VESTIBULAR SCHWANNOMA: EPIDEMIOLOGY, RISK FACTORS, AND QUALITY OF LIFE

by

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VESTIBULAR SCHWANNOMA: EPIDEMIOLOGY, RISK FACTORS, AND QUALITY OF LIFE

Oren Berkowitz, PhD

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INTRODUCTION:

The goal of this study has been to describe the epidemiology of vestibular schwannoma and explore potential risk factors for this tumor. Other goals of this study have been to look at the function and quality of life of patients compared with the general US population as well as outcomes after radiosurgery treatment.

METHODS:

A 1:1 matched case-control study was designed. Odds ratios were established based on multivariate conditional logistic regression models. Quality of life was measured with the Short-Form 36 Item Health Survey v.2 and audiograms measuring the non-tumor ear were collected and analyzed for comparison with normative US population data.

RESULTS:

Average age at diagnosis was 53 (StDev±12). More than 90% of the participants were Caucasian. Patients were evenly distributed by gender. Family history of cancer, a history of hay fever, managerial and professional occupations, and frequent dental x-rays were found to have an increased association with acoustic neuroma in multivariate models. Tobacco use and diabetes were found to have a significantly decreased

association with acoustic neuroma in multivariate models. Patients did not have significantly different quality of life scores or audiogram measurements of their non-tumor ear when compared to age-matched US population norms.

CONCLUSIONS:

Patients with (AN) have the profile of being Caucasian, either gender, in their 50-60's, and working in managerial, professional jobs. Hay fever, family history of cancer, and frequent dental x-rays are strongly associated with an increase risk of acoustic neuromas. Tobacco use and diabetes demonstrate a protective effect, although the mechanism of this is poorly understood. Patients maintain a quality of life similar to the US population. Acoustic neuromas do not affect hearing in the non-tumor ear.

PUBLIC HEALTH SIGNIFICANCE:

The epidemiology and risk factors of vestibular schwannoma are poorly understood. Continued research in this area will help to develop an understanding of brain tumor etiology and the role of potential carcinogens in the environment. Functional research will help to look at the role of surgical treatments and the degree of morbidity in these patients.

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PREFACE

Acknowledgements

I would like to thank the faculty and staff members of the Departments of Epidemiology and Neurological Surgery whose support made this research project possible.

Dedication

I would like to dedicate this work to my mother, my father (of blessed memory), Ariel, Shahar, and Ermantine.

1.0 INTRODUCTION

There is little known about the etiology of Vestibular schwannomas (also known as acoustic neuroma). This may, in part, be due to its relatively rare occurrence and benign growth pattern which makes it elusive and difficult to study. There are two causes of acoustic neuroma that are well understood. These are the hereditary bilateral form caused by a gene deletion that is known as neurofibromatosis type II (an NF-2 genetic mutation of the long arm of chromosome 22), as well as exposure to ionizing radiation.

Neurofibromatosis causes damage to the tumor suppressing protein neurofibromin which allows proliferation of tumor cells in nervous system tissue. Interestingly, genetic mutations of chromosome 22 have been found in a large proportion of the sporadic (unilateral) acoustic neuromas upon molecular genetics evaluation. [1] These patients may not have the systemic genetic mutations found in neurofibromatosis type-2 but they do have similar gene deletions within the tumor itself.

Significant associations have been fairly well established between ionizing radiation exposure and long-term risk of developing central nervous system neoplasm. These exposures include large nuclear events like the atomic bomb[2,3] and radiation treatments to the head and neck. [4-6]

Other exposures have been looked at as well such as radiofrequency and mobile phone technology, allergy and immunologic diseases, loud noise, and various other

demographic and environmental risk factors. These studies have shown inconclusive results and ar e often limited by several factors including small sample size and insufficient power, potential for study bias (including recall bias, misclassification bias, and diagnostic bias), non-validated and subjective data collection, and short study periods.

1.1 BACKGROUND

1.1.1 Biology

The acoustic nerve is one of twelve cranial nerves that emerge directly from the brainstem. It is also known as the eighth cranial nerve (eighth out of the twelve cranial nerves) or the vestibulocochlear nerve. It arises in the cerebellopontine area and travels through the internal auditory canal. It then separates into three branches at the internal auditory meatus. The superior vestibular portion innervates the vestibular utricle, the inferior vestibular portion innervates the vestibular saccule and the cochlear nerve portion innervates the cochlea.

Vestibular schwannomas tend to arise from the Schwann cells of the vestibular portion of the nerve just at the internal auditory meatus. The Schwann cells are responsible for producing the myelin sheath that surrounds the axon of a nerve. The tumor begins to grow through the boney portion of the internal auditory canal. Tumors can then continue to grow through the internal auditory canal into the cerebellopontine area.

Acoustic neuromas can develop bilaterally in people with the hereditary form but normally they develop unilaterally in people with the common, spontaneous form. The Vestibulocochlear nerve has several components. It is best known for its role in hearing and balance. In rare instances, acoustic neuromas can have a malignant transformation. Generally, though, acoustic neuromas are benign and slow growing lesions that tend to begin in the vestibular portion of the nerve and can affect several aspects of function. Typically the earliest signs and symptoms of a person with an acoustic neuroma are either hearing loss on the affected side, balance problems, vertigo, or a perception of noise in the ear known as tinnitus. These can occur as isolated symptoms or a combination of several.

