is confirmed by Mangham's review of 2004.

Hearing preservation in patients treated with radiosurgery and radiotherapy

Table 9 summarises recent publications describing radiotherapeutic treatment of vestibular schwannomas. In most series, the modality used is radiosurgery, or gamma-knife stereotactic radiosurgery (GKSRS). This technique consists of the administration of a single dose of high-level radiation targeted to the tumour employing high-resolution volumetric magnetic resonance

Table 9: Series describing radiosurgical hearing preservation and tumour control

Reference	Centre	Date range	Follow-up (months)	N	Type of DXT	Mean dose (marginal dose unless otherwise stated))	Selection criteria	Tumour control rate	Definition of tumour control	Hearing preservation	Complications
Pollock, 2009	Mayo Clinic, Rochester, USA	1990-2004	61	293	GKSRS	13 Gy	All patients	94% at 4 years after treatment	Tumour enlargement on two or more serial imaging studies	Not studied	N/A
Andrews, 2009	Philadelphia, USA	N/A	1st group: 12 2nd group: 15	89	FRST	1st group: 50 Gy 2nd group: 47 Gy	Patients with serviceable hearing	100% (but short follow-up)	N/A	Hearing preservation significantly more successful in lower dose cohort	N/A
Combs, 2009	Heidelberg, Germany	N/A	75 (median)	202	FSRT and GKSRS (compares two)	FSRT=57.6Gy (5X1.8 per week) SRS=13Gy	Growing tumours or progressive symptoms, 18% previous surgery	N/A	N/A	Same for both, but worse for higher doses of GKRS	N/A
Timmer, 2009	Nijmegen, Netherlands	2003-7	14	69	GKSRS	11 Gy	N/A	N/A	N/A	41% preservation of serviceable hearing, correlating with cochlea dose	N/A
Lobato-Polo, 2009	Pittsburgh, USA	1987-2003	64 (min. 4 years)	55	GKSRS	11 Gy	Young patients (<40 yrs.) 24% of patients had had previous surgery	96%	No further intervention	93% preservation of hearing in same class as pre-GKSRS	1 VII palsy (grade III), 2 cases of trigeminal neuropathy, both related to higher marginal doses given early in series
Wang, 2009 (article in Chinese: abstract only seen)	Shanghai, China	1994-2000	86	50	GKSRS	12.3 Gy	Elderly patients (range 60-80) with large tumours	94%	Reduction or stabilisation in tumour size	N/A	2 patients died due to tumour expansion post-treatment. 2 cases of facial palsy, 18 cases of trigeminal neuropathy

imaging to conform the radiation dose to the tumour bulk. Although traditional fractionated radiotherapy (FSRT) is also used to treat vestibular schwannomas (Combs, 2009, Thomas, 2007) with similar results in terms of tumour control, GKSRS offers advantages in patient convenience, and is the more commonly used technique.

Hearing outcomes

While most studies of surgical and conservative management traditionally employ AAO-HNS guidelines for reporting hearing outcomes, the majority of radiosurgical reports employ the Gardner-Robertson classification system, probably reflecting the neurosurgical (rather than neurotological) origin of these studies. As noted above the systems are equivalent, although the AAO-HNS includes audiological results in addition to the speech discrimination studies employed in the Gardner-Robertson system.

As seen in Table 9, most studies report rates of hearing preservation of between 60-80%. There is a strong correlation between hearing preservation and cochlear radiation dose seen in most series that address the issue (Timmer, 2009, Régis, 2008, Kano, 2007), as well as between hearing preservation and radiation dose generally (Andrews, 2009). Appropriately, Kano also finds better outcomes in those small tumours that are located in the medial part of the internal auditory canal: these tumours will allow radiosurgeons to avoid administering radiation to the cochlear more easily. Interestingly, Combs (2009) finds improved hearing preservation with FSRT than when high doses of marginal radiation are administered with GKSRS: it may be that in those patients with very lateral tumours in which a degree of cochlear radiation is inevitable, FRST should be offered preferentially in order to seek to avoid cochlear damage.

Putative mechanisms of hearing damage with radiotherapeutic techniques

While irradiation of the cochlea is most frequently recognised as a cause for hearing loss following radiotherapy or radiosurgery, Linskey (2008) suggests that the irradiation of the brainstem may also play a significant role. This is supported by evidence from Paek (2005), and in addition to damage sustained to the cochlear nerve, suggests a mechanism for hearing deterioration in cases where cochlear irradiation can be avoided. This factor may also explain why hearing preservation outcomes are found to be less successful in larger, more medially placed tumours undergoing irradiation that might allow cochlear sparing.

Summary of weaknesses in existing literature

1. The true natural history of vestibular schwannoma growth and non-growth is obscured by the manner in which data are reported:

- there is a population bias in a number of series.
- there is a lack of clarity in the description of the duration of follow-up.

2. Similar concerns related to reporting of follow-up data confuse an appreciation of hearing outcomes:

- hearing data is often reported as a secondary outcome, without dedicated description of follow-up data pertaining to hearing alone, rather than to 'follow-up' in general.
- hearing outcomes are reported in terms of preservation of hearing class: a measurement that is dependent upon duration of follow-up.

3. There are few attempts to statistically evaluate risk factors for growth in substantial case series of conservatively managed tumours.

4. There is little evidence offered beyond the anecdotal to support a particular management strategy: thus Meyer (2006) asserts that conservative management risks rendering the outcomes of surgery less successful without offering evidence.

5. There is a lack of an evidence-based protocol to guide the frequency of surveillance scans in conservatively managed patients.

Birmingham Database of Vestibular Schwannomas

The Birmingham database of vestibular schwannomas records information relating to all vestibular schwannomas (excluding patients with Neurofibromatosis Type II) managed in the Queen Elizabeth Skull Base Unit since 1997 under the care of the surgical supervisor of this thesis (RMI). Since this date, relevant clinical details have been stored in the ENT Department offices, allowing simple and rapid access to patient data. An electronic version of the database (Microsoft Excel) was created by the author of this thesis (TPCM) in 2004, and this electronic database has been maintained prospectively since that date, with updating of data every quarter.

Audit of data collection

In order to attempt to assess the quality of data collected in the database, a request was made to the audit department at Queen Elizabeth Medical Centre asking for a comprehensive list of all new patients treated in the hospital with a new diagnosis of vestibular schwannoma or acoustic neuroma in the years 2007 and 2008 (audit code CA2-02262-09). Unfortunately, clinical coding in the hospital only extends to patients treated as in-patients, and therefore no search could be carried out that identified patients treated only as out-patients: a group representing a significant proportion of patients seen in the hospital and included in the database.

A request was made to the audit department to recover data relating to patients treated surgically to remove an acoustic neuroma or vestibular schwannoma (Ca2-02262-09) in these years, and this search identified 5 and 16 patients in 2007 and 2008 respectively. The corresponding number of patients recorded in the database undergoing surgical treatment in

these years are 13 and 9. Interestingly, these figures are divergent. A number of possible reasons for this can be suggested:

1. The number of surgical cases recorded by the audit department may be less than those recovered by the database (as found in 2007) due to inappropriate coding systems.
2. The number of surgical cases recorded in the database may be less than those recorded by the audit department (as seen in 2008) because some vestibular schwannomas may be followed-up by the neurosurgical department.
3. A number of tumours are treated by other colleagues in the hospital: these patients are not recorded in the Birmingham Database.

Ethical approval

A submission was made to the local ethical committee chair (Dr S Bowman, South Birmingham Research Ethics Committee) in order to determine whether formal ethical approval for the studies described within the thesis was required. In response, Dr Bowman felt that the thesis represented an audit of an approved database, and as such was not subject to formal ethical approval in line with NRES guidelines. These communications are attached in the appendix to this thesis (Appendix 1 and 2).

Data security

Data are stored securely in the Queen Elizabeth Hospital, and on a password-protected computer. The database is registered with the hospital audit department and TPCM is registered with the Data Protection Agency.

Data fields

Demographic

All patients are registered with simple demographic data detailing age (at presentation) and sex.

Presenting data

The date of presentation (to our unit) is recorded, with details of presenting symptoms, duration of those symptoms, hearing and tumour characteristics and the management option chosen by the clinician and patient (i.e. conservative, surgery or radiotherapy). Presenting symptomatology is recovered from the letter written to the referring clinician. The symptoms described by patients are often multiple, and all are recorded. The duration of symptoms is recorded in months, and will usually refer to the onset of the earliest presenting symptom: the time recorded is subjective, but the patient is closely questioned. Hearing data at presentation includes pure tone audiometry and speech audiometry for both the affected and non-affected ear. Pure tone audiometry is recorded as an average of 0.5, 1, 2 and 3 kHz. Speech audiometry is recorded as the maximal percentage of words comprehended at any presenting volume.

Tumour measurements are recovered from the letter sent to the referring clinician and are as measured from the original MRI scan by RMI. Tumours in the internal auditory canal only are not measured, but in most cases, are described according to their location in the internal auditory canal (thus: 'medial' or 'filling the whole auditory canal'). Tumours extending into the cerebello-pontine angle are measured at the level of the cochlear parallel to the medial border of

the petrous bone. A record is made of the side of the tumour and whether the tumour is cystic or not.

Surgery

A full record is made of surgery undertaken, with details of any complications and outcomes in terms of tumour recurrence, facial nerve rehabilitation (with status recorded according to the House-Brackmann scale (House, 1985)), and hearing preservation. If a near- or sub-total surgical excision is performed, this is noted in the database. Facial nerve preservation is recorded as the status of the facial nerve after maximum recovery has taken place: if the facial nerve is impaired (House-Brackmann Grade III or worse) and less than 12 months have passed (a standard timeframe for neural recovery), the result is not considered 'complete'. If facial nerve reanimation surgery is performed, this is noted and the facial nerve status recorded both prior to and after any reanimation. Surgical complications such as cerebro-spinal fluid leak are recorded with details of any further procedures undertaken. Follow-up MRI scans to assess for residual tumour are generally carried out 3 years after surgery unless a less-than total tumour excision has taken place, in which case a follow-up scan will often be requested at a more early date.

Conservative management

Follow-up of conservatively managed patients is monitored and details recorded of any tumour growth (including growth rates), and any change in hearing. Patients with static tumours are scanned and seen at six months following presentation then at yearly intervals for two years. Thereafter, patients are scanned and seen after a further two years and then at five yearly

intervals (this policy has developed during the time of study: see Chapter 5). Any tumour growth will lead to either definitive treatment or an adjustment of the above management plan. In the database, patients are considered to be lost to follow-up if they default from the above schedule by more than 1 year: if they fall within this schedule, their duration of follow-up is calculated from the time of presentation until the time of data collection.

An effort is made to encourage patients to attend the Queen Elizabeth Hospital for both follow-up scans and follow-up clinic assessments. In some cases, however, where patients live far from the hospital, they are seen and scanned locally. In these cases, we encourage the clinicians managing them to send copy letters detailing their progress. In the absence of these copy letters, patients are considered lost to follow-up. Patients who are found to be lost to follow-up are contacted through their general practitioners or referring otolaryngologists if possible.

In the course of conservative management, a record is made of the patients' status at quarterly reviews of the database. Patients with static tumours are noted, as are those with tumours that grow at a very slow rate and are managed with continued observation. In cases of growth leading to a change in management, the treatment undertaken is noted, as is the time at which tumour growth was detected. A record is made of tumour dimensions at the time of tumour growth detection, and from this a tumour growth rate (in mm change in tumour diameter annually) is recorded. Hearing status is also noted, following principles outlined above.

Although an effort is made to record hearing data in all patients under observation, resource limitations make this difficult in those patients where hearing is perceived to be static, and for this reason, full audiometric data is not available for every visit.

Strengths and Limitations of the Database

Strengths

Consistency of assessment and data entry

As noted above, a potential confounding factor in reported series of conservatively managed vestibular schwannomas is the long duration of time over which the series is developed. This risks an introduction of inconsistency due to different teams assessing patients and different imaging modalities being employed to assess tumour dimensions. In the Birmingham series, this is avoided by a series of a relatively short duration (13 years to date). The period of data acquisition has been overseen by one clinician (RMI), who has seen all the patients included in the series and has employed a consistent approach to assessment in these patients. Furthermore, data entry has been carried out prospectively by one individual (TPCM) ensuring continuity of data over the period of acquisition.

Clarity of follow-up definition and lack of loss to follow-up

Good follow-up is a prerequisite to effective conservative management, and as demonstrated above, a source of potential bias in publications if not explicitly documented. In this series, we offer explicit definitions for follow-up (i.e. failing to be seen within 1 year of a scheduled clinical episode), thus allowing a clear understanding of the likely importance of such loss to follow-up. In many cases, patients 'lost' have in fact been seen in the clinic for a number of years with stable tumours, and as such are unlikely to be at risk.

Lack of population bias

Although initially following a policy of ‘selected’ conservative management - offering this modality to the elderly or medically unfit - increasingly our policy has become to offer all patients an initial period of conservative management if their tumours are of a size less than 2cm in the cerebellopontine angle. This reduces the population bias seen in other published series and allows a more robust analysis of, for example, growth rates in different population groups.

Limitations of the database

‘Front-loading’

As noted above in the discussion of published series of conservatively managed patients, there is a considerable bias introduced by the phenomenon of ‘front loading’, whereby a large proportion of the patients studied are recently recruited and have a short duration of follow-up. Thus in our series, the total number of patients under conservative management is 470, but of these, a disproportionate group (37%) have less than two years follow-up. 294 patients have greater than 2 years follow-up, but only 179 (38% of the series as a whole) have greater than 4 years follow-up. The effect of this phenomenon is to distort calculated rates of tumour growth by including large numbers of patients with only a short duration of follow-up.

Availability of MR scans for review of measurements

Although patients’ MR scans are now stored electronically, allowing easy comparison of tumour sizes, this technology has only been available for the past 6 years in our hospital. Previously, ‘hard’ films were taken, introducing logistical problems when attempting to recover

films in order to review growth rates in tumours over serial MR scans. This problem is exacerbated by the fact that original MR scans are often performed in outlying, referring hospitals. For this reason, it has been difficult to recover films in order to allow a systematic review of tumour growth. In the absence of such a review, our practise in compiling data has been to depend upon clinician assessment (RMI) documented in medical records.

Thesis aims and objectives

1. To address issues relating to the natural history of vestibular schwannomas (in particular growth and non-growth proportions and the natural history of hearing in observed patients). In analysing these issues, the thesis will pay particular attention to issues of follow-up, its duration and compliance.
2. To use the Birmingham database to explore risk factors for tumour growth or non-growth in observed vestibular schwannomas.
3. To provide an evidence-based protocol for the safe and efficient surveillance of conservatively managed vestibular schwannomas.
4. To address issues of vestibular schwannoma management (conservative, surgical and rehabilitative) supported by evidence from the Birmingham database.

Forthcoming Chapters

Chapter 1: *The natural history of vestibular schwannoma growth*

An analysis of growth rates among watched vestibular schwannomas, and a comparison with the world literature.

Chapter 2: *Risk factors for growth in watched vestibular schwannomas*

An analysis of features that suggest vestibular schwannomas are at greater or lesser risk of growth.

Chapter 3: *Hearing loss and preservation in watched vestibular schwannomas*

An analysis of hearing data in the context of the world literature.

Chapter 4: *An intention to treat analysis of conservative versus surgical management of vestibular schwannomas.*

A case-control study comparing facial nerve preservation in patients managed by either primary surgical or conservative management.

Chapter 5: *A protocol to direct the conservative management of vestibular schwannomas*

A discussion of issues relating to the formulation of a safe and effective regime to dictate the frequency of follow-up imaging in patients undergoing conservative management.

Chapter 6: *Functional surgery in the management of vestibular schwannomas: the prioritisation of the facial nerve over total tumour removal.*

Comparing outcomes of ‘neurologically-sparing’ less-than-total tumour removal with traditionally employed total tumour excision.

Chapter 7: *The rehabilitation of single-sided deafness with the bone-anchored hearing aid.*

Single-sided deafness is the most common disability of both conservatively and definitively treated patients with a vestibular schwannoma. This chapter will describe a study to assess the efficacy of the Bone-Anchored Hearing Aid (BAHA) in treating this condition.

CHAPTER 1: THE NATURAL HISTORY OF VESTIBULAR SCHWANNOMA GROWTH

A presentation of patient, symptom and tumour characteristics of vestibular schwannomas undergoing different management strategies and an analysis of growth rates among watched vestibular schwannomas.

Introduction

As previously discussed in the introduction to this thesis, an estimation of growth or non-growth in watched vestibular schwannomas is often complicated by questions of follow-up. In many series, a significant proportion of patients presented have a very short duration of follow-up, with a consequent tendency to under-estimate the proportion of growing tumours within the group. This chapter will summarise the Birmingham experience in terms of tumour growth in observed vestibular schwannomas, and will also discuss issues raised by the ‘front-loading’ of our series of watched tumours. Before addressing these issues, however, demographics of conservatively managed patients, with tumour characteristics and patient symptoms, are presented.

Patients undergoing conservative management: a comparison with patients managed with either primary surgery or radiosurgery

Method

Data collection

As detailed above, the Birmingham database is updated regularly, and data presented in this chapter was collected in January 2010. Conservatively managed patients are presented with patients managed with primary surgery or radiosurgery in order to provide comparison, and are assessed in terms of demographics, symptomatology, and tumour characteristics.

Table 10: Demographic details of patients managed conservatively or primarily in Birmingham

	All patients	Conservatively managed patients	Patients treated with surgery or radiotherapy as first treatment	Intracanalicular tumours	Small-Medium (Tokyo 1,2)	Moderately large - Giant (Tokyo 3+)
Sex Distribution	F: 371 (51%) M: 359 (49%)	F: 225 (48%) M: 243 (52%) <i>P 0.20¹</i>	F: 141 (55%) M: 115 (45%) <i>P 0.13</i>	F: 118 (48%) M: 130 (52%) <i>P 0.20</i>	F: 138 (49%) M: 145 (51%) <i>P 0.30</i>	F: 102 (57%) M: 78 (43%) <i>P 0.09</i>
Age (mean, range)	57 (18-88)	60 (22-88)	50 (18-81)	58 (22-86)	59 (21-88)	52 (18-81)

1. P values refer to a comparison between the sex-distribution seen within each category when tested against sex distribution seen within the group as a whole ('all patients').

Results

Patient demographics

Patient demographics are presented in Table 10. An interesting observation is that there seems to be a consistent weak trend towards a sex bias indicating that females are more prone to aggressive tumours than males. This is seen both in terms of tumours undergoing surgery vs. those that are watched and in terms of tumours of differing sizes, with women more likely to present with large tumours than men. This observation may explain the previously discussed

historical belief that vestibular schwannomas are more common in females than males: in a pre-imaging age where only the more aggressive tumours presented, it would be expected that a sex bias would be seen favouring females.

Symptomatology

As discussed above (see Introduction), symptomatology data is often problematic for reasons related to data collection and patient recollection. Notwithstanding, data related to symptomatology are presented in Table 11. As might be expected, those tumours that present while intracranial or at Tokyo Grade 1 or 2 (size of up to 2cm in the CPA) will generally present with otological or mixed vestibular and otological symptoms. Larger tumours are more likely to present with additional trigeminal nerve symptoms or with neurosurgical complications.

There is an interesting correlation between the duration of presenting symptoms, the size of tumour, and the initial management plan undertaken. Those tumours that are given definitive treatment as their initial management have a mean duration of symptoms of only 35 months, whereas those treated conservatively have a mean duration of symptoms of 57 months. A corresponding trend is seen in tumours of differing sizes, with larger tumours tending to present with a shorter duration of symptoms. This inverse association between symptom duration and tumour aggression is also found when analysing factors predictive of tumour growth, and will be explored in greater depth in Chapter 2 below.

Table 11: Presenting symptoms: conservatively and primarily treated patients.

Symptoms	All patients	Conservatively managed patients	Patients treated with surgery or radiotherapy as first treatment	Intracanalicular tumours	Small-Medium (Tokyo 1,2)	Moderately large - Giant (Tokyo 3+)
Otological symptoms:						
Hearing loss only:	146 (22%)	104 (24%)	30 (16%)	59 (26%)	52 (20%)	31 (19%)
Tinnitus only:	19 (3%)	14 (3%)	4 (2%)	11 (42%)	6 (2%)	2 (1%)
Mixed:	265 (40%)	197 (45%)	58 (30%)	88 (39%)	126 (49%)	45 (28%)
Vestibular symptoms:						
Vertigo or imbalance only:	15 (2%)	11 (3%)	2 (1%)	10 (4%)	3 (1%)	2 (1%)
Mixed vestibular and otological:	136 (21%)	91 (21%)	38 (20%)	49 (22%)	56 (22%)	28 (17%)
Trigeminal symptoms:	37 (6%)	7 (2%)	28 (15%)	3 (1%)	6 (2%)	28 (17%)
Facial nerve palsy:	9 (2%)	3 (1%)	6 (3%)	0 (0%)	3 (1%)	3 (2%)
Hydrocephalus:	26 (4%)	0	26 (14%)	0 (0%)	3 (1%)	22 (14%)
Incidental finding:	6 (1%)	6 (2%)	0 (0%)	6 (3%)	0 (0%)	0 (0%)
Duration of symptoms (any type), mean (range):	49 (1-360)	57 (1-360)	35 (3-192)	54 (1-360)	49 (3-360)	43 (3-240)
No data:	74 (11%)	33 (8%)	36 (14%)	21 (9%)	25 (9%)	18 (10%)

Tumour characteristics

Tumour characteristics are presented in Table 12.