If not treated early enough, the tumor can continue to grow and impinge on the surrounding nerves such as the trigeminal nerve and the facial nerve and even the glossopharyngeal nerve. This can cause symptoms such as facial numbness, facial pain, and facial weakness as well as difficulty swallowing. Very large acoustic neuromas can even begin to compress the brain stem and the fourth ventricle causing an obstruction of cerebrospinal fluid outflow. This can cause severe symptoms such as ataxia and hydrocephalus and can eventually lead to death.

1.1.2 Incidence and Public Health Concern

Acoustic neuromas are tumors originating from the eighth cranial nerve also known as the acoustic nerve. They occur just as often in women and in men and they tend to begin to grow in people around the age of 50.[7-9] They have, though been detected in people as young as their twenties and even teens. Historically, acoustic neuromas have

an incidence rate of just under 1 in 100,000 persons per year.[7,8] They account for approximately 6% of all brain tumors.[9] They account for over 90% of all nerve sheath tumors.[7]

Recent prevalence studies have looked at the prevalence of undiagnosed acoustic neuromas. The authors searched imaging databases looking specifically for acoustic neuromas that were found incidentally on scans that were performed for reasons other than audiovesibular abnormalities. The prevalence of unsuspected acoustic neuroma was found to be between 2 to 7 per 10,000 people, respectively.([9,10])

Natural history has shown the proportion of acoustic neuromas that will continue to grow to be at a rate of about 17% for intrameatal tumors and 29% for extrameatal tumors over the course of about five years if left for observation (cohort of 552 patients under observation management).[11] These growth proportion rates vary greatly in the literature, though; between 14% all the way up to 74% looking up to five years of follow up.[12,13]Some studies have even projected long-term growth to be up to 87%.[14]

A Danish study looked at the increasing incidence of Acoustic Neuroma in Denmark over the past few decades. Denmark has an incidence rate of acoustic neuroma that has been increasing from 5.1 per million per year in 1976 to 19.3 per million per year in 2001.[15] The study attributes the rate increase to the increase in better imaging technology such as CT and MRI. Interestingly though, the median age at diagnosis remains at 55 throughout this period. Also, the smaller tumors that are being picked up thanks to better imaging are being found in older not younger patients.

Tos, M (2004) has argued that the median size of acoustic neuroma at diagnosis has significantly decreased over the years in probable accordance with increased

imaging technology. He has also argued that the mean diagnostic delay for acoustic neuromas has been decreasing over the years.[8]He puts the mean patient and physician combined diagnostic delay as decreasing from 13 years to 7 years from the late seventies to the late nineties. As much as 22% of acoustic neuromas were diagnosed within the first symptomatic year. Stangerup,S.E. (2004) found in his study, the mean age at diagnosis remained stable and is even increasing.

There is evidence that the true incidence rate has been climbing over the past two decades. J M Propp, et al. (2006)[7] showed this by looking at data from the central brain tumor registry of the United States (CBTRUS) and from the Los Angeles County cancer surveillance program (LACCSP). She showed that statistically significant trends have been observed in vestibular schwannoma incidence of about 14% increase per year between 1992-1999 from the CBTRUS data. The LACCSP showed about a 6% increase in incidence between 1992-1998. Some have argued that this rise is due in part to the introduction of better diagnostic imaging such as CT and MRI. Again, she points out that the recent data should not have been affected since it covers the period after 1992 which would have already gone past the peak of CT/MRI availability. We do not see a sharp peak in incidence when looking at LACCSP data going back to the 1970's and early 80's when we would have expected it since this was during the introduction period of CT and MRI.[7,8]

J M Propp, et al. (2006) also analyzed a sub grouping of vestibular vs. non-vestibular schwannomas. While vestibular schwannomas have showed a significant increase in both CBTRUS and LACCSP analyses, non-vestibular schwannomas showed no significant increase in the LACCSP and even showed a decrease in the

CBTRUS analyses. This difference in incidence rates brings into question whether in fact this is an artifact of better diagnostic modalities.

2.0 EPIDEMIOLOGY AND ENVIRONMENTAL RISK FACTORS ASSOCIATED WITH VESTIBULAR SCHWANNOMA

2.1 INTRODUCTION

There is little known about the etiology of Vestibular schwannomas. There are only two causes of acoustic neuroma that are well understood. There is the hereditary bilateral form caused by a gene deletion; neurofibromatosis type II (an NF-2 genetic mutation of the long arm of chromosome 22), as well as exposure to ionizing radiation.

Acoustic neuromas are tumors originating from the eighth cranial nerve also known as the acoustic nerve. They occur just as often in women and in men and they tend to begin to grow in people around the age of 50.[7-9] They have, though, been detected in people as young as their twenties and even teens. Historically, acoustic neuromas have an incidence rate of just under 1 in 100,000 persons per year.[7,8](Although there is evidence that this incidence has been rising)[7] They account for approximately 6% of all brain tumors.[9] They account for over 90% of all nerve sheath tumors.[7]

The goal of this study has been to explore some of the potential risk factors that are not yet well understood. We drew from our sample of patients who have this tumor to investigate several exposures of interest. We have previously looked at low-dose

radiation exposure and mobile phone technology as these have shown conflicting results in the literature.[16] Only a few studies by Hardell et al[17,18] have shown any significant association. Several studies have shown some associations between acoustic neuroma and atopic disease.[19-21] We looked at allergy and immunologic diseases as a potential cause for neoplastic changes. Two studies have shown a decreased risk of acoustic neuroma in patients using tobacco[22,23] and we investigated smoking risk in this study. We evaluated loud noise and acoustic trauma as this has also shown conflicting results.[20,24-27] We described the various demographics of acoustic neuroma as well as lifestyle habits and occupational history.

2.2 METHODS

2.2.1 Design

A hospital based case-control study design was used. 1:1 matching was performed based on age (+/- 5 years) and gender. Recruitment goals were based on sample size calculations for appropriate power. Exposures were assessed based on the date of diagnosis of the case participant. This study received the approval of the University of Pittsburgh Institutional Review Board for Human Research and informed consent was obtained from all study participants.

2.2.2 Case Recruitment

Cases were recruited from the University of Pittsburgh's Gamma Knife® Radiosurgery database. Patients who were treated for acoustic neuroma between the years 1997-2007 were solicited for participation. Geographic recruitment was limited to the North American continent in order to avoid an ecological bias. Patients with Neurofibromatosis type 2 were excluded from this study.

Patients were contacted by written letter via the US Postal service. A questionnaire was mailed along with a pre-paid return envelope. Patients were given the option to fill out the questionnaire by hand or have it done over the telephone with a trained recruiter or to send it via email. A trained recruiter also checked every questionnaire that was completed for missing data points and contacted the participants via telephone to complete the necessary missing data.

A total of 822 patients underwent SRS for acoustic neuroma between 1997-2007. Limiting our target cases to people residing in North America, a total of 712 mailings were sent out and 272 (38.2%) initially responded. Fifty six (7.9%) patients were reported as deceased by their family members. Sixty two (8.7%) questionnaires were returned by the post office with no forwarding address. A second mailing was sent out 4 months later to the remaining patients who had not responded. Four hundred letters went out in the second mailing and 148 (37%) questionnaires were completed. In all, 420 (59% of 712 mailings) patients completed a survey. Of the completed surveys: 406 (96.7%) were returned via US postal service, 10 (2.8%) cases completed their questionnaire via email, and 4 (1.1%) questionnaires were completed via telephone interview at the request of the patient.

2.2.3 Control Recruitment

Controls were recruited within the Neurosurgery department of the University of Pittsburgh. A hospital based control group was chosen from the spine clinic because they are mostly frequented by patients with degenerative spine disease which makes them less likely to have a brain tumor. The participants were approached by a trained recruiter who remained onsite to help the participants with any questions and to check the questionnaire for missing data. Controls were matched to cases based on age (+/- 5 years) and gender. They were asked to complete the same questionnaire as the cases and they were instructed to recall their exposures as compared to the date of diagnosis of the matched case.

Controls were excluded if they had ever been diagnosed with a brain tumor. They were also excluded if they displayed any of the typical acoustic neuroma symptoms given the remote possibility of an undiagnosed tumor. Specifically, they were excluded if they had symptoms of unilateral hearing loss, imbalance/vertigo/dizziness, or ringing in the ear that was of unknown origin or undiagnosed. Controls were also paid ten US dollars for their time and participation.

Approximately 800 people came through our outpatient spine clinics for evaluation of their degenerative spine disorders during the recruitment period. Of the available potential controls, approximately 200 (25%) refused (the most common reason was insufficient time to fill out the survey) and 222 (27.8%) initially agreed to participate but did not complete the survey either because they were unable to be appropriately matched at the time of the interview or they met the exclusion criteria. A total of 378

(47.3%) controls completed the questionnaire and 353 were appropriately matched to cases.

2.2.4 Exposure Assessment

Subjects were asked to complete a written questionnaire. The questionnaire included sections on demographics, education, and lifestyle habits. Neurosurgical history was taken including previous head injury and previous brain surgery. Medical history was asked with an emphasis on atopic disease, autoimmune processes, and cancer (including family history of cancer). Environmental exposures such as loud noise and chemicals were assessed. Participants were asked if they were exposed to loud noise in their occupation according to how much of the time they were exposed and how often they used hearing protection. Recreational noise exposure was also assessed in the setting of loud hobbies such as instrument playing, music listening/concert attendance, gardening with power tools, machine shop work, target shooting/hunting, and ATV/motorcycle/racecar exposure. Chemical exposures were assessed and included tetrachloroethylene, petroleum products, vinyl chloride and chlorinated hydrocarbons, inks/dyes/paints/resins/solvents, pesticides/herbicides/fungicides, and heavy metals/welding fumes.

Occupational history was looked at by asking participants to list up to three principal lifetime occupations (including industry, occupation, and years worked). Their responses were then classified according to the US census coding for industries and occupations [www.census.gov] according to their chief lifetime occupation. Military service was also asked.

Further questions were asked regarding exposure to ionizing and non-ionizing radiation. These assessments included exposure to cellular and cordless phone technology, hand-held electronic devices, radiation-based medical imaging, and medical radiation treatments. The details of our radiation analysis have been presented[16] and will not be the main topic of discussion for this manuscript.

2.2.5 Statistical Analysis

A total of 420 cases and 378 controls participated. A total of 67 (16%) cases and 25 (6.6%) controls were excluded from the final analysis due to missing data or inadequate matching criteria and 4 of these cases were excluded due to a history of NF-2. Upon conclusive 1:1 matching, 353 cases and 353 controls were included in the final data analysis.