Table 12: Tumour characteristics: conservatively and primarily treated patients

	Intracanalicular tumours	Small-Medium (Tokyo 1,2)	Moderately large - Giant (Tokyo 3+)	Cystic tumours	Not recorded
Conservative	231	203	24	21	10
Surgery	13	69	134	18	9
Radiosurgery	4	11	23	1	3

As might be expected, there is a strong association between conservative management and smaller tumours, with larger tumours managed primarily surgically. Cystic tumours represent

approximately 5% of the tumours seen, although it should be recognised that cysts rarely form in intracanalicular tumours and therefore the proportion of cystic tumours among vestibular schwannomas with dimensions in the CPA is higher (at 9%).

Growth and non-growth in conservatively managed patients

As outlined in the introduction to this thesis, the aim of conservative management is to monitor tumours over time to determine whether definitive intervention is required. In this thesis, tumours are defined either as ‘not growing’, ‘growing requiring a change in management’ or ‘growing but not requiring a change in management’. The latter group is formed by patients persisting with conservative management usually because of a combination of tumour factors (very slow or inconsistent growth), or patient factors (old age or patient choice). In common with other published series, growth of ≥ 2 mm in diameter annually is considered significant enough to indicate growth, with less rapid growth confirmed over a number of years also being considered significant.

The importance of follow-up

As noted above, follow-up duration can have a significant influence upon the proportion of patients thought to have ‘growing’ vestibular schwannomas, with a tendency to under-estimate the risk of tumour growth. This is largely due to a disproportionate number of patients within the group having a short period of follow-up, and hence not demonstrating growth at the time of data collection. In our own series, there is a similar predominance numerically of patients with a short duration of follow-up, as demonstrated in Table 13.

Table 13: Number of conservatively managed patients with different duration of follow-up and proportion of patients within each group demonstrating growth.

Duration of follow-up	Patients showing no growth	Patients with growth, but not sufficient to alter management	Patients with sufficient growth to alter management
Minimum 6/12 (n.378)	278 (74%)	27 (7%)	74 (20%)
Minimum 18/12 (n.336)	238 (71%)	25 (7%)	73 (22%)
Minimum 30/12 (n.250)	172 (69%)	19 (8%)	59 (24%)
Minimum 42/12 (n.206)	143 (69%)	12 (6%)	51 (25%)
Minimum 60/12 (n.140)	93 (66%)	9 (6%)	38 (27%)

If those patients with at least 5 year’s follow-up (n. 140) are considered, then a proportion of approximately 66% demonstrating no growth is found. This proportion is somewhat smaller than that found (75%) if all patients with at least one follow-up scan are included. Interestingly, this figure of 66% is consistent with Hadjihoff’s data (2008) documenting the Toronto series of conservatively managed vestibular schwannomas (65% no growth). This cohort series has been maintained prospectively and offers the most comprehensive follow-up data of those series detailed in Table 5, and probably represents an accurate reflection of the natural history of tumour growth.

Analysis of patients lost to follow-up

The loss of patients to follow-up is defined for the purposes of this study (and thesis) as a failure to record an outcome for at least one year after an expected clinic appointment. Table 14 details the characteristics of those patients who have been lost to follow-up: it is noticeable that

patients who have been lost to follow-up do not differ markedly in demography, tumour characteristics, or the time at which they presented to the service from those patients managed conservatively as a whole. Tables 15 and 16 further characterise these patients.

Table 14: Patients under conservative management lost to follow-up (n.43): demographics and time of presentation

	Age	Sex	Tumour size	1997-2002	2002-2006	2006-
Lost	62	F:23 (53%) M:20 (47%)	I.can:24 (56%) CPA:19 (44%)	7 (16%)	14 (33%)	22 (52%)
All conservatively managed patients	60	F:225 (48%) M:243 (52%)	I.can: 230 (49%) CPA: 226 (48%) No data: 12	63 (13%)	137 (29%)	268 (57%)

Table 15: Cause of loss to follow-up (where known) and duration of follow-up achieved

Total n.	Refused follow-up	Moved abroad	Thought to be followed by other consultants ¹	Unknown
43	3	2	19	19

1. In cases where patients are under surveillance by other consultants, attempts have been made to update clinical progress, with some success. In other cases (cited here), no response has been obtained.

Table 16: Duration of follow-up achieved prior to loss to follow-up

Unknown n.	6/12	12/12	18/12	24/12	36/12	48/12	60/12
33	1	2	2	2	2	0	1

It should be noted that a considerable proportion of patients recorded as ‘lost’ are likely to be under surveillance in local referring hospitals: many patients prefer to be followed locally. In most cases, the team following the patient will inform our department of their progress. In a few cases (presented in Table 15), despite postal communication with referring teams, it has not been possible to obtain information about these patients.

Management approaches and referral patterns leading to a predominance of patients with a short duration of follow-up

As noted above, there is a tendency towards a greater number of conservative patients recruited during more recent years. In our series, this is due to two phenomena: a shift in management practise towards initial conservative management; and a growth in referral numbers to our service in recent years.

Shift in management

The database presented here represents treatment of vestibular schwannomas in Birmingham over the past 12 years, and during this time, treatment of these tumours has evolved to the position outlined in the introduction. While in the early years of the database, it would be common to offer surgical treatment to tumours graded at 1 or 2 on the Tokyo Scale, this

approach is now unusual unless the patient particularly requests definitive treatment. This practise shift is demonstrated in Figures 3 and 4.

Figure 3: Evolution in management of intracanalicular tumours over time

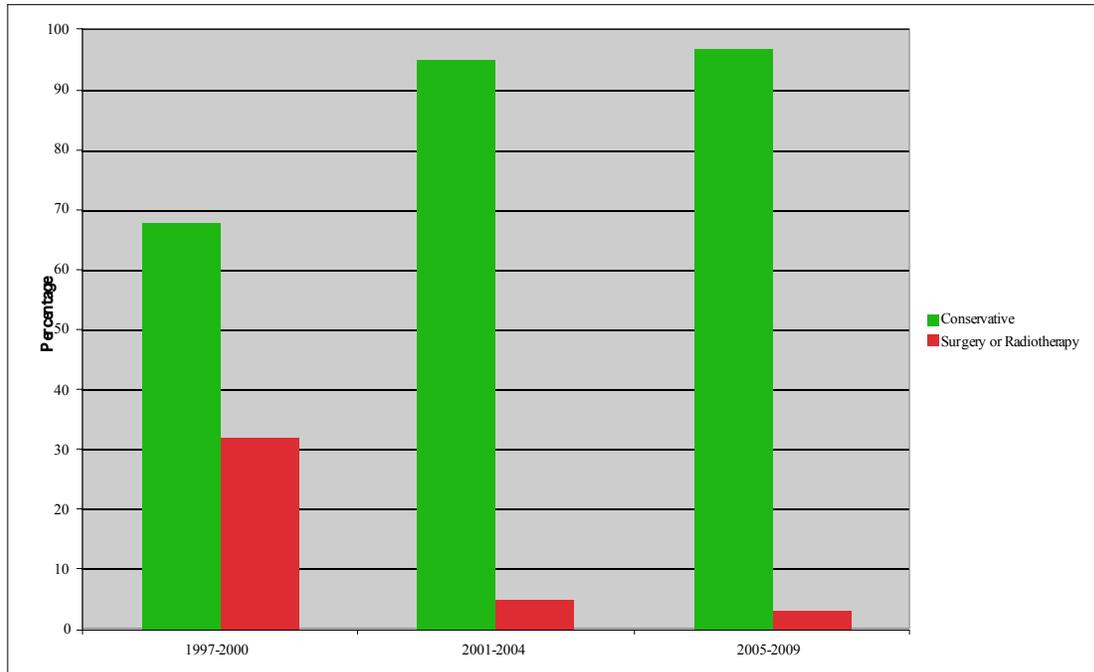
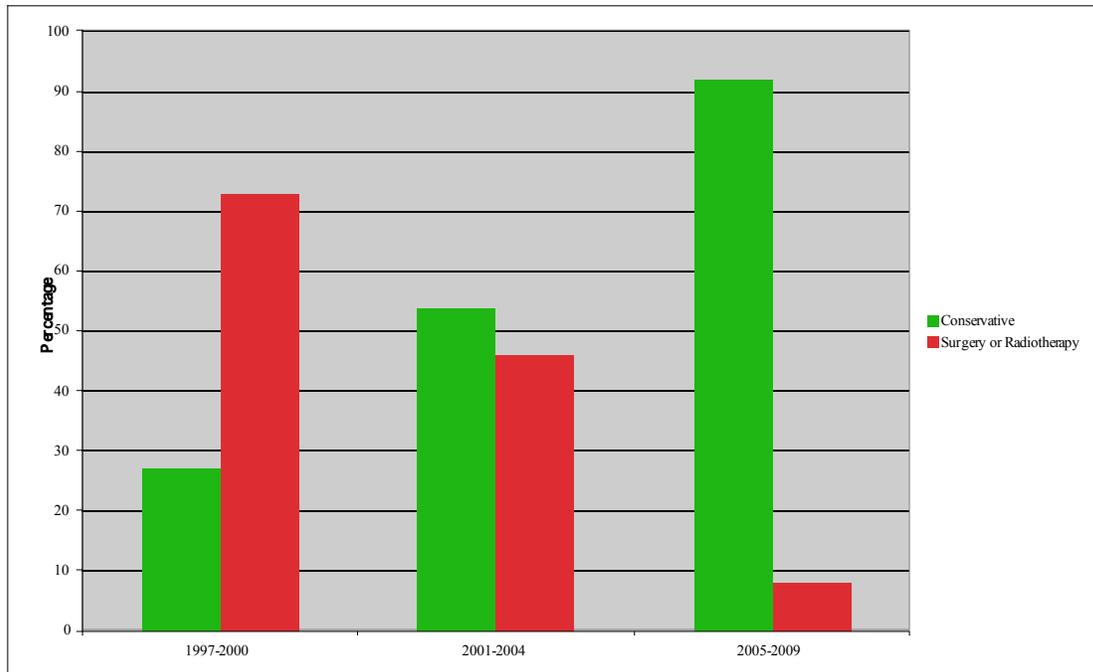


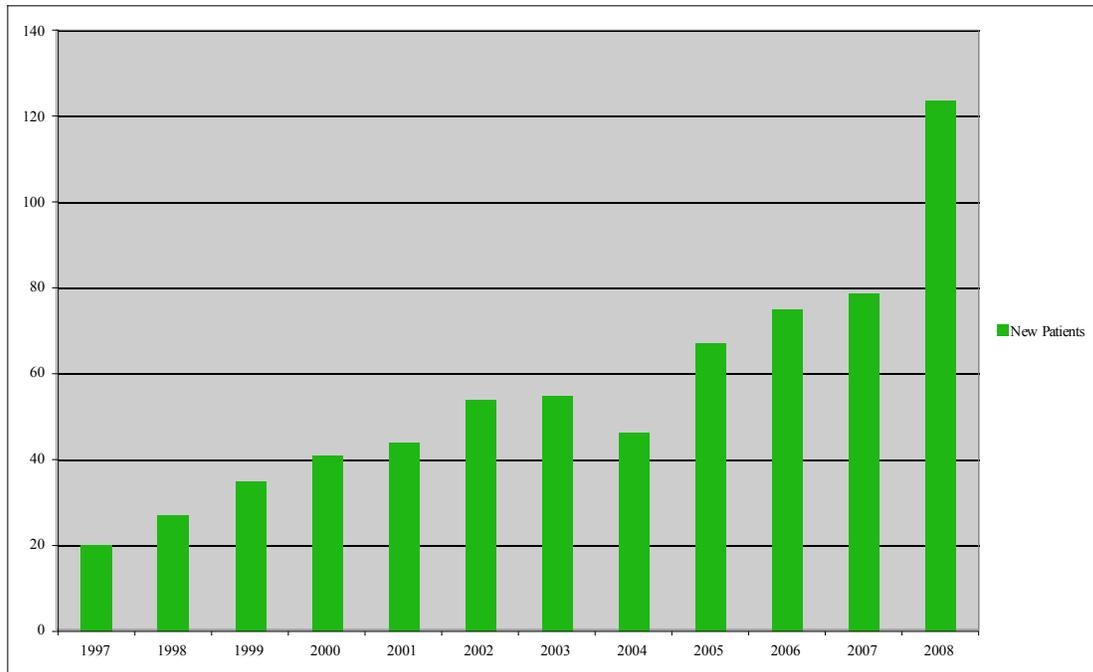
Figure 4: Evolution in management of small-medium sized tumours (Tokyo Grade 1-2) over time



Increase in referrals

A further increase in numbers of tumours managed conservatively with relatively short follow-up is caused by an increase in referrals to our service over time generally, demonstrated by Figure 5, which illustrates referral numbers in the years during which the database has been maintained.

Figure 5: Increasing referrals to Birmingham Skull Base Unit 1997-2008



Chapter conclusion

The aim of this chapter has been to characterise those patients undergoing conservative management within the Birmingham Skull Base Unit, and to determine an accurate understanding of the proportion of growing tumours among tumours managed conservatively overall. It is recognised that, in common with other published series of conservatively managed vestibular schwannomas, there is a predominance of patients with a relatively short duration of follow-up, caused by an increasing referral base and a philosophical shift towards conservative management in more recent years. The effect of this distortion is to suggest that a larger proportion of tumours (75%) do not grow when watched, than that which is more likely to be the case if longer-term follow-up is seen (66%).

An interesting observation seen in analysis of the characteristics of tumours managed conservatively when compared to those managed with primary surgery or radiosurgery is that these 'less aggressive' tumours are found to be more likely to present with a longer duration of symptoms, and to present in male patients. The following chapter, analysing risk factors for growth in observed vestibular schwannomas, will explore these issues further.

CHAPTER 2: RISK FACTORS FOR GROWTH IN WATCHED VESTIBULAR SCHWANNOMAS

An analysis of factors predictive of growth in conservatively managed vestibular schwannomas

Introduction

Prediction of growth in vestibular schwannomas is of obvious clinical relevance. If the clinician is able to say with certainty whether a particular tumour will or will not grow, s/he is in a position to remove considerable uncertainty from the patient, and to expedite treatment if required. The aim of this chapter is to analyse data relating to presenting symptomatology and demographics in patients managed conservatively in order to determine whether any factors are significantly predictive of growth.

Table 5 above summarises published series of conservatively managed vestibular schwannomas. In a number of these series, an attempt has been made to determine risk factors for growth. This chapter will explore whether the Birmingham experience reflects these findings and discuss the clinical relevance of risk factors in management.

Methods

Data collection

The study is confined to patients undergoing conservative management as an initial treatment modality, with the database updated in March 2010. Tumours were categorised as either 'growing' or 'non-growing'. The former group included any patients who had shown a

sustained growth in tumour dimensions. In most cases, these patients are treated definitively with either surgery or radiosurgery, but in a minority, conservative management is continued because of either tumour factors (very slow growth) or patient factors (old age or co-morbidities). Demographic data analysed consists of patient age at presentation and sex. Tumour data includes tumour size at presentation, laterality and cystic versus non-cystic. In considering tumour size, two analyses were carried out: the first compared intracranial (ICan) tumours with those extending to the cerebellopontine angle (CPA), the second comparing different sized CPA tumours. Finally the study compared duration of symptoms between the two groups of patients.

Although an analysis of the significance of different symptoms to growth or non-growth might seem an obvious study to perform, this has not been attempted for a number of reasons. Symptoms described by patients are numerous and often multiple: it would be very difficult, if not impossible, to perform analyses which determined the significance of (for example) a complaint of hearing loss and tinnitus in comparison to hearing loss and vertigo. A further impediment is the subjective nature of symptoms and variable recording by clinicians recording data during clinical assessment: duration of symptoms will be analysed, but it is recognised that this is a subjective report from the patient and should be viewed as such.

As described in the previous chapter, there is a tendency to under-estimate growth rates if patients with a shorter duration of follow-up are included in analyses. In this study, all patients with at least one follow-up scan are included, accepting that there will be a small proportion of

tumours categorised inaccurately as ‘non-growing’. To exclude patients with less than 2 or 4 years follow-up would considerably reduce the power of the study.

Statistical analysis

Analyses were performed using SPSS 16.0 for Mac. A Chi-squared analysis was used for categorical data, an independent samples T-test for continuous data.

Results

468 patients treated conservatively as an initial management plan were identified from the database. Of these patients, some 47 are awaiting a second scan and are excluded. A further 43 patients have been lost to follow-up, defined as having not been seen in the outpatient clinic within 1 year of an expected follow-up appointment. Of the remaining 378 patients, 101 (27%) have demonstrated growth of some description, while 277 (to date) have not.

Demographic results

Demographic results are presented in Table 17. In both analyses, the groups are markedly concordant, with no significant differences seen.

Table 17: Comparison of demographic data: tumour growth vs. tumour non-growth

	Non-growing tumours (n.=277)	Growing tumours (n.=101)	Statistical analysis
Sex distribution	F=135, M=142	F=46, M=55	<i>P</i> 0.58
Mean age (SD)	61 (12)	60 (12)	<i>P</i> 0.83

Tumour results

Results for differences between the two groups in terms of tumour characteristics at presentation are presented in Table 18.

Table 18: Tumour characteristics: tumour growth vs. non-tumour growth

	Non-growing tumours (n.=277)	Growing tumours (n.=101)	Statistical analysis
Laterality	L=139, R=134	L=54, R=46	p=0.82
Cystic vs. non-cystic	Cystic=10 (4%) Non-cystic=243 No record=24	Cystic=11 (12%) Non-cystic=83 No record=7	p=0.02
Size (ICan vs. CPA)	ICan=147 (54%) CPA=125 (46%) No record=5	ICan=34 (35%) CPA=64 (65%) No record=3	P=0.004
Size (CPA mean size)	1.2 (0.6)	1.2 (0.6)	p=0.66

Duration of symptoms results

Results for differences in duration of symptoms between the two groups are presented in Table 19. There is a statistically significant association between a short duration of symptoms and a tendency for tumour growth.

Table 19: Symptom data: Comparison of duration of symptoms between growth and non-growth groups

	Non-growing tumours (n.=277)	Growing tumours (n.=101)	Statistical analysis
Duration of symptoms, months (mean [SD])	66 (67)	40 (52)	<i>P 0.002</i>

Discussion

Although there have not been any molecular biological studies examining the differing characteristics of ‘static’ and ‘growing’ tumours that might identify, for example, particular genetic events leading to a more aggressive phenotype, some recent studies have suggested that angiogenesis may well play a part. Koutsimpelas (2007) compared vascular growth factor expression in 17 sporadic vestibular schwannomas and was able to demonstrate that apparently more ‘aggressive’ tumours (larger, with a shorter history of symptoms, and a denser microvasculature) were associated with increased levels of angiogenic expression. This study would suggest, and evidence of successful treatment of patients with advanced NFII with anti-VEGF monoclonal antibody also implies (Plotkin, 2009), that angiogenesis is of importance in determining tumour growth.

If this is the case - that some tumours are able to successfully stimulate angiogenesis while others fail to do so and remain static - it is regrettably the case that there are no biochemical markers available to the clinician that indicate angiogenic potential. It is, of course, not possible to biopsy the vast majority of vestibular schwannomas without risking significant damage to neighbouring structures, and the clinician is therefore compelled to seek clinical predictors of growth potential such as those presented below.

Significant findings

In this study, a number of significant predictors of growth have been identified associated with tumour characteristics and the duration of the symptoms reported by the patient. In terms of the tumour, there is a tendency for 'growing' tumours to be extending into the cerebellopontine angle at presentation, and for the tumour to be cystic. We have also demonstrated that the symptoms a patient presents with are likely to be of a shorter duration than those in patients with a static tumour.

The tumour characteristics identified are perhaps those that might be expected to be found. Tumours that are found to extend to the cerebellopontine angle at presentation are generally larger than those confined to the internal auditory canal (the majority of tumours originate within the canal). If it is thought that tumours become static because a maximal viable tumour size has been reached, it might be expected that tumours that have grown beyond the limits of the internal auditory canal are those with potential to grow further. Clearly, a proportion of growing tumours will be identified that are growing, but have not yet had time to reach the

cerebellopontine angle. Of note, there is no association between growth and the size of the tumour within the cerebellopontine angle: this would suggest that if there is a ‘terminal’ tumour volume (i.e. a volume beyond which tumours no longer grow), this can be relatively large, suggesting that conservative initial management of cerebellopontine tumours is a reasonable treatment option.