Descriptive statistics were used to describe the data including means and standard deviations, medians and ranges. Univariate analysis was performed using conditional logistic regression of matched variables to determine significant differences and associations between cases and controls. Odds ratios were obtained with associated 95% confidence intervals.

Final models were produced with multiple conditional logistic regression performed for a 1:1 matched study to determine the log risk of disease. Inclusion in the final model was based on the univariate analysis for each variable. Variables that were found to be statistically significant in univariate analysis were included in the final models. Several models were developed based on clinical relevance. Results were then interpreted at the $p<0.05$ significance level.

2.3 RESULTS

2.3.1 Demographics and Lifestyle Habits

The demographic characteristics of our study participants are shown in Table 2-1. The average age at interview of cases and controls was 60 (standard deviation (SD) ± 12) and the average age at diagnosis was 53(SD±12). More than 90% of the participants were White or Caucasian. Acoustic neuroma cases were evenly distributed by gender (49.6% male) and 73.1% of cases reported some college or higher education (≥ 13 years) compared with 49.6% of controls. More than 50% of the cases are residents of a tri-state area that includes Pennsylvania, Ohio, and West Virginia while more than 80% of the controls are. Distribution of marital status and employment status was similar among cases and controls. Results of the univariate analysis using conditional logistic regression revealed that demographic factors such as race, education, smoking, drinking and di abetes were found to be significantly different between cases and controls ($p<0.05$).

Table 2-1 Socio-demographic Factors and Lifestyle

	Case n(%)	Control n(%)
Total	353	353
Gender		
Male	175 (49.6)	175 (49.6)
Female	178 (50.4)	178 (50.4)
Age at Diagnosis		
<50	129(36.5)	134(38)
50-65	175(49.6)	167(47.3)
>65	49(13.9)	52(14.7)
Mean (±SD)	53(12)	53(12)
Current Age at Enrollment		
Mean (±SD)	60 (12)	60(12)
Residency[1]		
Tri-State Area[2]	199 (56)	322 (91)
Other	154 (44)	31 (9)
Race[1]		
White	343(97.7)	325(93.1)
Other	8(2.3)	24(6.9)
Marital Status		
Single	28(7.9)	28(7.9)
Married/Partner	279(79)	259(73.4)
Previously Married	46(13)	66(18.7)
Education[1]		
<13 years	95(26.9)	178(50.4)
≥13 years	258(73.1)	175(49.6)
Tobacco Packyears[1]		
Never Smoked	323(91.5)	185(52.4)
<20 pack-years	19(5.4)	77(21.8)
≥20 pack-years	11(3.1)	91(25.8)
Alcohol Intake[1]		
Never	98(27.8)	124(35.1)
<7 drinks per week	191(54.1)	143(40.5)
≥7 drinks per week	64(18.1)	86(24.4)
Diabetes[1]		
No	340(96.3)	316(89.5)
Yes	13(3.7)	37(10.5)

[1] P<0.05

[2] Pennsylvania, Ohio, West Virginia

A stratified univariate analysis by state residency was attempted based on the difference seen between the geographic distribution of cases and controls (cases outside of the Pennsylvania, Ohio, West Virginia vicinity: n=154(44%); OR=8.24, 95%CI=4.98-13.62). This was not possible due to the non-convergence of maximum likelihood estimates in several of the attempted regression models. In order to adjust for the difference in geographic residency, this covariate was included in all of the multivariate models.

2.3.2 Medical History

Family members with a history of cancer were found to be significant in the univariate analysis and this increased with increasing family members (1 family member OR=1.586, 95%CI=1.113-2.260, 2-3 members OR=2.066, 95%CI=1.350-3.161). The one-family member significance held up in two of our models but a trend could no longer be seen and it lost significance after adjusting for industry and occupation.

Table 2-2 Multivariate Analysis of Medical History and Cancer

Variable	Cases (n=353)	Controls(n=353)	cOR	95%CI	aOR[3]	95%CI	aOR[4]	95%CI	aOR[5]	95%CI
Asthma										
Never	319(90.4)	312(88.4)	1.0							
Ever	34(9.6)	41(11.6)	0.82	0.51-1.31						
Hay Fever										
Never	285(80.7)	320(90.7)	1.0		1.0		1.0		1.0	
Ever	68(19.3)	33(9.3)	2.52	1.56-4.09	2.18	1.08-4.37	2.47	1.19-5.11	4.40	1.46-13.26
Eczema										
Never	332(94.1)	341(96.6)	1.0							
Ever	21(5.9)	12(3.4)	1.75	0.86-3.56						
Immunologic Disease										
Never	341(96.6)	345(97.7)	1.0							
Ever	12(3.4)	8(2.3)	1.5	0.61-3.67						
Epilepsy										
Never	349(98.9)	350(99.2)	1.0							
Ever	4(1.1)	3(0.8)	1.33	0.30-5.96						
Cancer										
Never	322(91.2)	327(92.6)	1.0							
Ever	31(8.8)	26(7.4)	1.21	0.70-2.08						
Family History of Cancer										
None	109(30.9)	151(42.8)	1.0		1.0		1.0		1.0	
1 Relative	153(43.3)	138(39.1)	1.59	1.11-2.26	1.73	1.00-2.97	1.82	1.04-3.18	1.89	0.86-4.57
2-3Relatives	91(25.8)	64(18.1)	2.07	1.35-3.16	1.52	0.83-2.81	1.56	0.84-2.92	1.84	0.73-4.64

[3] Model adjusted for education, race, smoking, alcohol, diabetes, residency

[4] Model adjusted for education, race, smoking, alcohol, diabetes, residency, chemical exposure, loud noise exposure, family history of cancer, hay fever

[5] Model adjusted for education, race, smoking, alcohol, diabetes, residency, chemical exposure, loud noise exposure, family history of cancer, hay fever, dental x-rays, industry(professional, finance, transportation, manufacturing), occupation(managerial/professional, service, operators/fabricators/laborers), military service

All of our multivariate models showed a significant increased association with acoustic neuroma in people who have a history of hay fever (aOR=4.40, 95%CI=1.46-13.26) and this relationship existed after adjusting for education, race, smoking, alcohol, diabetes, residency, chemical exposure, loud noise exposure, family history of cancer, dental x-rays, industry(professional, finance, transportation, manufacturing), occupation (managerial/professional, service, operators/fabricators/laborers), and military service. Other medical history such as asthma, eczema, immunologic disease, epilepsy, or cancer did not reach significance (Table 2-2).

2.3.3 Environmental Exposures

Environmental exposures showed that there were more controls exposed to occupational noise and chemicals than acoustic neuroma cases (OR=0.417, 95%CI=0.298-0.585, OR=0.683, 95%CI=0.503-0.928 respectively). These factors were not found to be significant after adjusting for socio-demographic factors such as education, race, smoking, alcohol, diabetes, and residency. There was no significant difference in recreational loud noise hobbies.

Table 2-3 Multivariate Analysis of Environmental and Occupational Exposures

Variable	Cases (n=353)	Controls (n=353)	cOR	95%CI	aOR[6]	95%CI	aOR[7]	95%CI	aOR[8]	95%CI
Loud Hobbies[9]										
Never	94(26.6)	87(24.6)	1.0							
Ever	259(73.4)	266(75.4)	0.88	0.61-1.28						
Loud Occupational Noise										
Never	218(61.8)	151(42.8)	1.0		1.0					
Ever	135(38.2)	202(57.2)	0.42	0.30-0.59	0.68	0.37-1.26				
Occupational Chemical Exposure[10]										
Never	184(52.1)	152(43.1	1.0		1.0					
Ever	169(47.9)	201(56.9)	0.68	0.50-0.93	0.85	0.54-1.35				
Tobacco Pack-years										
Never Smoked	323(91.5)	185(52.4)	1.00							
<20 pack-years	19(5.4)	77(21.8)	0.16	0.09-0.30	0.14	0.07-0.29	0.16	0.07-0.34	0.11	0.04-0.30
≥20 pack-years	11(3.1)	91(25.8)	0.05	0.02-0.13	0.05	0.02-0.15	0.06	0.02-0.18	0.02	0.01-0.12

[6] Model adjusted for education, race, smoking, alcohol, diabetes, residency

[7] Model adjusted for education, race, smoking, alcohol, diabetes, residency, chemical exposure, loud noise exposure, family history of cancer, hay fever

[8] Model adjusted for education, race, smoking, alcohol, diabetes, residency, chemical exposure, loud noise exposure, family history of cancer, hay fever, dental x-rays, industry(professional, finance, transportation, manufacturing), occupation(managerial/professional, service, operators/fabricators/laborers), military service

[9] Target shooting/Hunting, Motorcycle/ATV/Race car, Concert Attendance, Musical instrument, Machine shop, Gardening/lawn maintenance with power tools

[10] Tetrachloroethylene, petroleum products, vinyl chloride and chlorinated hydrocarbons, inks/dyes/paints/resins/solvents, pesticides/herbicides/fungicides, heavy metals/welding fumes

Further analysis was performed on tobacco use and adjusted regression models were created. Pack years <20 and ≥20 were compared to never smoked and a protective trend was seen that was still present after adjusting for all other significant factors (education, race, alcohol, diabetes, residency, chemical exposure, loud noise exposure, family history of cancer, hay fever, dental x-rays, industry(professional, finance, transportation, manufacturing), occupation(managerial/professional, service, operators/fabricators/laborers), military service). The association is: (<20 pack years OR=0.11, 95%CI=0.04-0.30; ≥20 pack years OR=0.02 95%CI=0.01-0.12) (Table 2-3). To evaluate this for a potentially strong socio-demographic bias a post-hoc analysis was performed by stratifying smoking by education level (<13 years vs. ≥13 years) and tobacco remained statistically significant (chi-square p<0.0001).

2.3.4 Industry

There was a significantly higher association among cases who worked in the professional and finance industries and conversely among controls who worked in the transportation and manufacturing industries in the univariate analysis (OR=1.48, 95%CI=1.029-2.155; OR=2.46, 95%CI=1.218-4.984; OR=0.54, 95%CI=0.307-0.969; OR=0.50, 95%CI=0.263-0.950, respectively). These associations were not significant after adjusting for education, race, smoking, alcohol, diabetes, and residency. Manufacturing was no longer significant after adjusting for education, race, smoking, alcohol, diabetes, residency, chemical exposure, and loud noise exposure.