The strong association between tumour growth and cystic degeneration is also perhaps to be expected. Chapter 4 below will discuss in greater detail growth patterns in cystic tumours, but it is well-recognised (Benech, 2005) that cystic tumours show a propensity for rapid growth due to intra-cystic haemorrhage. It may be conjectured that a characteristic of a rapidly growing, ‘aggressive’ tumour is to have a more loosely organised arrangement of Antoni Type B cells: Nager (1993) has observed that these cells are prone to micro-cystic degeneration.

The observation that tumours are more likely to grow if they present with a short duration of symptoms is intuitive. As awareness of the importance of unilateral otological symptoms increases among physicians of all types, it is to be expected that a significant number of patients will be identified with a very long history of symptoms. In our database, 22% of patients present with reported symptoms of at least ten years duration: it is to be expected that a disproportionate number of this group of patients have indolent or static tumours. On the other hand, while there is a statistically significant association between a short duration of symptoms and growth, there is a large number of patients with a short history of symptoms who do not subsequently manifest growth; the converse is also the case (this is reflected by the large standard deviation figures seen in Table 19). Thus, of the 67 patients with a history of one year

or less, 56 do not manifest growth at subsequent follow-up, and of the 70 patients in our database with symptoms for longer than 10 years, some 7 have demonstrated growth to date.

It is interesting that we have not been able to demonstrate any significant association between tumour growth and female gender. As observed above, there is a historical tendency to see vestibular schwannomas as more commonly found in females with a ratio of 2:1 (Zülch, 1986, cited by Nager, 1993). This is not supported by our own database, and the large Danish database (Stangerup, 2009, personal communication): in these and other databases, there is an almost equal female: male sex distribution. In Chapter 1 we demonstrated an association between the female gender and more aggressive tumours that require definitive treatment as an initial management option.

It could be speculated (as above, see Introduction), that the reason for the traditional belief that vestibular schwannomas were more common in women than men could arise from the fact that tumours that historically presented to clinicians were those that grew beyond a certain size and therefore presented with significant symptoms; a situation more commonly found in female than male patients. If this were the case, we might expect to see a relatively high proportion of female patients within the group demonstrating tumour growth. The fact that we have not been able to demonstrate such an association calls into question the validity of the above theory.

Comparison with other studies

Studies assessing risk factors for tumour growth are presented in Table 5. There is a general concordance with our own findings: Malhotra (2009), Ferri (2008), Hajihoff (2008), Stangerup

(2006), and Battaglia (2006) have all demonstrated an association between larger tumours and growth. Symptomatology is less frequently investigated, but El-Bakkouri (2009) and Ferri (2008) have both found similar outcomes to those we have demonstrated in this study.

Clinical applicability of the study

If we have been able to identify some significant predictors of tumour growth potential, does this enable more effective clinical decision making? At present, our practice is to monitor almost all tumours that are less than 2cm in the cerebellopontine angle: those that are seen to grow are treated definitively. To predict with certainty that a particular tumour is at risk of growth would reduce anxiety on the part of the clinician and patient, would conserve resources and allow prompt treatment. It is well recognised that surgery is more prone to complications in larger tumours (Gormley, 1997, Kaylie, 2001, Mamikoglu, 2002), and there would be benefit in allowing treatment of tumours before a period of observation allowed growth to take place.

While we have determined that there are statistically significant associations between certain clinical features and a tendency to grow, it is not clear that these associations are strong enough to warrant a change in the management outlined above. As has been seen, while patients with a short history of symptoms are statistically more likely to demonstrate growth over time, there is also a large number of patients with a short history of less than one year who do not manifest growth. Similar observations can be made about tumour size: although tumours that are diagnosed within the internal auditory canal are less likely to demonstrate growth than those in the CPA, there are a large number of tumours that do not follow this pattern.

Were the risks of conservative management more significant (if, for example, there was a recognised risk of patients demonstrating rapid and life-threatening growth while under observation), then the associations demonstrated above might be more clinically applicable. In such a case, it would be useful to identify those tumours presenting the lowest risk of growth, and reserving these only for a careful conservative approach: the topic of whether harm is caused by conservative management will be addressed in Chapter 4 in this thesis below.

If in most cases, the risk factors identified are not powerful enough to warrant an abandonment of conservative management, it would be reasonable to use these indicators in order to guide management in cases that present a dilemma. Thus, with a tumour at the upper limit of what might usually be considered acceptable for an initial period of observation (extending 2cm into the CPA, for example), the clinician may be prompted to offer early intervention if the patient has a short history of symptoms, or to advise observation if the history is long. Cystic tumours represent a further dilemma: in our experience, these are particularly prone to growth: their management will be discussed in greater detail below in Chapter 5 of this thesis.

Chapter Conclusion

This study has demonstrated (in common with published reports), that there is a statistically significant association between tumour growth and a number of clinical findings. While these associations may not allow a clinician to predict with certainty whether a tumour is likely to demonstrate growth, they do allow an informed discussion with the patient and, in cases that present management dilemmas, may help direct treatment.

CHAPTER 3: HEARING LOSS AND PRESERVATION IN WATCHED VESTIBULAR SCHWANNOMAS

A presentation of the evolution in hearing in watched patients with vestibular schwannomas, an analysis of risk factors for deterioration or preservation and a discussion of outcome reporting methodology.

Introduction

Hearing loss is the most common presenting symptom troubling patients with vestibular schwannomas, affecting 89% of the patients in our database. Furthermore, the management of the hearing patient with a vestibular schwannoma is a source of considerable controversy among surgeons and physicians treating patients with these tumours. The aim of this chapter is to explore issues related to the natural history of hearing loss based upon data recovered from the Birmingham database.

In particular, attention will be paid to those patients who present with a small tumour and relatively normal or 'near-normal' hearing: the management of these individuals is particularly controversial. The study will thus focus upon individuals with Class A and B hearing (AAO-HNS Classification [see Table 6, Introduction]) treated with conservative management. In addition, an analysis will be made of initial hearing levels among all patients presenting with a vestibular schwannoma, identifying whether any risk factors dictate the severity of hearing loss at presentation.

While a number of publications have addressed the evolution of hearing in observed patients with vestibular schwannomas, (see Table 7) a clear view of the natural history of hearing loss is only slowly emerging. In many cases, hearing outcomes are presented as secondary (to, for example, growth), with a consequent lack of clarity with respect to important issues such as duration of follow-up. In other cases, definitions of ‘hearing preservation’ employed obscure a clear understanding: this chapter will address these issues and propose an alternative means of describing hearing preservation to that of ‘preservation within class’.

Methods

Analysis of hearing loss at presentation

Audiological assessment

All patients in the Birmingham Database in March 2010 were included in this component of the study. Patients are routinely investigated with both pure tone audiometry (PTA) and speech discrimination testing (SDS) at the time of their first visit to our department. Audiological data were recovered from patient records. With respect to pure tone audiometry (PTA), a mean of dBHL at 0.5, 1, 2 and 3 KHz was calculated, using masked bone conduction if performed. Speech discrimination studies (SDS) were recorded as the maximum percentage of words correctly identified, as indicated by the AAO-HNS classification system. Demographic data are recovered as previously described, as are data pertaining to tumour size.

Statistical analysis

Data were analysed using SPSS for Mac 16.0. For the comparison of means (duration of symptoms, age) an independent samples t-test was employed. To analyse categorical data

(gender, tumour types, treatment offered), a Pearson Chi-square test is used. A p-value of <0.05 is taken as evidence of a significant difference in results.

Analysis of patients presenting with ‘serviceable’ hearing and undergoing initial conservative management

Patients

Patients initially managed conservatively and presenting with a pure tone average (PTA, mean of thresholds at 0.5, 1, 2 and 3 [calculated as mean of 2 and 4 kHz]) of 50dB or less and the potential for 24 months follow-up were identified from the Birmingham database (updated in March 2011). Although speech audiometry is recorded routinely at presentation, it is not recorded routinely in follow-up due to resource pressures, and this audiometric data is not included in the study. Routine demographic and tumour data were recorded as was the duration of follow-up, defined as the time (in months) between the initial audiogram at presentation and the most recent recorded. Patients were excluded from the study if there were no available audiometric data following presentation.

In order to grade hearing deterioration, the rate of hearing loss relative to the contralateral ear was calculated. This calculation is summarised below:

$$\frac{([\text{Final PTA}-\text{Initial PTA}]-[\text{Final contralateral PTA}-\text{Initial contralateral PTA}])}{\text{duration of follow-up}}$$

This calculation was used in order to allow (by inclusion of the contralateral hearing) for any inter-test variability in addition to any presbycusis-related hearing loss occurring. To allow inclusion of cases where there was no contralateral hearing (n.=3), a mean annual fall in contralateral hearing was calculated from the group as a whole. A further classification of hearing preservation (largely for the purposes of comparison with other publications) was also made, defined as preservation of class of hearing (accepting that a complete assessment of AAO-HNS hearing class would require inclusion of speech audiometry values).

Data analysis

In the first instance patients with perfect hearing preservation (defined as the affected hearing deteriorating less than or at the same rate as the contra-lateral ear) were studied with reference to an equal number of patients with the poorest hearing preservation rates. In the second analysis, the group as a whole were divided into two groups equally with respect to their rate of hearing loss (see formula above). In both cases, groups were tested to determine an association between demographic data, tumour size and levels of hearing at presentation.

Statistical analysis

Analyses were performed using the software SPSS 16.0 for Mac. Groups were compared using either independent samples t-tests or chi-square tests as described above.

Results

Hearing loss at initial presentation

Findings are presented in Table 20. Of 729 patients registered on the database, 601 had sufficient data for analysis.

Table 20: Hearing levels at presentation: factors predictive of Class A/B or Class C/D hearing.

Hearing level at presentation	Age: mean (years) and SD	Sex	Duration of symptoms prior to presentation: mean (months) and SD	Tumour characteristics (intracanalicular or extending to cerebello-pontine angle)	Treatment offered at first presentation
Class A or B (PTA \geq 50 dBHL and SDS \geq 50% max.) n.= 311	53.3 (13)	M: 49% F: 51%	34.5 (38)	IAC: 41% CPA: 59%	Conservative: 68% Surgery: 26% Radiotherapy: 5%
Class C or D (PTA or SDS <50 dBHL or <50% max. SDS) n.=290	60.6 (12)	M: 50% F: 50%	65.6 (70)	IAC: 28% CPA: 72%	Conservative: 66% Surgery: 29% Radiotherapy: 3%

Cases without audiological data are presented in Table 21.

Table 21: Patients without audiological data at presentation (Total n. 128)

	Large tumour at presentation	Recent addition to database (proforma only without audiological data)	Private patients	Others (cause unknown)
n. patients	21	35	7	65

In some cases, tumours were large at presentation (n. >3cm CPA=21), and it is suspected that because surgery (which would be hearing-destroying) was planned, it was not felt worthwhile to perform an audiogram. In a number of cases (n. 7), patients are treated privately, and full data may not be available. A further group of patients are initially registered using a proforma that does not record audiological data (n. 35). Subsequently, fuller data from patient records are added. It is not anticipated that the latter two groups should significantly bias results, but it could be argued that the group presenting as an emergency (usually too unwell to undergo audiological tests and with other priorities) may represent a group with specific characteristics that contribute a (numerically small) bias to the study.

Table 20 records a number of significant findings. From this data, it would seem that patients with better hearing are younger, have smaller tumours, and suffer with their symptoms for a significantly shorter duration than their counterparts with poorer hearing. These findings will be discussed below.

Patients presenting with ‘serviceable’ hearing and undergoing initial conservative management

Patients

196 patients were identified initially. Of these, some 132 had sufficient data for further analysis. Of those patients without sufficient data (n. 64), 23 were removed from our conservative management protocol due to tumour growth before follow-up audiometry could be performed. 18 further patients were seen in our department at initial presentation, and then followed-up in

their local hospitals: attempts are made to recover data in these cases, and if possible, data are included in the study. In these 18 cases this was not possible. For the remaining 23 patients no clear reason can be found for a lack of follow-up data. Of the 132 patients studied, 112 (84%) had full audiometric data available for analysis (defined as an audiogram recorded at presentation and at the most recent follow-up visit as determined by our follow-up protocol). In these 20 cases of incomplete follow-up, the most recent available follow-up audiogram is included in the study. The demographic and tumour factors of the 132 patients included are presented in Table 22.

Table 22: Demographic and tumour data

Sex	Age, years: mean (range)	Tumour size: Intracranial only n.	Tumour size: Dimensions in cerebellopontine angle (CPA)(mean, range)
F: 63 M: 69	55 (25-82)	78	11mm (2-22)

Within the group, 8 patients demonstrated growth after an initial period of conservative management and were treated definitively (this in addition to the 20 patients described above). A further 15 patients demonstrated growth but remained within the conservatively managed cohort.

Hearing preservation

In the group as a whole, 39 (30%) patients preserved hearing when defined as preservation of hearing in the affected ear at the same level or better than that in the contralateral ear. If hearing preservation is defined as preservation of hearing in the same class as at presentation, then 77

(58%) preserved hearing. If those patients with less than 24 months documented hearing are excluded from the analysis, then these figures fall to 27 (26%) and 53 (51%) respectively. If those patients with less than 48 months documented follow-up are excluded, preservation rates are 14 (29%) and 22 (46%) respectively. Exclusion of patients with less than 60 months follow-up leads to hearing being preserved in 11 (37%) and 13 (43%) of the total. These findings are summarized in Table 23.

Table 23: Analysis of patients presenting with Class A or B hearing and managed conservatively (follow-up >24 months)

Hearing preservation	All patients (n. 132)	Patients with minimum follow-up 24 months (n. 104)	Patients with minimum follow-up 48 months (n. 48)	Patients with minimum follow-up 60 months (n. 25)
Preservation of hearing relative to contra-lateral ear	39 (30%)	27 (26%)	14 (29%)	13 (43%)
Preservation of class	77 (58%)	53 (51%)	22 (46%)	11 (30%)

When mean hearing loss rates are considered, a range of values are found. Excluding 39 patients preserving hearing perfectly (or better) relative to the contra-lateral ear, the remaining patients have a mean monthly hearing loss of 0.34dB (the equivalent of 4.1dB annually), with a range of (0.01-2.1). Of these 93 patients, 11 lost hearing at a rate greater than 10dB annually.

Risk factors for hearing preservation

An analysis of potential risk factors for good or poor preservation of hearing does not reveal significant prognostic indicators. A comparison of those patients with perfect or better hearing

preservation relative to the contralateral ear (n. 39) (referred to as ‘Group 1’ in Table 24) with the 39 worst ‘performing’ individuals (Group 2) demonstrates statistically insignificant differences in terms of presenting hearing levels and tumour size. These findings are repeated if the analysis is expanded by dividing the patients into two equally sized groups of hearing ‘preservers’ and hearing ‘losers’ (Groups 3 and 4) (see Table 24 for details).

Table 24: Analysis of potential risk factors for hearing preservation/degradation

	Sex	Age (mean)	PTA at presentation	Tumour size ¹
Group 1 vs.	47% female	54.6	28dB	47% small
Group 2	47% female <i>P 1.0</i>	58.4 <i>P 0.12</i>	30dB <i>P 0.46</i>	47% small <i>P 1.0</i>
Group 3 vs.	48% female	54.3	28dB	54% small
Group 4	47% female <i>P 0.86</i>	55.8 <i>P 0.46</i>	29dB <i>P 0.90</i>	57% small <i>P 0.86</i>

1. Tumour size is assessed by comparing intracanalicular tumours with those extending to the cerebellopontine angle, with the latter considered large tumours. In six cases, initial data with respect to tumour size were not available.

Tumour growth as a risk factor for hearing preservation

Tumour growth is a difficult parameter to study: many growing tumours sustain only very short follow-up, and as detailed above, a significant proportion lack follow-up data. Of those patients who have been followed and have undergone definitive treatment due to tumour growth (n. 8), two retained perfect hearing prior to definitive management. A more interesting group are those patients who have growing tumours that do not receive definitive treatment, but remain under

observation: in our study, some 15 patients have been followed in this way, with a mean follow-up of 47 months (range 16-140). Of these, two patients followed for 21 and 140 months have preserved perfect hearing relative to the contralateral ear, while the remaining 13 patients have a mean hearing loss of 0.5 dB/mth, equivalent to 6 dB annual hearing loss, suggesting that this group are a little more likely to lose hearing than the group as a whole, but that hearing loss is not inevitable.

Discussion

This study has examined hearing data drawn from the Birmingham database: the aim of this discussion will be to situate this data within the context of the world literature (summarised in Table 7, Introduction).

Hearing loss at original presentation

To the author's knowledge, this subject has not been addressed in the literature to date. Studies that assess hearing outcomes (see Tables 7, 8 and 9 *Introduction*) will generally focus upon outcomes from a particular treatment modality (i.e. surgery, radiotherapy or conservative management), rather than upon the group of patients as a whole. Our findings are twofold: we have demonstrated that patients presenting with poorer hearing are those with a longer duration of symptoms, and are older than those patients who present with either Class A or B hearing. While this finding is perhaps intuitive given the natural history of vestibular schwannomas, it suggests that hearing loss is a gradual, progressive phenomenon rather than a rapidly progressive or abrupt process.

Hearing preservation and deterioration in conservatively managed patients presenting with serviceable hearing

The study of the evolution of hearing in conservatively managed patients is more thoroughly addressed in the world literature. Some of the methodological difficulties with these studies have been discussed previously in the introduction to this thesis, but it is worthwhile re-iterating these briefly here:

-studies rarely clearly describe follow-up duration, frequently offering only a mean figure and not distinguishing between those in the cohort with a long follow-up and those with short follow-up. The effect of this is to allow the inclusion of a significant number of cases with very short follow-up and misleadingly 'good' hearing preservation.

-this effect is enhanced by the use of 'preservation within class' as a methodology for assessing hearing preservation.

A close examination of published data illustrates this effect: Grayeli (2005) details hearing results at serial visits: thus at the first visit, 41% of 105 patients tested have useful hearing (Class A or B), but by the 6th visit, only 8% of 13 patients fall into this category. Ferri's paper suggests a similar phenomenon: patients with preservation of hearing have a mean follow-up period of 44 months, whereas those with deterioration have a mean follow-up of 80 months. Clearly, if all patients show a gradual deterioration in hearing and the measure for 'preservation' is maintenance below a threshold (30 or 50dB), time of observation will be the most important determinant of hearing preservation. Our own study demonstrates this phenomenon (see Table 23).

We have found a rate of hearing loss to be a more useful outcome measurement. In addition, we have included a measurement of hearing in the contralateral ear in order to control the study. This is both to control for the effects of presbycusis and also to allow for inter-test variability (either due to patient, audiologist or device factors). Using this approach, we have demonstrated that a significant proportion of patients (25-35%) seem to preserve hearing perfectly while under observation: we would argue that this figure may remain stable over longer follow-up. A further 19% of the group as a whole lose hearing at a slow rate of less than 1dB annually. 10% lose hearing rapidly, at a rate of at least 10dB annually.

We have been unable to identify any significant prognostic factors for hearing preservation. Sughrue's review found an association between tumour growth and a lack of hearing preservation. Our study of a small number of growing tumours that are observed (n.15) would reinforce this finding: this group has a reduced rate of perfect hearing preservation (13%), coupled with an elevated rate of hearing loss among those with deteriorating hearing levels (6.3 dB annually).

Stangerup (2008) identified an association between perfect hearing at presentation, and hearing preservation over time. This paper defines 'preservation' as retention of AAO-HNS class of hearing, and an examination of our data illuminates potential confounding factors when using this approach: of 22 patients in our group presenting with 100% speech discrimination, some 6 (30%) are seen to preserve hearing relative to the contralateral ear, with the remaining patients losing hearing at a rate of 4.1dB relative to the contralateral ear. This finding is entirely

consistent with the hearing preservation seen within the group as a whole. In contrast, 16 (80%) preserve hearing if defined as preservation of AAO-HNS class: with limited follow-up, patients presenting with perfect hearing who lose hearing progressively at a rate of 4.1dB annually will retain Class A hearing for a number of years. We would argue that such patients should not be described as ‘preserving hearing’.

Lack of complete data represents a significant risk of bias in the presentation of case series, and we have made an attempt to clarify as much as possible any missing data within our study. We have taken as an initial patient group all those individuals presenting with hearing levels of ≤ 50 dB: from this group a significant proportion (33%) do not have further data available to us for study. As detailed above, these patients fall into three groups: those followed in other centres, some with growing tumours and a number for who no identifiable cause can be found to explain a lack of data. Finally, we have also identified a smaller group of patients with partial data (a further 16%): in these cases, audiometric follow-up is available but this does not extend until the most recent clinic visit as determined by our protocol for surveillance.

In some cases, we feel that bias is likely to be introduced due to these missing data. Our own study, in addition to Sughrue’s review would suggest that growing tumours have a tendency to lose hearing more rapidly than static tumours, and the lack of data with respect to these tumours should have the effect of ‘up-regulating’ rates of hearing preservation. On the other hand, we do not anticipate that the tumours followed in regional hospitals differ from those followed in our tertiary centre, and would suggest that this group of patients do not represent a significant source of bias. Those patients with a lack of data for no clear reason may either up- or down-

regulate outcomes: it may be that audiometry is not performed because hearing is unchanged, or because it is unrecordable.