Table 2-4 Multivariate Analysis of Industry and Occupation

Variable	Case (n=353)	Control (n=353)	cOR	95% CI	aOR[11]	95%CI	aOR[12]	95%CI	aOR[13]	95%CI
Employed	246(69.7)	236(66.9)	1.0	0.62-						
Not Employed	107(30.3)	117(33.1)	0.87	1.21						
Usual Industry	Case (n=330)	Control (n=304)								
Professional										
No	203(61.5)	208(68.4)	1.0	1.03-	1.0	0.67-				
Yes	127(38.5)	96(31.6)	1.49	2.16	1.27	2.41				
Business										
No	305(92.4)	286(94.1)	1.0	0.69-						
Yes	25(7.6)	18(5.9)	1.29	2.44						
Finance										
No	297(90)	291(95.7)	1.0	1.22-	1.0	0.85-				
Yes	33(10)	13(4.3)	2.46	4.98	2.42	6.91				
Trade										
No	303(91.8)	277(91.1)	1.0	0.47-						
Yes	27(8.2)	27(8.9)	0.84	1.50						
Transportation										
No	307(93)	267(87.8)	1.0	0.31-	1.0	0.44-				
Yes	23(7)	37(12.2)	0.55	0.97	1.16	3.06				
Manufacturing										
No	309(93.6)	270(88.8)	1.0	0.26-	1.0	0.10-	1.0	0.10-		
Yes	21(6.4)	34(11.2)	0.50	0.95	0.32	0.97	0.32	1.03		
Other										
No	281(85.2)	256(84.2)	1.0	0.55-						
Yes	49(14.8)	48(15.8)	0.91	1.49						

[11] Model adjusted for education, race, smoking, alcohol, diabetes, residency

[12] Model adjusted for education, race, smoking, alcohol, diabetes, residency, chemical exposure, loud noise exposure

[13] Model adjusted for education, race, smoking, alcohol, diabetes, residency, chemical exposure, loud noise exposure, family history of cancer, hay fever, dental x-rays, industry(professional, finance, transportation, manufacturing), occupation(managerial/professional, service, operators/fabricators/laborers), military service

Table 2-4 Continued

Usual Occupation	Cases(n=339)	Controls(n=331)	cOR	95% CI	aOR[11]	95%CI	aOR[12]	95%CI	aOR[13]	95%CI
Managerial/ Professional										
No	155(45.7)	240(72.5)	1.0	2.39-	1.0	1.85-	1.0	1.82-	1.0	1.45-
Yes	184(54.3)	91(27.5)	3.49	5.08	3.51	6.68	3.56	6.94	3.83	10.14
Technical/Sales/ Support										
No	273(80.5)	246(74.3)	1.0	0.51-						
Yes	66(19.5)	85(25.7)	0.73	1.05						
Service										
No	321(94.7)	293(88.5)	1.0	0.24-	1.0	0.24-				
Yes	18(5.3)	38(11.5)	0.44	0.81	0.55	1.26				
Precision Production/ Craft										
No	318(93.8)	310(93.7)	1.0	0.45-						
Yes	21(6.2)	21(6.3)	0.93	1.93						
Operators/Fabricators/ Laborers										
No	325(95.9)	274(82.8)	1.0	0.10-	1.0	0.15-				
Yes	14(4.1)	57(17.2)	0.19	0.38	0.41	1.10				
Variable	Case(n=352)	Control (n=353)								
Military service										
Never	294(83.5)	264(74.8)	1.0	0.30-	1.0	0.30-				
Ever	58(16.5)	89(25.2)	0.47	0.75	0.60	1.21				

2.3.5 Occupation

Univariate and multivariate analysis of occupational history showed that managerial/professional occupations were associated with cases (adjusted OR=3.83, 95%CI=1.45-10.14). Service occupations and operators/fabricators/laborers were associated with controls but none of these maintained significance in multivariate analysis. Multivariate models for occupation were adjusted for education, race, smoking, alcohol, diabetes, residency, chemical exposure, loud noise exposure, family history of cancer, hay fever, dental x-rays, industry(professional, finance, transportation, manufacturing), occupation(managerial/professional, service,

operators/fabricators/laborers), military service. History of military service was not significant after adjusting for education, race, smoking, alcohol, and diabetes (OR=0.53, 95%CI=0.283-1.015) (Table 2-4).

2.4 DISCUSSION

Significant associations have been fairly well established between ionizing radiation exposure and long-term risk of developing central nervous system neoplasm. These exposures include large nuclear events like the atomic bomb[2,3] and radiation treatments to the head and neck. [4-6]The only known hereditary risk is neurofibromatosis type 2. This causes damage to the tumor suppressing protein neurofibromin which allows proliferation of tumor cells in nervous system tissue.

2.4.1 Generalizability

Acoustic neuromas are benign yet potentially debilitating tumors. This generally slower growth pattern gives patients the ability and the motivation to seek out the most appropriate and high quality care. This often involves extensive research on behalf of the patient, who seeks to understand all available treatment modalities. This search frequently involves travel to a specialized center of care. Due to the relative rarity of these tumors, acoustic neuroma experts tend to be concentrated in large academic institutions and patients often need to travel significant distances from their home in order to receive appropriate care.

Based on an average incidence rate of 1 per 100,000 person-years and the 2000 USA census (total population 281,421,908 [www.census.gov]), we would estimate that 2,800 new acoustic neuroma cases were diagnosed in the USA every year within our study period. The University of Pittsburgh has performed Gamma knife Stereotactic Radiosurgery in approximately 100 acoustic neuroma patients per year for the past several years. This represents treatment of roughly 3-4% of all American cases of acoustic neuroma every year. Since approximately half of our patients (46%) are from Pennsylvania, this also represents the treatment of about 37% of the local acoustic neuroma cases in this department with Gamma Knife Radiosurgery (12,300,000 people living in Pennsylvania=1230 new cases to have been diagnosed over the ten year period between 1997-2007).

2.4.2 Limitations and Socioeconomic Differences

Choosing a hospital based control population can present several challenges. Although our case population is largely representative of North American acoustic neuromas, there is still a large proportion of our patients who have the means to travel for their care (out of state patients=44%) while the control group is a mostly local population (out of state controls=9%). In this study we can clearly see that there are some discrepancies between cases and controls with regards to geographic location, education, and occupation. We see that most of the univariate differences no longer exist after adjusting for socio-demographic factors in our analysis.

This being said, the strong association between cases and managerial/professional occupations (adjusted OR=3.83, 95%CI=1.45-10.14)

contrasted with a greater proportion of controls in the manual labor occupations and the manufacturing industry probably indicates a potential discrepancy in healthcare access and delivery. In the setting of a slow-growing tumor that can only be diagnosed via costly imaging tests such as a computed tomography or magnetic resonance imaging of the brain, discrepancies in healthcare access and diagnostic delay are likely to be seen. This type of significant difference has been seen in a previous study by Inskip P, et al (2003)[28]when looking at education and family income. It showed that there was an association between increasing family income, college education and acoustic neuroma (4 year college/graduate school OR=3.4/3.2, 95%CI=1.7-6.6/1.5-6.7; household income >75,000/year: OR=7.2, 95%CI=2.5-20; family income P-trend <0.001).

Unfortunately a more detailed analysis of race is not possible in this study due to the small amount of non-white acoustic neuroma cases. Interestingly, though, an ad-hoc look at our data revealed that 5 out of the 8 non-white cases had a managerial/professional occupation. This gives more weight to the argument that acoustic neuroma diagnosis is more likely associated with better healthcare access and socioeconomic status than race.

2.4.3 Acoustic Trauma

Loud noise has been found to be associated with acoustic neuroma in previous studies. These were all case-control designed studies that looked at occupational or recreational exposure to loud noise (Preston-Martin, et.al. (1989): occupational noise OR=2.2; C G Edwards, et al (2005): occupational/recreational noise OR=1.55; B Schlehofer, et al

(2007): occupational noise OR=2.31; M Hours, et al (2009) occupational/recreational noise OR=2.55). These were all interview and questionnaire based studies.

It is very difficult to validate exposures to loud noise and there is always the possibility of recall bias. A further study by C G Edwards, et al (2007)[25]attempted to look at noise in an objective way by taking noise exposure data from an occupational census in Sweden. This study found no significant association with loud noise exposure. Our data show that there was more occupational loud noise exposure and chemical exposure among controls but this was most likely just an artifact of the occupational differences and did not persist in multivariate analysis.

2.4.4 Atopic Disease

Studies have found significant acoustic neuroma associations with allergies and immunological disease. Brenner A, et al (2002)[19]found a positive association with hay fever, food allergy, and other allergies (OR=2.36, 95%CI=1.38-4.03; OR=3.01 95%CI=1.06-8.53; OR=3.81 95%CI=1.45-9.99; respectively). Schlehofer B, et al (2007)[20]found a positive association with hay fever (OR=2.20 95%CI=1.09-4.45). The biological plausibility is not very well developed or understood. There is evidence described by Neiters A, et al (2004).[21]that an association exists with polymorphisms in T-helper cell type1, T-helper cell type2, and cytokine genes related to hay fever and atopic disease and this chronic immune cell activation may be related to malignancies. Brenner A, et al (2002)[19]suggested that this may in fact be the result of a diagnostic bias. She argues that if allergic rhinitis contributes to Eustachian tube dysfunction and otitis media, a more thorough work up might ensue; resulting in the incidental diagnosis

of acoustic neuroma. Our study found a strong and significant association with hay fever that persisted in multivariate analysis (aOR=3.91, 95%CI=1.35-11.30).

2.4.5 Tobacco

Tobacco was seen to have a protective effect against acoustic neuroma in this study. The biologic plausibility of this effect is unclear but the protective effect of tobacco against acoustic neuroma has been reported in two previous publications. One prospective study of 1.2 million women in the United Kingdom found that there is a decreased risk among current smokers (Relative Risk=0.41, 95%CI=0.24-0.70, P=0.001) of developing acoustic neuroma.[22]A different case-control study in the UK and Nordic countries found that acoustic neuroma associated risk was significantly lower in current smokers who regularly smoked cigarettes (OR= 0.7, 95%CI=0.6-0.9).[23]A protective effect of tobacco on other brain tumors has not been seen. [22,23,29]It has been well established in the literature that smoking has shown a protective effect against Parkinson's Disease but the mechanism for this is poorly understood and most of the evidence points towards nicotine's dopaminergic and neuroprotective effects.[30] Schoemaker, MJ (2007)[23]and Benson, VS (2010)[22]put forth a hypothesis that the anti-estrogenic effect of tobacco[31]may be protective against acoustic neuroma. (This idea was developed because hormone-replacement therapy was found to be an elevated risk in acoustic neuroma development in another prospective study (Relative Risk=1.58 95%CI=1.02-2.45)).[32]Other hypotheses include a potential tumor suppression effect by tobacco or perhaps a diagnostic bias effect from people attributing symptoms such as

imbalance and hearing loss to smoking rather than pursuing diagnostic tests to rule out a brain tumor.