If our study does document regrettable lapses in complete data collection, other studies also have similar flaws. Stangerup offers a very clear description of missing data (presented in Table 2 of Stangerup, 2009), characterizing ‘ideal’ and ‘actual’ follow-up. Thus, for the 125 patients within his study that have potential for 5 years audiometric follow-up, only 67 (54%) have been followed for 5 years. Similarly, Flint describes 22 patients with serviceable hearing at presentation, but reports only 15 (68%) available for analysis. Even in a rigorously-maintained cohort study, such as that reported by Hajioff, 9 of 49 (18%) of patients followed do not have audiometric results available for analysis.

Chapter Conclusion

The management of the patient with a small to medium sized vestibular schwannoma (i.e. intracranial tumours and Tokyo Class 1 and 2) with good hearing at presentation is subject to controversy. While clinicians may dispute the upper size limit of lesions appropriate for initial conservative management, there is a developing consensus that a considerable proportion of tumours do not grow over time, and that initial observation is a reasonable treatment option. There is also an increasing awareness that hearing deteriorates gradually in the majority of patients treated conservatively, often apparently independently of tumour growth. A synthesis of these two principles has led some to argue that an early intervention to ‘save’ hearing before it deteriorates inevitably offers the patient the best opportunity for hearing preservation, despite an accepted risk of losing hearing due to either surgical or radiosurgical intervention.

In our experience between one quarter and one third of patients who do not have growing tumours can expect their hearing to remain stable with respect to the contralateral ear. A further one fifth will have a very slowly evolving hearing loss, and one tenth are likely to lose hearing rapidly. Of those that do lose hearing, the mean annual loss we have seen is 4.1dB with a (range of 1-25dB). Patients with growing tumours are more likely (but not guaranteed) to lose hearing at a greater rate than those with static tumours. Beyond this weak association (not proven statistically due to inadequate data for analysis), there would seem to be no statistically significant risk factors for hearing loss or preservation.

The author suggests that this data is novel in the literature to date. Hitherto, authors have either presented their data in terms of 'preservation in class' or in terms of mean hearing loss. As described above in detail (and demonstrated using our own data), a 'preservation within class' description is liable to lead to a confounding increase in a rate of preservation if follow-up is limited. Similarly, a mean rate of hearing change (as cited by Hajioff, 2008 and Malhotra, 2009) offers only a limited understanding of likely outcomes if there is significant variation within the group: the author would argue that these data offer firmer direction to patients considering the likely evolution of hearing if their vestibular schwannoma is observed.

CHAPTER 4: AN INTENTION TO TREAT ANALYSIS OF CONSERVATIVE VERSUS SURGICAL MANAGEMENT OF VESTIBULAR SCHWANNOMAS

A case-control study comparing facial nerve preservation in patients managed by either initial conservative or initial surgical management. This chapter represents an updated version of a study published previously by the author in the journal 'Clinical Otolaryngology' (Martin, 2008).

Introduction

Central to this thesis is the concept of conservative management of vestibular schwannomas: a management strategy that allows the study of tumour growth patterns and their secondary consequences, such as the progression of hearing loss in watched lesions. The data presented here is critically dependent upon the accumulation of a significant database of 'watched' patients with growing or static tumours: without the management strategy outlined in the introduction to this thesis, this database would not have been developed.

It is important to recognise, however, that conservative management remains a debated strategy. Traditionally, the strategy has been seen as one that should be reserved for elderly patients or those who are unfit for surgical treatments due to medical comorbidities (Nedzelski, 1986). As recently as in 2005, in a 'meta-analysis' of conservative management – more accurately described as a compendium and summary of published case series - published in *Laryngoscope* (the leading international journal of otolaryngology), the technique was described as 'controversial' (Smouha, 2005).

‘Wait and scan’ or ‘conservative’ management was initially proposed in the mid-1980’s (Nedzelski, 1986) and has become increasingly accepted (among some clinicians) over the past two decades. As described elsewhere in this thesis, in our department conservative management takes the form of an initial clinical assessment when the patient is seen with the diagnostic MRI scan. If the tumour is small or medium sized (<2cm in the cerebellopontine angle (CPA)), and the patient agrees, the scan is repeated after an observation period of 6 months dating from the initial scan. Thereafter, assuming the tumour has not grown, scans are repeated according to the protocol described in the following chapter. Follow-up continues life-long. If the tumour demonstrates evidence of growth (generally a change in maximal diameter of >2mm annually), then definitive treatment is offered (surgery or radiotherapy). The attractions of conservative management as a strategy are obvious: in a case where a tumour does not grow, a patient avoids a major otoneurological procedure that requires a protracted recovery period with considerable morbidity attached. Following this argument, it would seem logical to pursue an initial period of observation in all patients whose tumours are not of a size that demand urgent removal due to a high risk of incipient intra-cranial complications.

There are, however, counter arguments to this approach, which focus on the increased growth of the tumour during the period of observation. It is well-recognised that the rates of facial nerve paralysis for all types of vestibular schwannoma surgery increase with size of tumour (Gormley, 1997, Kaylie, 2001, Mamikoglu, 2002), and it follows from this observation that patients who have been ‘watched’ and ‘failed’ conservative management will suffer more complications than those who undergo an operation at the earliest opportunity. It is also recognised that hearing can

deteriorate while patients are under observation (see Chapter 3), and observed patients are at risk of missing an opportunity for hearing preservation surgery. Furthermore, it is argued that growth in acoustic neuromas is unpredictable, and it is unsafe to leave a tumour in a young patient untreated that may grow sporadically at an unspecified time in the future, perhaps long after the patient has been lost to follow-up. Advocates of early surgical intervention often cite these arguments when suggesting that conservative management should be reserved for those patients who are elderly or unfit for ‘definitive’ (i.e. surgical or radiotherapeutic) management (Meyer, 2006).

Regrettably, no randomised studies exist that compare the efficacy of different management techniques employed to treat vestibular schwannomas. In the absence of such studies, this chapter presents a case-control study with an intention-to-treat analysis comparing the primary surgical outcome in vestibular schwannoma surgery (facial nerve preservation).

Methods

Database

As previously, data are taken from the Birmingham Vestibular Schwannoma Database, updated here in January 2010. Details of data collection and recording with respect to surgery and conservative management are discussed in the introduction to this thesis (Introduction, section ‘Birmingham database of vestibular schwannomas’).

Study design: Intention-to-treat analysis

An ‘intention-to-treat’ analysis is one in which two or more treatment options are compared, with analysis of results made based upon the initial treatment group allocated, even when individuals in that group may have received treatment from another therapeutic arm. This form of analysis is employed to prevent bias that may occur when high risk patients move from a conservative management arm to a more interventional one. An example sometimes cited might be an analysis of medical versus surgical treatment for ischaemic heart disease: some patients (the high risk individuals), may begin in the medical arm and then move (due to treatment failure) to the surgical arm: for the purposes of analysis, those ‘surgical’ patients must be analysed with the ‘medical’ rather than the ‘surgical’ group, otherwise they will bias the outcome in favour of medical treatment. In this study, patients who undergo conservative management initially, but then demonstrate growth and are treated surgically are analysed in the ‘conservative’ rather than the ‘surgical’ arm.

Design of surgical and conservative ‘arms’

As discussed above in this thesis (see Introduction, section ‘Treatment, Conservative Management’), patients undergoing initial surgical management are most commonly those patients with tumours measuring greater than 2cm in the cerebellopontine angle (CPA), whereas those undergoing conservative management are those that are either intracranial (not extending to the CPA, but located in the internal auditory meatus), or measuring less than 2cm extending to the CPA. To devise arms that consisted solely of ‘initially surgically’ and ‘initially conservatively’ managed patients would be misleading: those grouped in the surgical ‘arm’ would have presented with tumours of much greater size than those in the conservative arm and

their tumours would not have been suitable for conservative management, leading to a irrelevant comparison.

In order to avoid this problem, only those patients treated with initial surgical management who might have been eligible for conservative management are included in the study. To this end, all patients with tumours measuring <2.5cm in the CPA are included in the surgical arm:

historically in our department, these patients were managed more aggressively than at present.

An upper limit of 2.5cm was chosen because this allows the maximum number of surgical patients to be studied while allowing for appropriate conservative ‘control’ subjects.

The conservative arm of the study is designed in order to match the surgical arm described above, with priority in matching given to those two factors - tumour size and duration of follow-up – that are considered most likely to be of relevance to the study. Tumour size is of importance because of the known association between surgical outcomes and tumour size, follow-up duration because it is only through surveillance that change in tumour behaviour is recognised with conservative management. Many more tumours of small-medium size are managed conservatively than with initial surgical management, and therefore it is possible match patients in this arm to those in the surgical arm.

Matching was carried out by ‘batching’ patients in groups according to tumour size, and then selecting those patients with the longest duration of follow-up. Thus: in the surgical group, 13 patients were treated with CPA tumours that measured between 0 and 5mm. In order to find conservatively managed matches, all those patients with tumours of that size were grouped and

the 13 patients with the longest duration of follow-up were chosen. The process was then repeated with CPA tumours measuring 5-10mm, with the largest group of tumours measuring 20-25mm.

Data analysis

Facial nerve preservation rates are recorded according to the most recent clinical assessment made, assuming this is at least 12 months following surgery (12 months is a standard reporting time for facial nerve outcomes after surgical treatment and reflects the fact that nerve recovery after surgery may not be maximal until this time has elapsed [Mamikoglu 2003]). If the most recent data is less than 12 months following surgery, and the facial nerve outcome is greater than grade II, the patient is excluded. In some cases, a good facial nerve outcome is recorded relatively soon after surgery and thereafter not recorded: such patients are not excluded. In one case, facial nerve rehabilitation has been carried out: in this case, the rehabilitated facial nerve outcome is reported.

Conservatively managed patients are considered to have normal facial nerve outcomes unless otherwise recorded, as are patients treated with radiotherapy. In both cases, an abnormal outcome would be unexpected, and therefore it is not unreasonable to consider omission of the information as indicative of normal facial function. In all cases, the most recent facial nerve outcome (using the House-Brackmann scoring system [House, 1985]) is recorded.

House-Brackmann Facial Nerve Scoring System

The House-Brackmann System for grading the function of the facial nerve (House, 1985) is the most commonly used among many available, and that employed in our department. Its strengths include that it is relatively easy to apply, and consistent between assessors. A weakness is that the six grades (I-VI with I representing normal function and VI representing complete lack of function) are designed to enable the above described strengths rather than to reflect the severity of the disability. Thus the severity of disability suffered in a move from grade I-II is unlikely to be of exactly the same handicap as a move from grade III-IV. Equally, inter-patient effects may be different: it may be that a twenty-year-old young woman would feel the effects of a grade II palsy more acutely than a seventy-year-old man would suffer from a grade III palsy.

Unfortunately, there has not been a study validating the scoring system against patient self-assessment, thus making quantification of handicap difficult.

Statistical analysis

The two arms of the study were compared for equivalence and assessed in terms of facial nerve outcome using SPSS for Mac 1.6. The groups were compared in terms of patient demographics (age and sex) and tumour size at presentation. Appropriate independent samples t-tests and chi-square tests were used.

Statistical analysis of facial nerve outcomes differs considerably when compared to the technique employed in the study published in 2008, with an improvement in methodology. In the original study, groups were not matched, and comparison was made between facial nerve outcomes for all conservatively managed tumours and surgically treated tumours that may have

been suitable for conservative management. A calculation was made to generate 'expected' facial nerve outcomes for conservatively managed patients with data drawn from the surgical cohort. The 'observed' and 'expected' outcomes were then compared for equivalence. The flaw with this approach was that our calculations treated the facial nerve grading system scores in a manner appropriate for continuous but not ordinal data.

In the current study for this thesis, the means of testing facial nerve outcomes has been adapted in order to make the calculations more appropriate for the assessment of ordinal data. Thus, facial nerve outcomes are categorised as either representing a 'good' outcome (House-Brackmann grades I or II) or a 'less-than-good' outcome (House-Brackmann III-VI). The decision to classify grades I and II as 'good' reflects other published studies of facial nerve outcome data (Mamikoglu, 2003). The resulting data is then assessed for a statistically significant difference with a Chi-square test.

Results

The study 'arms' are summarised in Figure 5.

Figure 5: Study arms

Surgical arm

217 patients underwent primary surgery



100 suitable for conservative management included in study



2 patients awaiting surgery, 4 inadequate follow-up



Total surgical arm= 94

Conservative arm

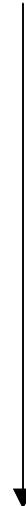
Initial group (matched for size to surgical arm), **n=94**



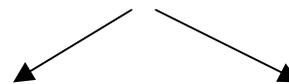
no growth: n=59



growth not requiring intervention: n=7



significant growth requiring treatment n=28



Surgery n=16 Radiotherapy n=12

Surgical arm

From the database, 217 patients who had undergone primary surgical treatment of a vestibular schwannoma were identified. Of these, 100 vestibular schwannomas were sized <2.5cm in the CPA, and might have been considered eligible for conservative management. 2 patients had not yet received treatment, and were therefore excluded from the study. A further 4 patients were excluded due to inadequate follow-up. The 94 remaining patients are presented in Table 25. 75 patients in this group have a 'good' outcome (House-Brackmann I-II), 19 a 'less-than-good' outcome (House-Brackmann III-VI).

Table 25: Demographic and tumour characteristics of patients treated with primary surgery

Total patients	Mean age	Sex distribution	Tumour size at presentation	Surgery type	Facial nerve preservation outcomes
n.=94	50.1	F=43 M=51	Intracranial: 13 0-0.5 ¹ CPA: 14 >0.5-1 CPA: 16 >1-1.5 CPA: 15 >1.5-2.0 CPA: 30 >2.0-<2.5 CPA: 6	Translabyrinthine: 60 Retrosigmoid: 34	I=49 II=26 III=17 IV=1 V=1 VI=0

1. Sizes are in cm, measured (as previously described) as the maximal axial length of the tumour parallel to the petrous at the level of the cochlea

Conservative arm

As described above, patients managed conservatively from the database were matched with those from the surgical group to avoid a significant disparity in tumour size. Details are presented in Table 26.

The mean follow-up in the conservatively managed cases chosen was 81 months (range 12-154). Within the group, the rate of growth leading to definitive treatment was 30%. 89 patients in this group have a ‘good’ outcome; 5 a ‘less-than-good’ outcome.

Comparison of groups

There was no significant difference in sex distribution between the groups (Chi-square test). There was a statistically significant difference in the mean age of patients in the two groups.

Table 26: Demographic, tumour and outcomes in conservative arm

Total patients	Mean age	Sex distribution	Tumour size at presentation	Outcome of conservative management	Facial nerve preservation outcomes
n.=94	61.6	F=43 M=51	Intracranial: 13 0-0.5 CPA: 14 >0.5-1 CPA: 16 >1-1.5 CPA: 15 >1.5-2.0 CPA: 30 >2.0-<2.5 CPA: 6	No growth: 59 Minimal growth: 7 Growth requiring further treatment: 28 (Surgery: 16 Radiotherapy: 12)	I=87 II=2 III=5 IV=0 V=0 VI=0

Those in the surgical group were younger (mean age 50 (SD 10) vs. 62 (SD 11)) than those in the conservative group ($p=0.000$, CI -15 - -8). This difference in age between the conservative and surgical groups studied reflects a general age bias towards youth in patients in our database that are managed definitively at presentation (see Chapter 1, Table 10). It is not thought to be relevant to the study undertaken here: to match for age would have necessitated a reduction in duration of follow-up available to the conservative arm studied. Tumour size was a little larger (mean 14mm vs. 13mm) in the surgical group, but this difference was not statistically significant.

Mean facial nerve outcome: comparison between groups

Chi-Square test evaluating the difference between the groups in terms of facial nerve outcome was highly significant ($p=0.002$).

Discussion

The aim of this study has been to compare outcomes between two different treatment modalities used to manage small-medium sized vestibular schwannomas: primary conservative management and primary surgical management. In the absence of any randomised, controlled trials addressing the topic, a case-control study using an intention to treat design has been developed. The cases are those patients undergoing surgical treatment for vestibular schwannomas with controls (matched for tumour size) drawn from our database of conservatively managed patients. Despite caveats to be discussed below, this study offers strong evidence that initial conservative management (with appropriate secondary ‘definitive’ management) offers the best opportunity of facial nerve function preservation for patients presenting with a small-to-medium sized vestibular schwannoma.

Limitations of the study

Retrospective design

As noted above, there are no prospective, randomised studies that explore this question. This is perhaps understandable given the history of the topic. Initially, conservative management was seen as a treatment suitable only for those with medical co-morbidities or advanced age: to many practitioners, to randomise young healthy patients to a conservative treatment arm would have been unethical. Subsequently, as conservative management became more acceptable, randomisation to surgery would have posed similar ethical difficulties.

There are, of course, other benefits to a prospective study design. It would have been preferable, for example, to submit patients to independent assessment of facial nerve function: there is an

obvious temptation for the assessor to upgrade outcomes, particularly if he is the operating surgeon (as was the case in our study). In this study, any effect of such a bias would be negated: there would be the same felt in both arms, hence reducing any impact.

Limited outcome measurement: lack of hearing data

In this study, we have only measured one outcome: facial nerve preservation. There are other outcomes that could be considered, including hearing preservation, patient satisfaction and economic considerations. Some of these issues have been previously addressed in the literature, and will be addressed below. The previously published study (Martin, 2008) that forms the basis of this chapter did address hearing preservation, and found a significant preservation of hearing within the conservative group relative to those patients treated with hearing preservation surgery. Table 27 reproduces these data.

Table 27: Original data relating to preservation of hearing (as published in Martin, 2008)

Patients managed conservatively at first consultation	Patients managed surgically at first consultation
Total n. 59 (Class A n. 23, Class B n. 36)	Total n. 30 (Class A n. 15, Class B n. 15)
Demographic characteristics at presentation:	Demographic characteristics at presentation:
Sex distribution: F 30, M 29	Sex distribution: F 15, M 14
Tumour size: n. Intracranial= 41	Tumour size: n. Intracranial= 8
n. CPA= 18	n. CPA= 21
Mean CPA= 0.9cm	Mean CPA= 1.0cm
Mean follow-up: 45 months	
Outcomes (includes growth patients):	Outcomes:
n. with documented audiological follow-up: 41 (mean duration of follow-up: 45 months)	n. with follow-up: 30
(n. Class A =15, n. Class B=26)	
Class A	Class A
n. preserving Class A hearing: 7	n. preserving Class A hearing: 1
n. from Class A moving to Class B: 7	n. preserving Class B hearing: 2
n. from Class A moving to Class C/D: 1	n. preserving Class C/D hearing: 2
n. with no hearing: 0	n. with no hearing: 10
Class B	Class B
n. preserving Class B hearing: 12	n. preserving Class B hearing: 2
n. dropping to Class C or D: 13	n. preserving Class C/D hearing: 3
n. rising to Class A: 1	n. with no hearing: 10
n. with no hearing: 0	
n. preserving hearing Class A or B: 26 (63%)	Total n preserving hearing Class A or B: 5 (17%)

In this chapter, hearing preservation has not been addressed for a number of reasons. Most importantly, to compare conservative and surgical management in this way is less appropriate for this outcome than for facial nerve function. Chapter 3 has demonstrated that hearing loss in conservative management is common and generally slowly progressive: most patients will lose

their hearing, but this end-point will often be delayed for a number of years. Patients who undergo hearing preservation surgery will either lose their hearing immediately, or it will be maintained: it is not expected to progressively decline at a greater rate following surgery than that seen in presbycusis. To compare these two modalities with relatively short follow-up, therefore, would seem a little disingenuous: the issue of hearing preservation is perhaps better considered by examining a large cohort of conservatively managed patients (such as our own), while also examining a large cohort of surgically-managed patients from the literature. An observation made in our previous study and supported by data in Chapter 3 (see Table 24, Chapter 3) is that only a small proportion of patients lose candidature for hearing preservation surgery during the period of observation before tumour growth becomes manifest (n. 2 of a total of 12 individuals).

Other outcome measurements

The psychological effect of a partial facial nerve palsy upon patients cannot be under-estimated. Even those results classed as ‘good’ by the surgeon (House Brackmann grades II and III) may be seen as disfiguring by patients. A recent survey of 2,372 members of the Acoustic Neuroma Association (response rate 82%) who had undergone surgery for a vestibular schwannoma found that 45% of patients experienced facial weakness post-operatively, and in 72% this was permanent. 28% of all respondents to the survey felt significantly affected by facial weakness, and 30% felt their quality of life had suffered following surgery (Ryzenman, 2005). Although mortality is extremely rare in vestibular schwannoma surgery in the modern era, other complications such as CSF leak post-operatively can be troublesome as can be symptoms such as headache and imbalance.

The psycho-socio-economic cost to patients of vestibular schwannoma surgery has been studied by Pritchard *et al.*, (2003). These authors point out that many patients with vestibular schwannomas are at the peak of their life-time earning power, and that a significant proportion (34%) are unable to work for more than six months following surgery: they calculate the economic cost to each patient at £11 220 each. Psychologically, 75% felt anxious about whether ‘they would ever be normal again’ and 39% of patients were depressed post-operatively; similar findings were reported by carers of patients with acoustic neuromas. Another study (Sandooram, 2003) comparing quality of life between patients undergoing conservative management, surgery and radiotherapy found a significantly higher quality of life in conservatively managed patients.

Chapter conclusion

This chapter reports a case-control study comparing facial nerve preservation rates in patients managed with primary surgery and with primary conservative treatment. The study design follows principles of ‘intention-to-treat’ reporting ‘failures’ of conservative management undergoing surgery or radiotherapy within the conservative group. The study finds strongly and statistically significantly in favour of conservative management with respect to preservation of the facial nerve.

CHAPTER 5: A PROTOCOL TO DIRECT THE CONSERVATIVE MANAGEMENT OF VESTIBULAR SCHWANNOMAS

A review of data in order to develop a protocol to enable safe and cost-effective conservative management of vestibular schwannomas minimising superfluous investigation and loss to follow-up. This chapter represents an updated version of a study published previously by the author in the journal 'Otology and Neurotology' (Martin, 2009). The work presented here was awarded a prize for the best trainee presentation at the British Skull Base Society Meeting (London, 2010).

Introduction

Although the view is controversial, it has gradually become accepted by many clinicians that conservative management can represent effective treatment to stand next to 'definitive' established treatments (surgery or radiotherapy), and is not merely a compromise therapy reserved for those unfit for interventional management. The aim of this paper is not to discuss the validity of conservative management *per se*, but rather to present a protocol to guide the frequency of imaging follow-up employed.

Conservative management of vestibular schwannomas is evolving, and to date, little has been proposed in the form of a protocol to guide clinicians with respect to the frequency and timing of follow-up scans. Clearly, the priority is not to allow rapid tumour growth to pass un-noticed, but at the same time, it is important to minimise unnecessary investigations with attendant costs in terms of resources and patient time. In order to devise such a protocol, we have reviewed our

database of conservatively managed patients to determine temporal patterns of growth. We have assessed the timing of detection of growth, and also sought trends in different rates of growth.

In approaching the study, a number of key questions are asked related to the timing of monitoring radiological investigations. The first question pertains to the timing of the initial scan following diagnosis: when should this be carried out in order to detect rapidly growing tumours? The second to the timing of subsequent scans: how often should these be carried out? Finally, it is important to consider whether scanning can be discontinued at any stage in the management of patients with apparently stable vestibular schwannomas.

Methods

Historical surveillance regime

As previously outlined in this thesis, all patients with small or medium-sized tumours presenting to the Birmingham skull base unit are offered an initial trial of conservative management. Tumours fulfilling these criteria are either intracanalicular or ≤ 2 cm in maximum diameter in the cerebellopontine angle (CPA). If the patient agrees, a follow-up scan takes place at 6 months, then annually thereafter for 5 years. If a tumour is demonstrated to grow (defined as growth of >2 mm/yr. in maximal diameter, or persistent more indolent growth over a longer timescale), the patient is offered expeditious intervention in the form of either surgery or radiotherapy, dependent upon tumour and patient factors, hearing status, and patient preference. In some cases, where patient and tumour factors indicate, surveillance continues.

Data collection

The Birmingham database of vestibular schwannomas carries data pertaining to all patients managed in the above way from 1997-. As previously outlined, demographic data and the outcomes of conservative management are recorded in the database, updated for the purposes of this chapter in January 2010. Patients being managed with primary conservative management were reviewed. Those awaiting a follow-up scan following diagnosis were not examined further. A record of those lost to follow-up was made: this is defined as there being no record of attendance within 6 months of an anticipated out-patient visit. The effect of this is to include patients within this category who may have been followed for some time before being lost.

A record of the number of scans attended by each patient within the series of conservative management was also made. It has been previously noted that within all series of conservatively managed patients, there is a tendency for there to be many more patients with shorter, rather than longer follow-up, and our series is no exception. A central argument within this chapter is the redundancy of later scans in detecting tumour growth, and it is important to recognise that a significant proportion of patients have been imaged at this stage within the series. It should be recognised that these data are drawn from the duration of follow-up, rather than from an actual calculation of attendances for radiological surveillance.

Patients who had demonstrated growth during observation were analysed further with the aim of answering the following questions:

1. Did the tumour demonstrate growth during the time of surveillance?

2. If so, at what time following diagnosis was growth manifest?
3. What was the rate of growth seen?

Data pertaining to tumour growth are taken from patient records. As previously described (Introduction), tumours extending to the CPA were measured in their greatest dimension parallel to the petrous ridge. The records were searched to determine the timing of detection of growth following the patient's initial clinic presentation.

Results

Outcomes of conservative management

Table 28 presents details of patients considered during the study. Of 471 patients under conservative management, some 421 had been seen at least once following diagnosis (50 patients are awaiting follow-up). From this group, 99 patients had demonstrated tumour growth over time. It should be noted that not all of these patients have been treated definitively with either surgery or radiotherapy: some 26 continue to be monitored due to very slow tumour growth, medical co-morbidities, patient choice, old age, or a combination of these factors.

A protocol such as that presented below is highly dependent upon effective follow-up. In Table 28, a loss to follow-up rate of 10% is reported, based upon a rigorous definition that considers a patient 'lost' if they are not seen in the out-patient department within 6 months of an anticipated review appointment. This figure is similar to those published by other series (see Table 5). In reality, the number of patients genuinely 'lost' within our series is likely to be less than this. Included within the group are a number of patients who have voluntarily refused further follow-

up due to old age or claustrophobia preventing further scanning: in these cases, at least one follow-up scan has been able to rule out a rapidly growing vestibular schwannoma.

Table 28: Patients under conservative management

Total number of patients:	471
Number with at least one follow-up scan:	421
Number displaying growth:	99 (24%)
Number not growing or regressing:	281 (67%)
Mean follow-up in this group:	51 mths
Number lost to follow-up (4 patients failed to attend any follow-up, 2 patients actively refused follow-up due to age):	41 (10%)

In other cases, patients may be lost from follow-up after a number of serial attendances: such individuals are unlikely to be at significant risk from a rapidly growing vestibular schwannoma. Finally, a number of patients are under surveillance by local otolaryngologists after attending the Birmingham skull base clinic for their first review: although attempts are made to ensure contact is maintained between local teams and our centre, this is not always achievable. While these patients may be defined as ‘lost to follow-up’ in this chapter, they are unlikely to be at significant risk. Further details of patients lost to follow-up are provided in Chapter 1.

Tumour growth rates

Figure 6 below and Table 29 present details of tumour growth rates. In 92 cases it was possible to calculate a growth rate.

Figure 6: Growth rates in growing tumours

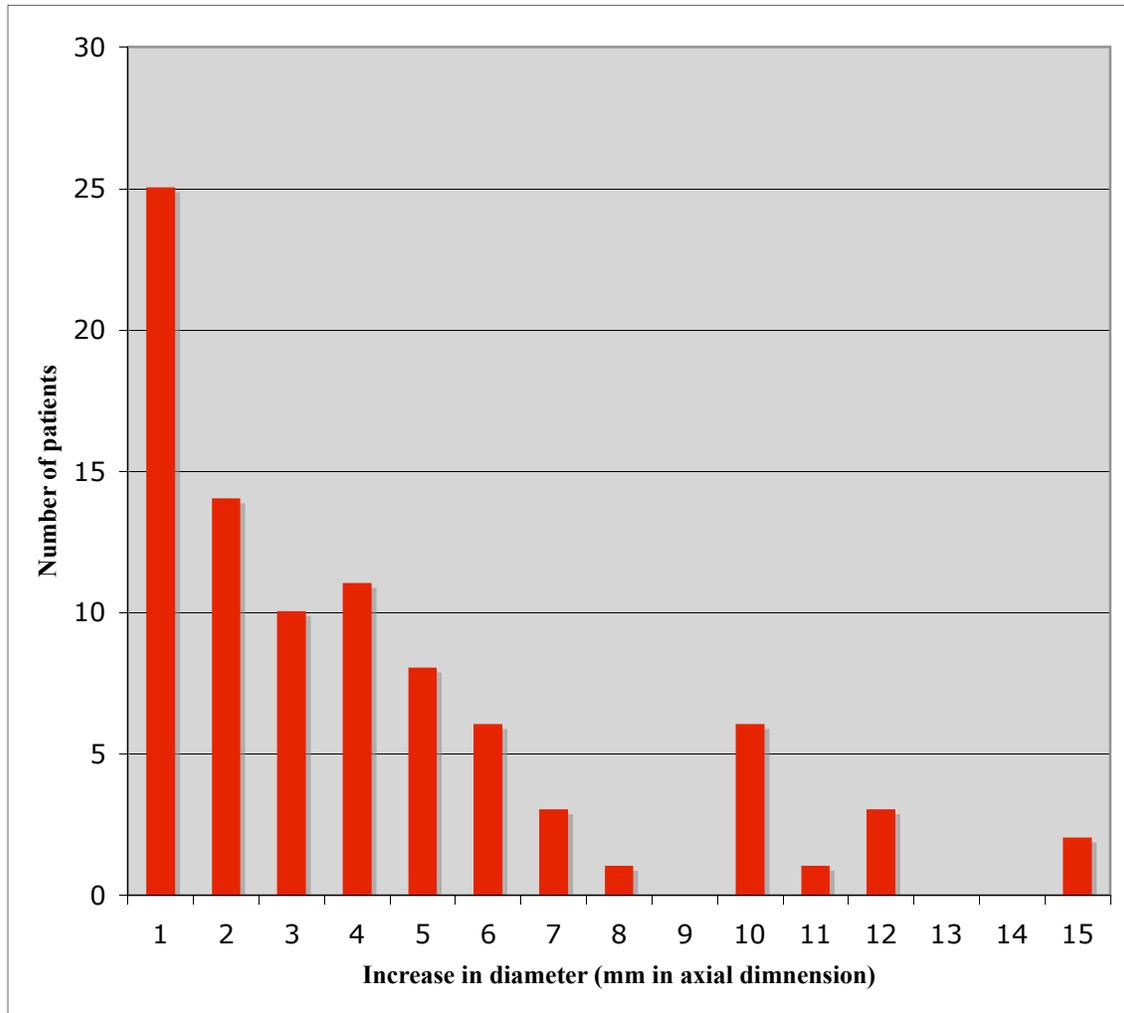
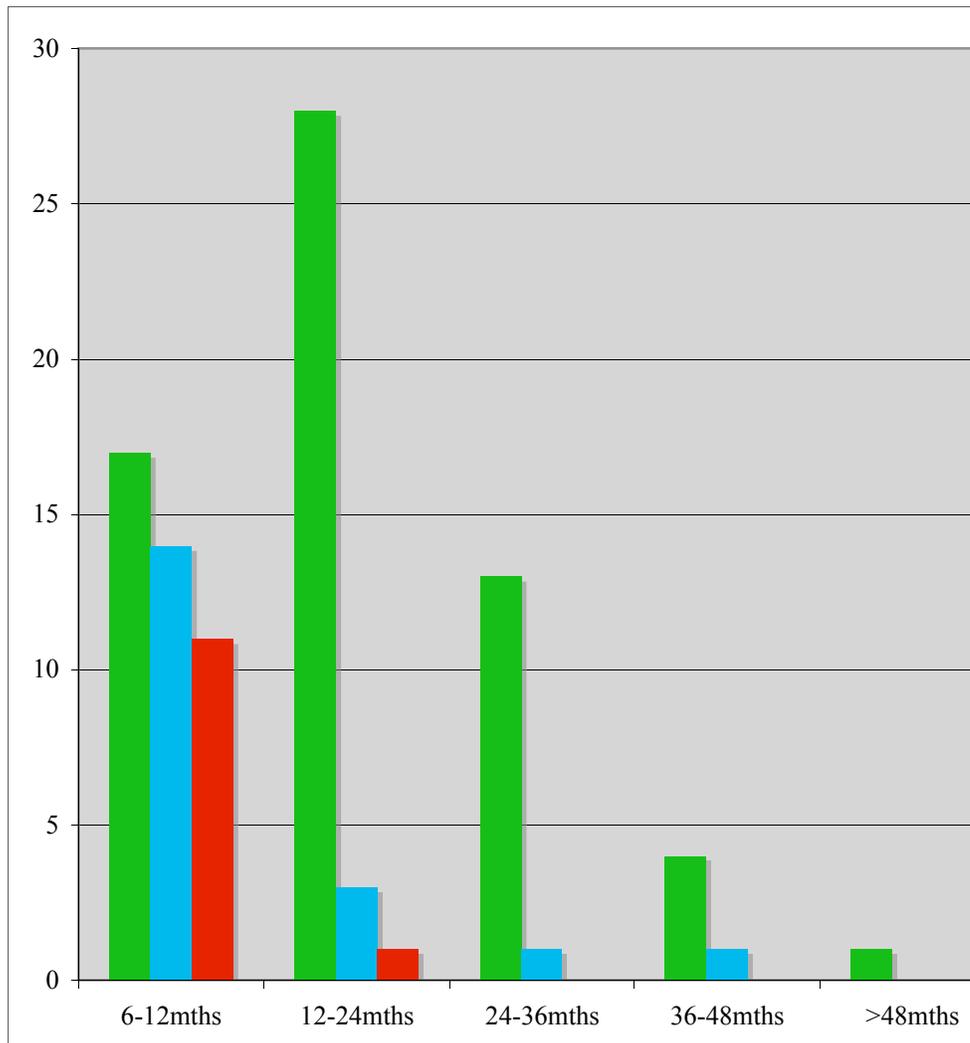


Figure 7 below illustrates the time at which tumours were found to be growing.

Figure 7: Time of detection of growth with tumour growth rates



Key: Green: 0-4mm annually

Blue: 4-10mm annually

Red: >10mm annually

The growth rates found illustrate clearly the variability of growth rates among tumours. While the majority of tumours grow slowly, with rates of between 0.5 and 4 mm annually, there are a significant number that grow much more rapidly. The misleading impression given by

publishing ‘mean’ growth rates that include non-growing tumours has been discussed previously in this thesis (see Introduction and Martin, 2005), and an awareness of the variability of growth rates emphasises the importance of this argument further.

Table 29: Clinical characteristics of differentially growing tumours

Growth rate (increase in annual axial diameter, mm)	Cystic	Intracanicular (%), mean CPA size
0-4 mm n=62	9%	33% I.can, 11 mm
4-10 mm n=18	11%	28% I.can, 12 mm
>10 mm n=12	42%	18% I.can, 15 mm
All watched tumours	0.5%	50% I.can, 12 mm

While the numbers of rapidly growing tumours are relatively small, a number of trends are noticeable. The first and most important is the significance of a cystic morphology. As has been demonstrated in Chapter 2 of this thesis, intra-tumoral cysts are strongly predictive of growth within vestibular schwannomas. Table 29 illustrates that cystic tumours are both more likely to grow than solid tumours, but are also more likely to grow rapidly: of those tumours that grew at a rate of more than 10 mm annually, almost half contained intra-tumoral cysts. A further observation is that there is also a weak trend towards smaller tumours showing less rapid growth than larger tumours.

Figure 7 illustrates the time at which tumours were found to be growing. Of interest is the fact that the majority of growing tumours are identified at either the first or second surveillance scan

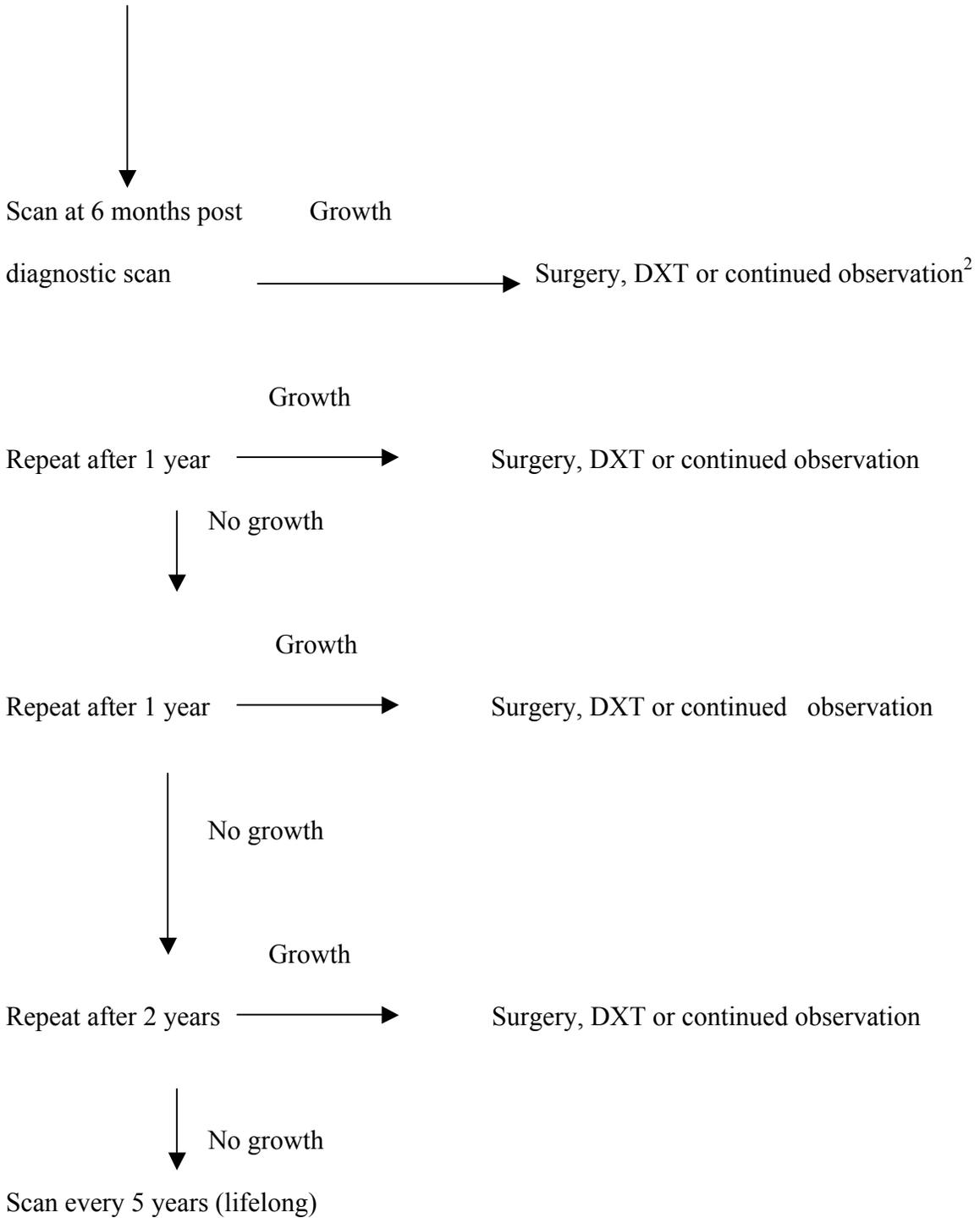
following diagnosis. This is particularly true of those tumours that represent the greatest risk to patients: those that are rapidly growing. Tumours that are after a number of review visits at which the tumour was not felt to be growing are almost exclusively those tumours that demonstrate slow growth. In one case only, growth was detected more than 4 years after initial presentation: in this case the tumour was found to have grown only 4mm over the course of 6 years.

Proposed protocol for conservative management and rationale (see Figure 8)

If conservative management of acoustic neuromas is to prove successful, it must achieve two broad aims. The first is to identify growing tumours in a timely fashion so that the change in tumour dimensions does not prejudice outcomes in terms of facial nerve preservation and an opportunity for hearing preservation surgery. The second is to ensure patient compliance with follow-up: although our series suggests that tumour growth will be manifest in the first few years of surveillance, long-term follow-up of large patient series is not available, and it is vital that patients remain under active surveillance in order to chart the natural history of a tumour that can be life-threatening if left untreated. A treatment algorithm such as the one proposed below can, achieve both these ends.

Figure 8: Proposed protocol for the conservative management of vestibular schwannomas

Solid tumour, size intracranial or <2cm in CPA, opt for conservative management



In our series, a decision to intervene and to offer definitive treatment (i.e. surgery or radiotherapy) has been taken in 90% of patients before 2 years have elapsed, thereafter, the proportion of scans that reveal growth becomes much smaller. Clearly, a negative scan is reassuring to both clinician and patient, and provides useful data to explore the natural history of acoustic neuromas, but it also represents a considerable burden in terms of imaging services. For this reason, the protocol presented advocates that an initial follow-up scan takes place at 6 months, then at annual intervals for two years. A further scan after 2 years have elapsed will detect those rare tumours that demonstrate an early non-linear growth pattern. Following this period, we recommend repeat imaging every 5 years to continue lifelong. Our experience of long-term follow-up of patients with acoustic neuromas is evolving, but we have to date followed some 80 patients for at least five years, and none of these patients have manifested growth after 5 years.

An area of debate lies in the size of tumours that should be considered for conservative management at the outset. Stangerup (2006) suggests managing tumours of <15mm in the CPA conservatively. We have successfully managed larger tumours (up to 27mm) in this manner, although would only routinely treat those <20mm in this way. Clearly, in cases where tumours are larger, a number of patient and tumour factors can be taken into account to guide therapy. In the case of a young patient with a 15mm tumour, a short duration of symptoms, serviceable hearing and a willingness to undergo surgery, for example, conservative management may not be appropriate. On the other hand, an elderly patient with a very long history of symptoms, a 25mm tumour and medical co-morbidities might be an excellent candidate.

If Chapter 2 of this thesis has demonstrated the difficulty of predicting whether vestibular schwannomas are likely to grow under observation or not, it is clear that in the case of cystic tumours, the risk of growth is particularly high. As seen previously, these tumours represent a disproportionate number of growing tumours and as seen in this chapter, are highly likely to demonstrate rapid growth. In some cases, cystic degeneration occurs in a previously ‘solid’ tumour, but in others, cysts are present from diagnosis, and such tumours should only be managed conservatively with great caution.

Discussion

Series that have described conservatively managed acoustic neuromas to date have generally described a group of patients who have been accumulated over a relatively long period of time (see Table 5). These patients have been managed conservatively for various reasons (medical problems, old age, or patient preference), and there is rarely a description of a structured approach to the timing of follow-up scans. We believe that the series we present here is relatively unusual in that the patients presented have been managed conservatively from the outset, with an initial period of conservative management advocated in almost all cases of small-medium sized tumours that present to our service, regardless of age. This has been particularly true latterly, as has been previously discussed in this thesis. This approach to the management of acoustic neuromas has necessarily led to the accumulation of a large cohort of patients with tumours that are being followed with serial imaging: at present, we have some 472 patients who are being monitored for evidence of tumour growth, and each year we are adding a further 80-100 patients to this group. Clearly, such a cohort represents a significant burden to our neurotological imaging service.

Most authors have hitherto recommended annual follow-up scans after an initial scan at 6 months (Glasscock, 1997, Flint, 2005). Raut (2005) advocates these scans to continue lifelong. While we concur that surveillance should continue indefinitely, we feel that such frequent scanning is unnecessary. While a number of authors (Stangerup, 2006, Raut, 2005) have noted an unpredictable pattern of tumour growth, in our series, the majority of patients (91%) have demonstrated growth within three years, a finding echoed by Wiet (1995). In the largest published series of conservatively managed acoustic neuromas published to date, Stangerup (2006) has also observed that growth becomes manifest within 5 years. For this reason, we are reluctant to suggest that patients should be recalled on an annual basis after this time period has elapsed. Clearly, long-term follow-up of acoustic neuromas is lacking, and we would therefore be reluctant to discharge patients who would appear to have an apparently static tumour. The period of five years is an arbitrary figure for intermittent follow-up following the initial surveillance episode, but should allow us to remain in contact with patients without obliging them to attend too frequently.

Stangerup (2006) has published a protocol to guide conservative management suggesting annual scans for five years, a further two scans after years 7 and 9, and finally a scan after 14 years prior to discharge. While our protocol broadly follows this regime, we differ in three important areas. We believe an initial scan at 6 months is a valuable tool, and will identify a considerable number of growing tumours, in particular those that most represent a threat to patients in terms of the complications of definitive treatment in cases of failed conservative management. Secondly, we advocate less frequent scans in the period following this initial

interval scan- tumours that are identified at this stage are likely to be indolent in nature. Finally, we would suggest that follow-up be lifelong, carried out every five years: as stated above, the natural history of acoustic neuromas in the long term has yet to be fully described.

Fundamental to the success of conservative management is effective follow-up. The danger in losing patients with known pathology is evident- Glasscock (1997) reports a case of a patient lost to follow-up who re-presented after over three years with a significantly enlarged tumour and subsequently died from surgical complications. In our own series, a rate of 10% loss to follow-up is reported using a rigorous definition, and for reasons outlined above, it is unlikely that all the patients within this group are at risk of the fate described by Glasscock. Despite this, a number of principles can be followed to ensure maximal compliance with follow-up. It is essential that patients understand clearly the rationale of the treatment they receive and the responsibility they have to attend for follow-up: in some cases where a chaotic lifestyle threatens to make this unrealistic, conservative management may not be appropriate. We also make every attempt to ensure that follow-up is convenient: many patients are scanned at their local hospitals, thus reducing the distance travelled to attend appointments at the tertiary referral centre. We also feel that reducing the number of follow-up scans should have a positive effect upon follow-up: if a patient feels they are continually having to attend for scans that are negative, they may be inclined to default.

Chapter Conclusion

The aim of this chapter has been to design a protocol for the timing of surveillance scans based upon evidence provided by over ten years of conservative management. The Birmingham series is the second largest single series of conservatively managed acoustic neuromas in the published literature to date. Furthermore, this large cohort of patients has been collected due to an evolving management policy of treating all tumours that are intracanalicular or <2cm in the CPA conservatively. Such a policy inevitably leads to a significant accumulation of patients requiring radiological follow-up. Existing recommendations in the literature advocate annual follow-up to continue indefinitely, a practise that would exert an exponential burden upon an imaging service. Review of our series of conservatively managed patients over the past ten years reveals that the majority of patients (90%) who will demonstrate tumour growth do so before three years have elapsed: the remaining 10% have become manifest within 6 years of presentation. We have presented a protocol that focuses upon regular follow-up in the first 5 years, with greatest intensity during the initial period when growth is most commonly detected. We believe that further growth may be seen, however, and advocate 5-yearly follow-up thereafter. We feel that the initial 6 months scan is of paramount importance, and will identify the majority of tumours that represent a considerable threat to patient health. Cystic tumours represent a particular threat to patients, and should only be managed conservatively with great caution. It is to be hoped that longer- term follow-up will allow this protocol to be improved and modified.

CHAPTER 6: FUNCTIONAL SURGERY IN THE MANAGEMENT OF VESTIBULAR SCHWANNOMAS: THE PRIORITISATION OF THE FACIAL NERVE OVER TOTAL TUMOUR REMOVAL

A case-control study examining the effect of a less radical approach to surgical tumour excision. This chapter represents a modified version of a paper published in the Journal of Laryngology and Otology (Martin, 2012).

Introduction

In tandem with the conservative approach to management of vestibular schwannomas in the outpatient setting, there has been a parallel move towards a less aggressive surgical model in the operating theatre. Whereas the surgical team traditionally saw the complete removal of the tumour as the primary object of surgery, current practice is to prioritise the preservation of facial nerve function; often at the expense of tumour removal. The aim of this chapter is to assess the impact of this change in surgical philosophy.

To date, the focus of this thesis has been to discuss various elements of conservative management of vestibular schwannomas with the reservation of surgical treatment for those tumours that demonstrate growth over time. There has been little focus upon the outcomes of surgery itself beyond providing comparison with outcomes for patients managed with a conservative ‘watch-and-scan’ as a primary strategy (see Chapters 3 and 4). The aim of this chapter is to turn attention to surgical outcomes (specifically facial nerve preservation) in patients who have been managed with surgery that does not aim to completely remove tumour.

The chapter will demonstrate that there has been an evolution in surgical practice within the Birmingham series that mirrors that in overall management. Increasingly, there is a tendency to take a more conservative approach to surgery: while the original philosophy of the surgical team favoured a total tumour resection, this has been modified, particularly since 2007, with a policy now to undertake near-total surgical excision if dissection of tumour from the facial nerve proves difficult.

Issues relating to this area have not been fully addressed in the literature search performed in the introduction to this thesis, and this chapter will therefore begin with a discussion of issues relating to sub- and near-total tumour removal. Following this, data will be presented to assess the evolution in management in Birmingham and the results of surgery.

Literature search

Search strategy

PubMed was searched using the terms: ‘vestibular schwannoma’, ‘surgery’, ‘partial’, ‘sub-total’, ‘near-total’, ‘recurrence’ and ‘limited’. From identified articles, further articles were identified for study.

Background

As also seen in the history of ‘watch-and-scan’ management described above, a ‘conservative’ approach to surgery for vestibular schwannomas dates to the mid-1980’s when Silverstein (1985) recommended sub-total resection of tumours in elderly patients with large symptomatic tumours. Historically, a decision to limit resection to a sub-total or near-total excision has been

made either pre-operatively (as above in patients for whom a lengthy procedure might prove difficult), or intra-operatively, when total resection of tumour adherent to the facial nerve rendered the procedure likely to cause significant neurological deficit, or when adverse intra-operative events (for example haemorrhage) led a surgeon to abandon the operation (Freeman, 2007).

The obvious benefits of partial surgical resection are a reduced surgical duration, and perhaps more significantly, the opportunity for improved functional outcomes: an aggressive pursuit of tumour that is adherent to the facial nerve can result in trauma manifest either as nerve division, stretching or ischaemic damage resulting in adverse outcomes post-operatively. The principle risk of less-than total removal are that the tumour residuum will re-grow necessitating further treatment.

Sub-total vs. near-total

Traditionally, a distinction has been drawn between ‘sub-total’ and ‘near-total’ excision of tumour. The terms have been defined in the 2003 Consensus on Reporting Results in Vestibular Schwannomas (Kanzaki, 2003): a ‘sub-total’ tumour removal removes less than 95% of the original tumour bulk during surgery, whereas a ‘near-total’ tumour excision is more complete. While not all articles discussing these issues adhere to this definition, the terms ‘sub-‘and ‘near-total’ are used commonly. Most series find that in terms of recurrence, there is a significantly higher risk of this occurring if a sub-total excision is achieved (Bloch, 2004, Seol, 2006, Freeman, 2007).

An interesting finding by Godefoy (2009) casts doubt upon the accuracy of surgeon's assessment of the extent of tumour resection as judged intra-operatively. In this paper, Godefoy examined the records of 51 patients treated surgically. The patients were distributed evenly between those in which the surgeon had judged him or herself to have performed 'total', 'near-total' or 'sub-total' excisions. Subsequently, a correlation was sought between post-operative MRI estimates of tumour excision and the surgeon's intra-operative assessment. MRI classification of sub- versus near-total excision followed the consensus definition described above (Kanzaki, 2003). While there was a perfect correlation between surgeon and post-operative MRI with respect to whether total or incomplete excision had been achieved, there was only a poor correlation with reference to 'sub-' versus 'near-total' excision.

The implications of Godefoy's findings are interesting. It is perhaps to be expected that the 'errors' found in the surgeon's assessment tended towards an over-confidence with respect to tumour excision. Thus, while the surgeon felt that 15 cases represented 'near-total' excision, the post-operative (blinded) radiological assessment found that only 4 cases fell into this group. Those cases where the surgeon felt that a 'sub-total' excision had taken place were all confirmed to be such. It is perhaps natural that a surgeon should wish to think that he or she has effected a more complete resection than is the case: complete tumour resection is an important principle in surgery, and to leave tumour behind represents a 'failure' for most surgeons. There will of course, be great variation between the way in which surgeons report such matters, but Godefoy's paper points to a potential flaw in those reports that do not independently measure tumour remnant in order to determine whether a resection is best described as 'sub-' or 'near-total'.

Facial nerve outcomes

While medical co-morbidities or intra-operative complications may necessitate a planned (or unplanned) ‘de-bulking’ or sub-total excision, the most common motivation for less-than total tumour excision is to avoid excessive manipulation of the facial nerve and hence to minimise post-operative facial nerve impairment. As previously discussed, there is a strong correlation both in our own series of operated tumours and in the literature generally (see Chapter 4) between tumour size pre-operatively and post-operative surgical outcomes. An early paper by Kemnick (1991) suggested that facial nerve outcomes (90% Grade I and II following the House Brackmann classification) in medium-large tumours undergoing a planned less-than-total resection could achieve those more usually associated with smaller tumours. More recently, Godefoy (2009) found a lower proportion of poor facial nerve outcomes (Grade III-VI House Brackmann) in patients who had undergone sub- or near-total resection when compared to those who had undergone total excision (13% vs. 42%). Conversely, although Seol (2006) reports better facial nerve outcomes in the immediate post-operative period for patients undergoing less-than total excision, this finding is not sustained in longer follow-up, with differences losing statistical significance. Of interest in this paper will be to determine whether our series reflects what might intuitively seem to be likely (as demonstrated by Godefoy and Kemnick), or that found by Seol.

Recurrence rates

As discussed above, the principle risk posed by incomplete tumour excision is tumour recurrence. An early report from Japan (Sakaki, 1991) analysed outcomes in 51 tumours that

had been completely or incompletely excised. Recurrence in totally excised tumours was not seen, but in sub-totally and near-totally excised tumours was common (25% and 29% respectively). Similar findings were subsequently reported by El-Kashlan (2000) who analysed 39 incompletely excised tumours and found growth on subsequent surveillance in 44%: of these, 59% required further treatment.

Freeman (2007) has offered more optimistic results in a much larger series of patients than either of those described above. In a total series of 1,083 patients with vestibular schwannomas treated surgically, 866 underwent total surgical excision, with a revision rate of only 0.5%. 128 near-totally excised tumours are described, with a revision rate of 1.6%, and a further 43 sub-totally excised tumours required revision in 26% of cases: in all cases there are impressively long periods of follow-up that are close to ten years. It should be recognised that these results report rates of revision rather than recurrence: there may be a number of cases where tumour remnant remains under surveillance despite slow growth.

From these studies, the importance of definition is clear: Freeman defines 'near-total excision' as 'tiny fragments of tumour capsule left behind, usually on the facial nerve': anything greater than this in bulk is considered a sub-total excision. In a large tumour, therefore, a 'sub-total' excision following this definition could easily represent less than 5% (the definition offered by the 2003 Consensus Document). The implication from these studies would be that there is a low risk of recurrence in those excisions where genuinely minimal amounts of tumour material have been left behind, but this risk increases significantly if bulky tissue remains (irrespective of the 95:5% definition offered by the 2003 Consensus Document).

The two definitions of ‘near-total’ outlined above represent quite significant differences in terms of tumour volume. If the ‘tiny fragments’ described by Freeman may account for perhaps a few cubic millimetres or less of tumour, then 5% of the original tumour could consist of up to 1.7 cubic centimetres in a 4cm tumour. If (as Freeman suggests), ‘tiny fragments left behind’ become non-viable due to poor vasculature, then it cannot be assumed that a tumour remnant of significant bulk would also become non-viable. It could therefore be argued that the poorer recurrence rates in some series found in near-total tumour excisions relative to those seen in Freeman’s series are found because the tumour remnant is a significant, viable tumour mass rather than non-viable ‘fragments’. Clearly, in assessing the risk of recurrence in any series of ‘near-total’ tumour excisions, it would be interesting to know whether the tumour residuum is a matter of tumour fragments or a more sizeable mass.

Methods

Patients

The Birmingham Database was searched (June 2010) to identify patients undergoing surgery. Those with inadequate data (either a lack of intra-operative information or a lack of post-operative facial nerve evaluation) were excluded from the study.

Data recovered

A record was made of demographic details recording patient age at the time of surgery and patient sex. The size of tumour at surgery was noted as was the surgical approach. The operative notes were reviewed to determine whether a ‘total’, ‘sub-total’ or ‘near-total’ tumour

removal was achieved. Where possible, a note was made of the location of any tumour remnants, and of any particular difficulties during the procedure. In terms of functional recovery, a record was made of facial nerve status (House-Brackman Classification, 1985) at the first post-operative visit (usually at two weeks following surgery), at three months following surgery and after one year. Facial nerve outcomes are those achieved with rehabilitation. A record was also made of any rehabilitation of the facial nerve, whether in the form of physiotherapy or surgery (passive or dynamic). Finally, details of any post-operative imaging were recorded.

Study design

As noted above, there has been an evolution in surgical practice towards a more conservative approach to surgery over time in Birmingham. In order to assess the effect of this change, two groups of patients are studied: those undergoing ‘functional’ surgery (a term used because the aim of surgery is to preserve nerve function), and those undergoing ‘excisional’ surgery (in this group the aim will have been to remove tumour with nerve function important but subordinate to the first aim). After discussion with the surgical team responsible for the cases studied it was felt appropriate to define these groups chronologically: a date of April 2007 was felt to represent a time at which a more functional approach was adopted.

Although the philosophy guiding surgery is as outlined above, it is important to recognise that there has never been a rigid approach to the prioritisation of tumour excision over facial nerve preservation. Thus if tumour dissection from the facial nerve proved very difficult, it has always been the case that the surgeon may elect to leave fragments of tumour *in situ* in order to try to

avoid facial nerve trauma (hence the inclusion of a number of patients with incomplete tumour excision in the ‘excisional’ group).

Comparison between groups

As outlined above, two groups were generated: the first undergoing surgery before April 2007 and classified as ‘excisional’, the second undergoing ‘functional’ surgery. The groups were studied in order to determine any differences in facial nerve outcomes, with the primary outcome represented by facial nerve function (House Brackmann Classification, 1986) at 12 months following surgery. Secondary outcome measures were facial nerve function at three months and the need for revision surgery or further treatment. Tumours in the ‘functional’ surgery group are significantly larger than those in the ‘excisional’ group, and for this reason, a modified ‘excisional’ group has been created by removing smaller tumours from the analysis.

Examination of operative records

An analysis was made of operative records in order to determine any factors that may have affected the preservation of facial nerve function. Particular attention was paid to facial nerve sacrifice or inadvertent damage. Where possible, a record was made of the location of any tumour fragments left *in situ* during sub- or near-total tumour excision.

Post-operative imaging

In cases where post-operative imaging was available, a record was made of findings in order to assess the risk of tumour recurrence. Because the majority of patients undergoing functional

surgery are awaiting follow-up imaging, data were grouped in terms of degree of resection (allowing an assessment of potential tumour re-growth following less-than-total resection).

Statistical analysis

In order to compare rates of facial nerve preservation between the functional and the modified excisional group, outcomes at three months and one year were classified as either 'good' (Grades I-II) or 'moderate-poor' (Grades III-VI). The two groups were then subjected to a Chi-Square analysis (SPSS 16.0 for Mac).

Results

Patients

229 patients were identified with a minimum potential follow-up of one year following surgery. Of these, 216 had sufficient data for analysis. A total of 44 patients underwent surgery after or during April 2007, while 172 underwent 'excisional' surgery prior to this date.

Demographics, tumour size and surgical approaches

Excisional group

This group contained 90 females and 82 males with a mean age of 52 (range 19-82). The mean tumour size (at the time of surgery, measured in the axial plane parallel to the petrous bone at the level of the cochlear) was 22mm (range 2-50mm). 35 operations employed the retro-sigmoid approach to the tumour, 137 the translabyrinthine. Total tumour removal was achieved in 137 cases, with sub-total excision in 9 and near-total excision in 26.

Functional group

This group consisted of 23 females and 21 males with a mean age of 49 (range 23-83). The mean tumour size (measured as above) was 27mm (range 3-50). The approaches used reflect the excisional group (retrosigmoid 8, translabyrinthine 36). Total tumour removal was achieved in 10 cases, subtotal in 6 and near-total in 28. These data are summarised in Table 30.

Table 30: Demographic, tumour and surgical approach used in groups studied

	Age	Sex	Tumour size	Approach	Tumour excision
Excisional group (n.=172)	52 (range: 19-82)	Female: 90 (52%) Male: 82 (48%)	22mm (range: 2-50mm)	Trans-labyrinthine: 137 (80%) Retrosigmoid: 35 (20%)	Total: 137 (79%) Near-total: 26 (15%) Sub-total: 5 (3%) No record: 4
Functional group (n.=44)	49 (range: 23-83)	Female: 23 (56%) Male: 21 (41%)	27mm (range: 3-50mm)	Trans-labyrinthine: 36 (81%) Retrosigmoid: 8 (19%)	Total: 10 (23%) Near-total: 28 (64%) Sub-total: 6 (14%)

Findings at surgery

It is not possible to statistically evaluate these data, but it is possible to identify a number of factors that may have influenced decisions at the time of surgery, and also to identify in some cases the location of tumour remnants in cases where total tumour excision was not achieved. In 14 cases where total tumour removal was achieved, the facial nerve was either knowingly sacrificed or unintentionally damaged during surgery, while this did not occur in cases where less than total tumour removal took place. In all but four cases, the nerve was primarily repaired.

In near-total tumour excision, the most common location for tumour remnants was on the facial nerve. Of 57 near- and sub-total excisions, data were available in 43 cases to determine the location of tumour left in situ: in 41 cases this was adherent to the facial nerve, usually medial to the porus acusticus. In most cases of 'near-total' excision, terminology implies that the bulk of tumour left in situ is very small: terms such as 'small fragment', 'microscopic fragment' and 'small nubbin' are used. In a small number of 'near-total' excisions (n.=3), a more mathematical description is used: the surgeon describes '>95% removed' or 'left on facial nerve medial to porus (5%)'.

Facial nerve outcomes (also presented in Table 31)

Excisional group

At the first post-operative visit, excellent results (Grade I and II) were achieved in 62 patients (36%), moderate (Grade III and IV) in 42 (25%) and poor in 67 (39%). At three months, these figures were respectively: 91 (53%), 19 (11%) and 61 (36%). At one year, these had improved to: 113 (66%), 42 (24%) and 17 (10%).

Functional group

At the first post-operative visit, excellent results (Grade I and II) were achieved in 25 patients (68%), moderate (Grade III and IV) in 3 (8%) and poor in 9 (24%). At three months, these figures were respectively: 31 (72%), 5 (12%) and 7 (16%). At one year, these had improved to: 34 (77%), 10 (23%) and 0. Of the 34 patients with good facial function at one year, 27 (61% of the total) were considered to have normal facial nerve function (grade I) at one year: this compares with 38 (33%) in the modified excisional group. At both 3 months and at one year,

the difference in outcomes between the ‘functional’ group and the modified ‘excisional’ group were significantly different (p=0.002 and 0.027 respectively).

Table 31: Facial nerve outcomes in different groups studied

	Ist post-operative visit	At three months following surgery	At 12 months following surgery
Excisional group (n.=172)	Grade I and II: 62 (36%) Grade III and IV: 42 (25%) Grade V and VI: 67 (39%) Not scored: 1	Grade I and II: 91 (53%) Grade III and IV: 19 (11%) Grade V and VI: 61 (36%) Not scored: 1	Grade I and II: 113 (66%) Grade III and IV: 42 ¹ (24%) Grade V and VI: 17 (10%)
Excisional group with correction for tumour size (n.=115)	Grade I and II: 30 (26%) Grade III and IV: 26 (23%) Grade V and VI: 58 (50%) Not scored: 1	Grade I and II: 51 (45%) Grade III and IV: 10 (9%) Grade V and VI: 53 (46%) Not scored: 1	Grade I and II: 66 (57%) Grade III and IV: 32 ³ (28%) Grade V and VI: 17 (15%)
Functional group (n.=44)	Grade I and II: 25 (68%) Grade III and IV: 3 (8%) Grade V and VI: 9 (24%) Not scored: 7	Grade I and II: 31 (72%) Grade III and IV: 5 (12%) Grade V and VI: 7 (16%) Not scored: 1	Grade I and II: 34 (77%) Grade III and IV: 10 ⁴ (23%) Grade V and VI: 0

Facial nerve rehabilitation

In a number of cases, facial nerve rehabilitation, whether passive or dynamic, surgical or conservative, has been offered to patients with impaired facial nerve function. In the functional group studied, rehabilitation has been largely in the form of physiotherapy (n.=2), and in one case, oculoplastic surgery. In the excisional group, a variety of surgical and non-surgical techniques have been employed: these are summarised in Table 32.

Table 32: Facial nerve rehabilitation techniques employed in excisional group of patients

Passive	Passive surgery	Dynamic surgery
Botulinum toxin injection: 12	Gold weight: 15	Facial-hypoglossal
Facial physiotherapy (exercises/ facial stimulator): 30 ¹	Tarsorrhaphy: 9 Medial canthoplasty: 8 Brow lift: 4	anastomosis: 10 Other dynamic procedures: 6

1. This figure records individuals for whom facial physiotherapy was a sole treatment modality: it does not include those receiving physiotherapy as an adjunct to other rehabilitative treatment.

Follow-up imaging

Routine follow-up imaging (MRI) is performed either at two years following surgery or at one year following surgery if there is thought to be a significant tumour residuum. Due to the short duration of follow-up in the functional group, follow-up imaging is assessed with reference to the degree of tumour excision, rather than to the groups used in analysis above.

Tumour recurrence in near-totally excised tumours

Near-totally excised tumours have been followed for a mean period of 69 months (range 18-152 months). Patients are routinely offered a post-operative scan at two years, and in 18 cases, this scan is awaited. In the remaining 35 cases, a significant proportion do not have any detectable tissue remnant seen on MRI (24 cases, 68%). A further 9 patients have fragments of residual tumour seen on MRI, while in two cases, there is evidence of tumour growth: tumour was not visible at the initial post-operative scan in one case, but measured 8mm at three years; in a second case recurrent tumour was not detected until five years following surgery.

Tumour recurrence in sub-totally excised tumours

In those 15 cases where sub-total tumour excision was performed, 12 had attended for follow-up scans, with a mean follow-up of 63 months (range 15-121). From this group, three patients demonstrated significant re-growth of residual tumour and required further treatment.

Tumour recurrence in totally excised tumours

In this group of 147 patients, six are awaiting follow-up scans. In one case among the remaining 141 patients with a mean follow-up of 82 months (range 20-149), there has been recurrence. In a further four patients, small fragments have been detected that have remained stable over time: the remaining 136 cases (96%) have not shown evidence of tumour residuum or recurrence.

These data are presented in Table 33.

Table 33: Tumour recurrence in groups studied

	No detectable tumour on MRI Scan	Residuum (stable)	Tumour re-growth	Awaiting first post-operative scan
Total excision (n. 141, ¹ follow-up 82 months mean)	136 (96%)	4 (3%)	1 (1%)	6
Near-total excision (n.35, follow-up 69 months mean)	24 (68%)	9 (26%)	2 (6%) ²	18
Sub-total excision (n.12, follow-up 63 months mean)	1 (10%)	8 (67%)	3 (25%)	3

1. Follow-up and n. recorded refer to patients who have undergone follow-up scans.

2. Operative records did not suggest that the remnant of tumour left *in situ* was bulky: in one case, the remnant was described as a ‘small nubbin’.

Discussion

The aim of this chapter has been to evaluate the effects of a ‘functional’ surgical approach adopted in recent years. The effect of this approach is to favour the preservation of facial nerve function over the resection of tumour tissue. Table 31 demonstrates that this approach has been impressively successful in reducing the proportion of our patients that suffer with significant facial nerve lesions at one year following surgery. These benefits are seen both at initial post-operative follow-up, and sustained at later review after one year. Perhaps most significantly, we have been able to demonstrate preservation of normal facial function (House Brackmann grade I) in 61% of cases undergoing surgery for medium-large vestibular schwannomas. Furthermore, we would anticipate that a considerable number of secondary rehabilitative procedures (illustrated in Table 33) can be avoided as a result of this shift in practice.

The ‘cost’ of these benefits to our cohort of patients has been an increased rate of ‘less-than-total’ tumour resections. Thus in the ‘excisional’ group, rates of total tumour removal are 79% while in the ‘functional’ group they are only 23%. The obvious risk posed by this change in practise is to lead to a significant growth in tumour recurrence over time: to date follow-up is inadequate to accurately measure rates of tumour recurrence in the functional group.

A review of recurrence rates within the group as a whole would suggest that while recurrence is more common in ‘near-total’ procedures than in ‘total’, the difference is small. Of 141 totally excised tumours, only 1% have demonstrated recurrence: the equivalent proportion of near-totally excised tumours is 6%. Recurrence in sub-totally excised tumours would appear to be at a markedly higher rate (of 25%), although even in this group where a significant bulk of tumour

has been left *in situ*, there is a significant proportion of tumours that do not demonstrate further growth. These findings echo the literature discussed above and suggest that the inconsistencies in surgical assessment of intra-operative tumour residue demonstrated by Godefroy are happily absent from our study.

If an increased rate of tumour recurrence is inevitable following ‘functional’ surgery, it is important to assess the significance of this change. In the first place, patients undergoing less-than-total tumour resection require regular follow-up with imaging surveillance. It is our current practice to perform an initial MRI scan at one year following surgery and to repeat this every two years: three scans demonstrating stability would allow a relaxation of this regime.

Secondly, recurrence in some cases will require further treatment (others may allow surveillance): in the majority of cases this will take the form of radiosurgery, a treatment that is generally well-tolerated by patients. It is our experience that when the risks and benefits of functional surgery are explained to patients, they are happy to adopt the approach in preference to excisional surgery.

Chapter Conclusion

This chapter has demonstrated that with a ‘functional’ approach to vestibular schwannoma surgery, significant improvements can be made to facial nerve outcomes. In 77% of cases at one year, normal or near-normal facial function is preserved in a cohort of patients with medium to large vestibular schwannomas. This compares with our earlier results of 57% (when adjusted for tumour size). This move towards functional surgery has presumed benefits in quality of life, and reduced economic burdens in terms of rehabilitative procedures and therapies. The shift in

philosophy has led to an increased burden of post-operative surveillance and an elevated risk of tumour recurrence, the effects of which are yet to be seen, but are not expected to outweigh the benefits outlined above.

CHAPTER 7: THE REHABILITATION OF SINGLE-SIDED DEAFNESS WITH THE BONE-ANCHORED HEARING AID

Single-sided deafness is the most common disability affecting patients with vestibular schwannomas, whether treatment has been conservative, surgical or radiotherapeutic. This study evaluates the success of the most commonly used intervention to treat single-sided deafness: the bone-anchored hearing aid (BAHA). A version of this chapter has been published in the journal 'Clinical Otolaryngology' (Martin, 2010). The work presented here was awarded a prize for the best trainee presentation at the British Skull Base Society Meeting (Cambridge, 2009).

Introduction

Single-sided deafness (SSD) is the most common disability to affect patients with vestibular schwannomas. At presentation, some 13% of patients in the Birmingham Database have no recordable hearing in the affected ear. As has been seen in previous chapters, a significant proportion of those individuals treated conservatively will lose hearing progressively while being watched, as do a significant number of patients treated with radiotherapy (see Chapter 3 for details). All those patients treated surgically with the translabyrinthine approach will lose hearing as an inevitable consequence of the operation, which depends upon the functional (if not physical) destruction of the inner ear in order to secure access to the internal auditory canal.

The handicap produced by SSD is threefold: 'the head-shadow effect', a loss of the ability to localise sound, and a reduction in the discrimination of speech in a noisy environment (Welsh,

2004 and Douglas, 2007). The ‘head-shadow effect’ refers to the handicap produced by the loss of perception of sounds that originate on the affected side. Thus a patient who has a left sided deafness will struggle to hear somebody speaking on their left-hand side if they are looking directly ahead (while driving a car, for example). The SSD individual will often be able to hear sounds that originate on the deaf side with their hearing ear, but there is a degree of attenuation of 10-20 dB that can be significant if the original sound intensity is low, or if there are competing factors (such as noise) in the environment.

Sound localisation and the discrimination of speech in noise are both functions that depend upon binaural input. In a normally functioning individual, auditory information from each cochlea is processed in the brain-stem and auditory cortex in order to localise sound in space: the effective localisation then allows for a discriminatory selection of either useful (i.e. ‘speech’) or useless (i.e. ‘noise’) sound, with the central up-regulation of the former and down-regulation of the latter (‘squelch’). The process is dependent upon inter-aural time and volume discrepancies, with considerable neural decussation at the brain-stem level (Grothe, 2010): the loss of one cochlea profoundly limits an individual’s ability to perform these sophisticated processes.

The effect of SSD upon individuals is demonstrated by these statements offered by patients participating in the study described in this chapter:

'...I have found hearing in monotone saddening to the point of depressing as I am a music fan...It has been hardest to learn how to live with peoples' attitude as they do not understand a disability they cannot see...'

'It is very difficult to hear people in crowded pubs. When people shout my name in the large warehouse that I work I find it difficult to pin-point where the voice is coming from.'

'I hate being deaf on the one side. My head hurts with all the sounds, in fact sometimes I stop listening because of the concentration you have to do (sic) just to listen.'

'It is a very strange experience! I can hear perfectly in some contexts but am completely 'disabled' in others. Not being able to locate sounds is a problem... Meetings which are social in context...become extremely challenging, the effort involved in trying to hear is exhausting in groups.'

These statements illustrate the functional problems experienced by patients with SSD, but also demonstrate the difficulties (emotional, social and occupational) that accompany the condition.

Traditional rehabilitation of unilateral deafness has relied upon the 'CROS' (Contra-lateral routing of signal) hearing aid: a device that consists of a microphone located on the deaf side of the head that conveys sound to a conventional hearing aid at the hearing ear. While tolerated by some, the CROS aid is often perceived as uncomfortable and cumbersome, and carries the

disadvantage of occluding the hearing ear. The aim of this chapter is to describe a study assessing the success of a new device for the rehabilitation of SSD: the BAHA.

The BAHA is reliant upon the effective transmission of sound direct to the inner ear by bone-conduction, with the bone-conducting device attached to a titanium implant that is fixed behind the patient's ear. Osseointegration (the growth of bone into microscopic fissures in the surface of the titanium) ensures a secure fixture of the abutment and allows for efficient transmission of sound (Tjellstrom, 1995). Thus while traditional bone-conduction hearing aids are dependent upon maintaining pressure upon the skin that is adequate to ensure a good contact with the underlying bone (producing a device that can be uncomfortable and cumbersome), many patients are able to use a BAHA without being aware of its presence (Bonding, 1992). Initially, the BAHA was offered for otological conditions characterised by a conductive hearing loss (i.e. congenital aural atresia) or infection precipitated by conventional hearing aids (i.e. in problematic mastoid cavities). More recently, the device has been offered for the rehabilitation of SSD. In this context, the BAHA is sited behind the patient's affected ear, and the device transmits sound via bone conduction to the contralateral cochlea.

Initial reports suggested that the BAHA offered a number of benefits: greater patient tolerance than the CROS hearing aid, improved speech-in-noise comprehension, and patient satisfaction (Vaneecloo, 2003, Niparko, 2003, Hol 2005, Lin 2006). An early report even suggested the BAHA could offer improved sound localisation via 'pseudo-stereophony' (Vaneecloo, 2003) although this claim was not substantiated by later publications (Hol 2005, Lin 2006).

In this chapter, data are presented detailing the experience of the first 58 patients treated for SSD with BAHA in the Queen Elizabeth Medical Centre, and Selly Oak Hospital, Birmingham. An analysis of surgical results and complications, patient satisfaction, spatial hearing and speech discrimination in noise testing is undertaken. The study aims to answer two key questions. Firstly, is the BAHA successful in the rehabilitation of the disability presented by SSD? Secondly, is the BAHA when used for this indication successful when compared to its use for other clinical indications?

Methods

Patient recruitment

Patients fitted with BAHA to treat SSD were identified from a database of 1250 patients fitted with BAHA for all indications. All those treated for the indication of SSD and with at least 3 months BAHA use (58 patients including non-users) were invited to participate in the study. Our first patient treated for SSD was fitted with a BAHA in 2002. Patients with SSD are usually identified in general clinics or in referring hospitals and undergo full audiological assessment in a specialised BAHA clinic. They are then offered a headband trial of the device, usually lasting 4 weeks. Thereafter, further audiological review takes place before a medical consultation: if the patient is satisfied with the headband trial, surgery is offered. Patients were fitted with either a Compact or Divino BAHA (*Cochlea*, Sydney, Australia). At the time of testing, 16 patients were fitted with a Divino device, 37 with the Compact (there were 5 non-users). There were no significant differences in outcomes between the two groups.

Table 34: Demographic details of fitted patients

Age	Sex	Cause of unilateral deafness	Duration of unilateral deafness	Contralateral hearing	Complications
Mean: 56	M: 19 F: 39	Vestibular schwannoma: 27	<10 years: 32 >10 years: 26	<20dB: 28 >20dB: 24 Unknown: 6	None: 37 Non-user/ abutment removed at patients' request: 5 ² Fixture failure: 5 ³ Soft tissue infection/ overgrowth: 12 ⁴
Range: 30-79		Post-surgery, other illness: 15 ¹ Childhood illness or congenital: 7 Sudden onset hearing loss in adulthood: 9			

1. In most cases, these individuals had undergone otological surgery.
2. These patients asked to have the abutment removed because they did not feel it offered any benefit.
3. The abutment failed in four individuals, and in one patient, the abutment failed on two occasions. Two of the patients with abutment failure were patients who had undergone surgery for excision of an acoustic neuroma.
4. In most cases, infection or soft tissue overgrowth was minor: in 2 cases, revision surgery was necessary.

The research took place in two phases: an initial cohort of 45 patients were invited to attend for speech discrimination testing (speech-in-noise), and to complete the speech and spatial qualities of hearing scale (SSQ) questionnaire (Gatehouse, 2004). Later in the same year (2007), a further 13 patients were contacted who completed both the SSQ and the Glasgow Benefit Inventory (Robinson, 1996) (postal survey). For logistical reasons, it was not possible to offer speech discrimination testing to this cohort. Patients failing to respond to initial requests were sent the questionnaires on two further occasions.

In total, 58 patients were contacted and asked to complete the questionnaires. The mean duration of follow-up was 28.4 months (range 3-41 months). The demographic details, cause

and duration of unilateral deafness, and status of hearing in the contra-lateral ear are presented in Table 34: it is important to recognise that not all patients studied with SSD are patients who have vestibular schwannomas.

Controls

In order to provide normal comparisons for the SSQ instrument, a further 67 patients with SSD without BAHA were asked to complete the questionnaire, with 49 responding. From this group, the majority (n.=40) were patients with acoustic neuromas managed within our department either surgically or conservatively. The remaining controls were patients with SSD awaiting BAHA assessment. Responding control patients were of a similar age (mean 56, range 38-79 years) and sex mix (29 females, 20 males). In this group, 65% reported normal contra-lateral hearing, 23% impaired and 13% poor.

Speech discrimination testing in noise

Testing was carried out following a standard protocol (UK Cochlear Implant Study Group: POCIA protocol) using Bamford-Kowal-Bench (BKB) sentences in multi-talker babble ('noise') in 3 conditions: presenting speech from the 0° position (i.e. in front of the subject), with noise presented either from the 0° position, from a position ipsilateral to the BAHA or one contralateral to the device. Noise was presented at two levels, initially at the same level as the speech and then at 5 dB more intense (i.e. signal-to-noise ratios of 0 and -5dB, respectively). If a patient scored less than 20% of sentences correctly identified with the first level, the more difficult test was not attempted. The testing was carried out both with the BAHA switched on, and with it turned off: the order being randomly allocated to counter any learning effect. The

results were analysed by comparing the differences in scores when the BAHA was turned on or off (for statistical details, see below).

Glasgow Benefit Inventory (GBI)

The GBI is a validated measure of patient benefit consisting of 18 questions divided into 3 groupings assessing social, physical and general patient benefit from an intervention (Robinson, 1996). Each item gives a score of between 1 and 5 (with 3 representing ‘no change’), and results are presented as figures around the neutral mark with a corrective calculation to create a maximum score of +100 and a maximum negative score of -100. Previous reports of GBI scores in BAHA usage (for varying indications, not solely for the rehabilitation of single-sided deafness) have reported scores of +20 to +45 depending upon the indication for surgery (McLarnon, 2004).

Speech, Spatial and Qualities of Hearing Scale (SSQ)

The SSQ was developed by Gatehouse and Noble in order to characterise disability in hearing speech in competing contexts and assessing the directional, distance and movement components of spatial hearing (Gatehouse, 2004). The questionnaire consists of 50 items scoring 1-10 and is divided into three domains or ‘scales’: speech hearing rating (SHRS), spatial rating (SRS) and sound qualities rating (SQRS). Three questions that refer to the use of two hearing aids (items 3.15, 16 and 17) were omitted from the study.

Open questions

In addition to the formal instruments described above, patients were encouraged to offer open comments about the BAHA. These were often extremely enlightening, although caution must of course be exercised when drawing conclusions from such observations. Among other questions, BAHA users were asked when they found the BAHA most useful, whether they used the device every day, what they would change about the device and whether they would recommend it to a friend with a similar condition.

Statistical analysis

The analyses were performed using SPSS version 16.0 for Mac and Minitab. SSQ results showed a normal distribution, and therefore a parametric test (independent samples t-test) was used to test for inter-group differences. A *post hoc* power calculation found a power of 84% to detect a significant difference (95% confidence) of 1 mean point on the SSQ between cases and controls. The GBI showed a skewed distribution, and therefore a median value for results is offered, and sub-group analysis employs the Mann-Whitney U test. In order to assess intra-individual differences in SiN testing, paired analyses were undertaken (paired t test of the differences of means). A p-value of <0.05 is taken to be significant in all analyses.

Ethical considerations

The study is registered with the audit department of the Queen Elizabeth Medical Centre. At the time of designing the study, it was felt that ethical approval was not required. Subsequently in the review process, it was suggested that it would be appropriate to seek ethical approval for the project. A consequent request for retrospective ethical assessment was rejected by the local

ethics research committee (no such mechanism exists within the United Kingdom). In response to a description of the study, however, the South Birmingham Ethics Committee Chairman judged that the work could be considered (for the purposes of publication) as ‘service evaluation’.

Results

Speech discrimination testing in noise (SiN)

19 patients (42% of the 45 patients invited in the first phase of the study) attended for SiN testing. In each testing position, for each patient, the most ‘challenging’ test was used for analysis (i.e. with noise 5 dB more intense than speech, unless the patient was unable to carry out this test). Of note, none of the differences detected between having the BAHA activated or inactivated were significant. Results are presented in Table 35. There was a trend towards benefit in wearing the BAHA when noise was presented to the hearing ear and speech from the front. This benefit, however, was countered by a detrimental effect found when noise was presented to the BAHA, and thus acted as a distracting intrusion. Both p-values approached significance ($p=0.06$), but were equal, suggesting that the benefit offered to SiN hearing when noise is presented to the hearing ear may be equal to the negative effect produced by transmission of noise by the BAHA when speech is presented to the hearing ear.

Table 35: Results of Speech-in-Noise Testing (19 subjects, paired t test of differences)

	Mean difference ¹ (SD)	p-value	95% confidence interval
S ₀ N ₀ (noise and speech presented in front of subject)	-0.37 (12.5)	0.90	-6.4– 5.6
S ₀ N _B (speech in front, noise to BAHA side)	-5.3 (11.4)	0.06	-10.8 – 0.2
S ₀ N _{.B} (speech in front, noise to non-BAHA side)	8.1 (17.5)	0.06	-0.4 – 16.5

1. The mean difference is the difference between the mean scores for testing with the BAHA turned on or off. Negative values reflect a reduced level of comprehension and *vice versa*.

Speech, Spatial and Qualities of Hearing Scale (SSQ)

Of 53 patients who were still BAHA users at the time of the study, 46 completed the SSQ (87%). Results for the 3 sub-sections of the questionnaire are presented in Table 36.

Table 36: Results of SSQ questionnaire

	Controls (n.=49)	Cases (n.=46)	Statistical difference
	Mean (1SD)	Mean (1SD)	p.-value (95% CI)
Speech hearing rating scale (SHRS)	45 ¹ (19)	50 (18)	0.16 (-2.2 – 13)
Spatial rating scale (SRS)	33 (21)	32 (20)	0.71 (-6.8 – 9.8)
Sound qualities rating scale (SQRS)	67 (14)	65 (17)	0.56 (-4.6 – 8.4)

1. Scores represent a percentage of the total score available.

None of the differences between the cases and controls achieved statistical significance. A sub-group analysis of BAHA users did not reveal any statistically significant difference in outcomes in any domain of the SSQ (see Table 37), although analysis of the effect of duration of deafness prior to fitting of the device gave a p-value very close to significance ($p=0.053$).

Glasgow Benefit Inventory

Of the 53 BAHA users at the time of data collection, 42 (79%) completed the GBI. There was an overall score of +11 (range -61 - +64), with a score in the general domain of +10, a social domain of 0 and a physical domain of 0. The median score of +11 was significantly different from 0 ($p<0.001$). A sub-group analysis revealed a significantly higher satisfaction (+15 median, $p=0.02$) among patients with a longer duration of deafness, echoing a trend seen in the SSQ. These data are presented in Table 37.

Open questions

These responses must be treated with circumspection, but we feel they can be revealing. In general, most patients expressed approval of the BAHA, although the warmth of their approval is tempered, and it must be remembered that a substantial proportion of those fitted, $n=5$, (9%) are non-users. These patients were implanted with an abutment, fitted with a BAHA and subsequently asked to have the fixture removed, feeling that the device was not helpful and in most cases (4/5) did not respond to the survey: we must assume that their responses to these questions would have been negative. Of 45 patients who expressed an opinion, 32(71%) said they would recommend the BAHA to a friend with a similar problem, 8(18%) were ambivalent, while 5 (11%) were clear they would not.

Table 37: Sub-group analysis in BAHA users (SSQ and GBI)

	SSQ Mean Total Scores (SD) ¹	SSQ p-value ²	GBI Median	GBI p-value ³
Aetiology:				
V. Schwannoma n.=21	48 (18)	0.72	11	0.99
Others n.=25	50 (14)		11	
Duration of deafness:				
< 10 years n.=23	44 (14)	0.053	5	0.02
>10 years n.=23	53 (17)		15	
Contralateral hearing				
Normal ⁴ n.=24	49 (15)	0.80	8	0.11
Impaired n.=20	50 (16)		15	
Duration of BAHA use:				
Long (>29 mths) n=23	48 (12)	0.96	11	0.91
Short (<29 mths) n=23	48 (21)		11	

1. Means and standard deviations refer to the total score for the SSQ and GBI.

2. T test employed.

3. Mann-Whitney U Test employed.

4. 'Normal contralateral hearing' is defined as <20 dB HL PTA.

Users were also asked when they found the device most helpful, whether they used it on a daily basis and if there were any situations where they would remove the BAHA. 61% of patients wore the device every day, 17% most days, and 9% 'hardly ever' or 'never'. In general, patients felt the BAHA most useful in 'one-to-one conversation' or in small groups of people. It can be helpful to a driver who has a deaf ear aimed towards a passenger, or to individuals in meetings who may find it difficult to position themselves to hear all those present. One patient commented that the BAHA is '*useful to me (when) I attend meetings and (when I) play a violin*

on my 'good' side', another that they would turn on the device: 'in quieter surroundings where conversation is coming from both sides.'

Less positively, many commented that they found the noise made by the BAHA in windy situations irritating, and some felt cosmetically embarrassed, particularly in situations where the device was exposed (at the hairdresser, for example). The BAHA was generally not found to be useful in situations where patients felt there was excessive background noise. One patient wrote: *'I personally find that the BAHA has very marginally improved my hearing. [In]...areas where I would have hoped of an improvement, i.e. ...talking and listening to people where there is competing noise, it is of no use.'*

Discussion

Synopsis of key findings

This is the first study to employ the SSQ to assess the functional benefit of the BAHA for the rehabilitation of SSD. Douglas (2007) used this instrument to examine hearing disability in SSD (comparing 44 cases with 128 controls), and found significantly poor scores for the SSD group in the domains of speech (SHRS), and spatial hearing (SRS): the qualities of speech (SQRS) subscale appeared to be less affected. The work presented here reflects these findings in that it has demonstrated a similar trend towards impairment in the SRS and SHRS domains, with sparing of the SQRS. Disappointingly, however, the study failed to identify any significant difference in outcomes between control patients with SSD and those that have been rehabilitated with the BAHA.

This is the largest study assessing patient satisfaction with the BAHA for SSD using the Glasgow Benefit Inventory to date. Overall scores (+11), while positive (and significantly different from 0), were disappointing, and lower than those reported for other BAHA indications in the literature (see below). Interestingly, the study has identified a significant trend towards benefit in those with a longer duration of deafness, and this is reflected in a non-significant trend in the SSQ. It is possible to speculate that the cause for this finding is that the rehabilitation offered by the BAHA (essentially the amplification of attenuated sound that originates on the deaf side) is most appreciated by those with no memory of true stereophonic hearing. A further interesting finding from sub-group analysis is that satisfaction and perceived function would appear to be stable over time: a finding echoing a recent prospective study evaluating a number of outcomes over time in 8 patients (Newman, 2008).

A cause for concern lies in the significant minority of patients who report dissatisfaction with the device or who have asked for the device to be explanted. 5 patients asked to have their BAHA abutment removed: perhaps significantly, all these patients had lost their hearing in adulthood (although not all within the last ten years). None of this group suffered significant complications related to surgery, although one did complain of pain in addition to a lack of benefit from the device. Cause of SSD in this group reflects the group as a whole: 3 lost hearing due to a vestibular schwannoma, 1 due to Menière's disease, 1 as a complication of stapedotomy. 4 of these patients did not respond to the survey: 1 patient responded and then subsequently asked to have the BAHA explanted: this individual scored -8 on the GBI.

In addition to this group, 5 further patients would not have recommended their device to a friend, and 8 others were ambivalent. Although 33% of patients described the intervention as a ‘great success’ 44% felt it was a partial success only and 17% described the device as a partial failure. Two patients who responded to the questionnaire felt the device was a ‘complete failure’, and it must be expected that those patients who asked for the device to be removed would share this opinion.

Comparison with other studies

As outlined in the introduction to this chapter: the disability caused by SSD is three-fold: the attenuation of sound originating on the deaf side (‘the head shadow’), failure to segregate speech from noise, and an inability to localise sound. Initially, the BAHA seemed to promise an answer to all three of these disabilities (Vaneecloo, 2000), but subsequent studies cast doubt upon initial claims that the device could generate ‘pseudo-stereophonic hearing’ (Niparko, 2003, Hol 2005, Lin, 2006). While the latter studies were unable to demonstrate sound localisation, they did claim improvements in speech-in-noise hearing using the BAHA – a conclusion also drawn by a small (n.=7) prospective study published recently (Lindstrom, 2009).

This latter conclusion of improved speech-in-noise hearing warrants further examination. Hol and Linstrom found that when speech was located anteriorly, and noise was directed to the BAHA-wearing ear, the BAHA impaired hearing, although the results were reversed when the noise was presented to the normal hearing ear. In our study, similar results were found for the 19 patients we were able to test. These findings shed light upon the rehabilitation offered by the

BAHA: the aid acts as a microphone to detect sound on the deaf side - and as such is successful - but it is also detrimental if that sound is unwanted. It is this benefit detected most in our study (through open questions and trends seen in the SHRS): patients report an improvement in hearing in relatively quiet situations, or in those situations where their position is fixed (such as in driving a car). Interestingly, this is the benefit suggested by a study examining the theoretical benefit of bilateral BAHA use and the use of BAHA in SSD (Stenfeld, 2005). This capacity, however, should not be confused with an ability to enhance ‘speech-in-noise hearing’: a more sophisticated process than simply the ability to access all sound available in the periphery. The distinction is important, because speech-in-noise hearing handicap is often the issue that most exercises patients with a hearing loss.

The GBI has been used a number of times to assess benefit in BAHA usage (Arunachalam, 2001, Dutt, 2002, McLarnon, 2004). McLarnon surveyed 73% of 94 patients and analysed subgroup scores grouped by indication for the device: patients with mastoid cavities, chronic active otitis media, congenital atresia and otosclerosis scored +30, +37, +45 and +28 respectively. Interestingly, the study included 3 patients with unilateral deafness after vestibular schwannoma surgery: these scored +24. Our own results (+11) suggest that this indication offers less satisfaction to patients than others, and this echoes Tringali’s recent survey of 118 patients with BAHA fitted for SSD (Tringali, 2008).

Chapter Conclusions

Although the patients studied in this chapter are not exclusively patients who have been diagnosed with vestibular schwannomas, this group forms the largest number of patients

studied. Furthermore, there has not been any significant difference demonstrated between outcomes in patients with different SSD aetiologies (see Table 37), and it would seem reasonable to draw conclusions about the efficacy of rehabilitation of SSD caused by vestibular schwannomas from this study.

Regrettably, the findings presented here suggest caution rather than enthusiasm when considering rehabilitation for SSD with BAHA. It is clear from this and other studies that while some patients benefit from the BAHA, this is less than that derived from the BAHA when used for other indications. Furthermore, it seems increasingly clear that while the BAHA is able to rehabilitate one element of the handicap created by SSD (the ‘head-shadow’), this rehabilitation is only beneficial if the sound transmitted is of use to the patient: if the sound is noise, this transmission is unwanted. Finally, there is increasing evidence that those more sophisticated functions lost in SSD (sound localisation and speech in noise discrimination) cannot be rehabilitated with the BAHA. Those individuals who have known binaural hearing (such as those who have lost hearing relatively recently due to a vestibular schwannoma) are likely to be disappointed with the results of BAHA surgery if the extent of rehabilitation that they can hope for is not clearly explained.

CONCLUSION

The aim of this thesis has been to explore issues relating to the natural history and management of vestibular schwannomas with the resources offered by the Birmingham database. This conclusion will attempt :

- to suggest appropriate management strategies for differing tumours based upon evidence offered in the thesis and in the published literature.
- to propose avenues for future research in the field.

Suggested management for differing categories of vestibular schwannoma

Intracranial and Tokyo 1 and 2 solid tumours without useful hearing

These small-medium sized tumours that measure up to a maximal size of 2cm in the cerebellopontine angle should be managed with an initial period of conservative management to determine whether tumour growth is persistent or has arrested. As demonstrated in chapter 1, some 65% of watched tumours with a minimum of 5 years follow-up will not grow beyond the dimensions with which they originally present. This data is not unique in the world literature, as previously discussed (Introduction, literature search and Table 5), a number of case series have documented tumour stasis over time. Nevertheless, this thesis does offer a solidity of data, in particular due to the explicit documentation of follow-up. By excluding from analysis those patients with follow-up of duration less than five years; an important confounding factor - the inclusion of patients who may demonstrate growth, but have not to date – is eliminated from the data.

The aim of detecting risk factors for growth in this group of tumours is undertaken in chapter 2. The study identifies two clear risk factors for growth: tumour size and a short duration of symptoms. Similar findings have been published by other groups (see Table 5), and our data lends support to this work. As previously discussed, the suggestion that a patient is 'high risk' for growth does not always lead to a deviation in management away from that outlined above. It has not been the practise of the Birmingham team to advocate a change in treatment strategy based upon these findings to date, but it may possibly be advantageous to patients to suggest primary radiosurgical treatment in cases with a short duration of symptoms and a large tumour. If such tumours grow rapidly (the maximal rate of growth we have seen in our series is 2cm annually), they can potentially loose the opportunity for stereotactic radiosurgery. There is potential for further research to explore this area of study, in addition to the pursuit of other markers of growth in vestibular schwannomas (see 'Further avenues of research' below).

Chapter 4 demonstrated that in terms of facial nerve outcomes, patients who are managed in this manner enjoy better facial nerve outcomes than those who are managed with primary surgery. This data counters arguments made by advocates of primary surgery (Meyer, 2006) who suggests that conservative management should only be offered to selected patients because of the risk of tumour growth leading to poorer facial nerve outcomes as larger tumours undergo surgery. There is no doubt that a theoretically poorer outcome will be achieved in tumours that are a little larger when coming to surgery because of a period of observation, but this small deficit is outweighed by the benefit enjoyed by the group overall. To the author's knowledge, the publication associated with chapter 4 (Martin 2008) is the only study to employ an intention-to-treat analysis to compare outcomes in the two treatment modalities studied.

Chapter 5 details the design of an evidence-based protocol for the timing of scans following induction of patients into conservative management. Although other groups have proposed strategies for surveillance (Stangerup, 2006), these have not been supported by evidence in the manner presented here and in the publication associated with chapter 5 (Martin, 2009). This protocol is novel in particular in stressing - and providing evidence for - the utility of a surveillance scan performed six months after the initial diagnostic scan. This scan has been successful in detecting a number of rapidly growing tumours and in their detection, allowing their expeditious treatment. A further feature of this protocol is the reduction in scans demanded over time in comparison to other authors who advocate surveillance on an annual basis (Hajihoff, 2008). This reduction in scan frequency is both likely to be economically advantageous (although no formal economic analysis has been undertaken (see below: 'Further avenues of research'), in addition to possibly enhancing patient compliance.

Intracranial and Tokyo 1 and 2 cystic tumours without useful hearing

As has been demonstrated in both chapters 2 and 5, cystic tumours present a significant threat in terms of both demonstrating growth and in terms of the speed of growth. The nature of 'growth' when referred to cystic vestibular schwannomas is of interest. As noted in the introduction to this thesis ('histopathology'), vestibular schwannomas are characterised histologically by two tissue types: Antoni A and B. The latter tissue is loosely packed and prone to cystic microdegeneration (Nager, 1993), and in some 5% (in our series) of cases, this degeneration becomes macroscopic. This leads to a rapid expansion in dimension of the tumour, as we have demonstrated. Hitherto, we have advised against conservative management for these tumours

(Martin, 2009), and this would seem to be reasonable. A caveat might be that results for microsurgery are reported by some authors (Moon, 2007, Characid, 2000) – but not all (Peccadillo, 2009) – to be less favourable in cystic tumours. The response of cystic tumours to radiotherapy is reported to be favourable in terms of long-term tumour bulk reduction (Sheraton, 2000), and it would seem appropriate to offer early radiotherapy to patients presenting with cystic vestibular schwannomas.

Intracranial and Tokyo 1 and 2 with useful hearing

This group of patients are of particular interest and probably represent the group for who management poses the greatest controversy. In chapter 3 it has been demonstrated that a significant proportion of patients (approximately one third) presenting with good hearing maintain that hearing at the same level over medium term follow-up. Some 15% of patients will lose hearing rapidly while under observation, the remaining 50% of patients losing hearing at a mean rate of 4.1dB annually. The technique employed to measure hearing preservation (hearing loss relative to the contralateral ear) is novel in the literature and is, the author argues, more useful than the technique of preservation within class, particularly when follow-up is short. Unfortunately, there are no reliable risk factors that may predict which patients are likely to lose or preserve hearing beyond tumour growth: a ‘risk factor’ that effectively directs management.

Given the data presented in chapter 3 and summarised above, the author would argue that observation probably offers the best opportunity for hearing preservation for patients presenting with small-medium sized tumours. In our experience, hearing preservation surgery is successful in approximately 50% of cases: those for who it is not successful will lose hearing suddenly and

will not compensate for that loss as well as patients who sustain a gradual erosion of hearing (as will occur in a hearing loss that develops while under surveillance). Similarly, results of radiosurgery are in our experience less successful than those often reported in the literature (see Table 9). There are indicators that certain tumours may be less at risk of losing hearing due to radiosurgery (in particular those located medially that can be treated with a cochlea-sparing dose), but it is not clear that this should be offered to patients in whom growth has not been demonstrated.

Tumours Tokyo Grade 3

These tumours measure between 2 and 3cm in greatest dimension in the cerebellopontine angle. These tumours can be treated with either conservative, radiotherapeutic or surgical management. In general, our approach has not been to offer conservative management as a first line treatment for these tumours, principally because in the event of growth, there is a chance that patients will no longer be eligible for radiotherapy treatment. Series have reported outcomes from radiotherapy offered to patients with tumours larger than 3cm, but results are generally poorer than those found when treating smaller tumours. Mandy (2010) reports a series of 25 cases, in which 5 patients suffered new facial nerve injury, and there was a recurrence rate of 16%. Our limited experience of managing tumours measuring >2cm in the cerebellopontine angle conservatively has been to see growth in 6 tumours: 43% of the total. This small sample would suggest that growth in these tumours is probably more likely than in the population as a whole (rate 35%), but probably not inevitable.

Tumours Tokyo Grade 3,4 and 5 treated surgically

In cases where surgical treatment is undertaken, priority is given to the preservation of the facial nerve, with an intra-operative assessment of adhesion of the tumour capsule to the nerve and the degree of nerve attenuation to determine whether total or near-total tumour resection should be undertaken. Chapter 6 assesses the outcomes achieved taking this approach, and suggests that the technique is effective in preserving nerve function, with 61% preservation of normal facial nerve function in a group of patients with a mean tumour dimension of 27mm. Importantly, only 6% of patients sustained Grade IV facial nerve injuries, with no outcomes worse than this. The cost of less-than-total tumour excision is an increased rate of recurrence (seen in 6% of near-total excision procedures, comparing unfavourably with a rate of 1% in totally excised tumours). This rate of recurrence is low, and we would anticipate treatment of recurrent tumours with radiosurgery to be successful, although to date follow-up and experience is lacking.

Rehabilitation of single-sided deafness

Chapter 7 assessed departmental experience with the bone-anchored hearing aid (BAHA) to treat single-sided deafness, a significant handicap for patients with vestibular schwannomas. Unfortunately, our experience with this device has been mixed. In cases where patients have specific listening needs that respond to the lifting of the head shadow, the device is of benefit. For other handicaps caused by single-sided deafness (speech-in-noise hearing, sound localisation), the hearing aid is not helpful. Individuals who are not prepared for the benefit offered (and the limits of that benefit) may feel that the BAHA is a disappointment. Such patients can then feel acutely those negative factors inherent to the device (wound healing

issues, cosmetic embarrassment, noise from wind) that might otherwise be overlooked. The research presented in chapter 7 has been useful in allowing effective counselling of our patients and, it is to be hoped, enhancing their perceived benefit.

Further avenues of research

The management of mildly impaired hearing patients with small-medium sized tumours
As mentioned above, these patients present a dilemma for management. In many cases, the tumours they harbour do not require treatment in order to halt tumour growth, but hearing loss is progressive. In the United States, a jurisdiction with a more aggressive approach to management of vestibular schwannomas, surgery would in many cases be offered, usually employing a middle fossa surgical approach. Outcomes in the world literature for this surgery are detailed in Table 8 and suggest hearing preservation rates at levels of 50%. Our own experience of 36 patients operated upon via the retro-sigmoid route are presented in Table 27: 8 individuals have preserved useful hearing of grade A or B (24%). In contrast, radiotherapeutic series detailing hearing report outcomes of 50-80% preservation.

While these outcomes appear impressive, our own experience is less positive: as detailed in chapter 3, patients with serviceable hearing referred for radiotherapy for definitive treatment have in all cases lost that hearing (although we would acknowledge that only 5 of 11 patients treated in this manner had adequate data for analysis). To the authors' knowledge, there is no well-designed study comparing conservative with radiotherapeutic hearing preservation, and such a study, designed prospectively to ensure adequate follow-up of conservatively-managed patients, would be helpful in directing management of this group.

An economic analysis of the impact of increasingly conservative management of vestibular schwannomas

This thesis has detailed a number of ways in which the management of vestibular schwannomas is changing. In particular, there is a reduction in surgical management with an increase in both conservative and radiotherapeutic management. Furthermore, the nature of surgery is changing with an emphasis upon less-than-total tumour excision. The economic ramifications of these changes are various, both for the health care system and also for patients undergoing treatment. A thorough health economic study assessing these changes would be of value in planning services needed to manage the condition in future years.

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APPENDIX

Contents

Letter to Dr Bowman, Chair, South Birmingham Research Ethics Committee
Reply to above

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