2.4.6 Low Dose Radiation

Our previously reported analysis of low dose radiation exposure that was part of our case-control study showed that frequent exposure to dental x-rays at least once every 2-5 years (adjusted OR=2.28, 95% CI= 1.16-4.48) and once a year (adjusted OR=2.01, 95% CI=1.01-3.98) compared to those less than once every five years is associated with acoustic neuroma. This association was present in multivariate models adjusted for socio-demographic factors, medical history, and occupational history. No significant association was found with cellular phone use and acoustic neuroma. [16]

2.5 CONCLUSIONS

Acoustic neuromas remain a relatively rare tumor with a poorly understood etiology and risk factors. Although prospective cohort studies are the ideal standard for establishing risk, a case-control design remains an appropriate method for studying this rare tumor with an incidence rate of about 1:100,000 person-years. Better healthcare access likely plays a role in the diagnosis of this tumor. Hay fever is strongly associated with an increase risk of acoustic neuromas. Acoustic noise trauma was not found to be associated with acoustic neuroma but this exposure requires more objective and validated measures in order to further investigate this as a potential risk factor. Tobacco

use demonstrates a protective effect against acoustic neuroma development but this mechanism is poorly understood and tobacco remains a public health problem and a significant risk factor for much more common malignancies.

3.0 HEALTH-RELATED QUALITY OF LIFE OUTCOMES AFTER GAMMA KNIFE RADIOSURGERY FOR ACOUSTIC NEUROMA: A COMPARISON TO THE NORMAL POPULATION

3.1 INTRODUCTION

Relatively few published studies are available to define the long term health related quality of life of patients who undergo one or more management options for acoustic neuroma, also known as vestibular schwannoma.[33-35] Most such studies have compared outcomes after one or more various treatment modalities but fail to compare management outcomes to general population norms. Quality of life outcomes are increasingly important to acoustic neuroma patients given their choice of treatment options and the recognition of a tumor at earlier stages. Early recognition has been facilitated by the widespread use of magnetic resonance imaging (MRI) for patients with symptoms of imbalance or hearing dysfunction. Using a newly developed survey methodology and the Short-Form 36 Item Health Survey (SF-36),[36] the present report evaluates the long term outcomes of acoustic neuroma patients who underwent Gamma Knife ® radiosurgery and compares these outcomes to published outcome data in the US normal population.

3.2 METHODS

3.2.1 Survey Design

As part of a comprehensive study of both risk factors for development of an acoustic neuroma as well as long term outcomes, we developed a survey instrument that covered potential etiological factors as well as comprehensive outcome data. This study received the approval of the University of Pittsburgh Institutional Review Board for Human Research and informed consent was obtained from all study participants.

3.2.2 Patient Recruitment

Patients were recruited from the University of Pittsburgh Gamma Knife Radiosurgery database, which included 1475 patients who underwent Gamma Knife stereotactic radiosurgery (SRS) at the University of Pittsburgh Medical Center for a new or recurrent acoustic neuroma in the interval between August, 1987 and December 31, 2010. In order to maximize potential follow up in patients who underwent SRS since the integration of the MRI for treatment planning, we selected patients who underwent SRS between the years 1997-2007. The patients were given the Acoustic Neuroma survey questionnaire and a Short Form 36-Item Health Survey v2.0 (SF-36). All patients were contacted by written letter via the United States postal service. A questionnaire was mailed along with a pre-paid return envelope. Patients were given the option to fill out the questionnaire by hand or have it done over the telephone with a trained recruiter or to send it via email. The majority of patients opted to complete their questionnaire via

postal service (339, 96%), ten patients via email (3%) and four via telephone interview (1%).

Eight hundred and twenty two acoustic neuroma patients were treated with (SRS) between 1997-2007. A total of 420(51%) patients consented to the survey and ultimately 353 (43%) patients completed the necessary components to be included in this final analysis. Two patients had missing data and did not complete the SF-36 portion of the questionnaire. The Mean age of the participants was 60(standard deviation ±12) years old at the time of the SF-36 questionnaire. Mean age at diagnosis of the acoustic neuroma was 53 years (standard deviation ±12). Median interval from date of diagnosis to (SRS) was 3 months (range 0-265), median time from (SRS) to this study was 63 months (range 18-141). Average tumor volume was 0.5cm3 (range 0.012-17.3) and median radiation dose to the tumor margins was 13Gy (range 7-30). Thirty (8.5%) patients had undergone a prior surgical resection before SRS. Three (0.9%) patients had undergone prior fractionated radiation therapy before SRS.

Table 3-1 Demographics and Tumor Descriptives

Acoustic Neuromas Treated between 1997-2007	822
Patients In Study	353 (43%)
Median Tumor Volume	0.5cm3 (range 0.012-17.3)
Median Dose of Radiation to Tumor Margin	13 Gy (range 7-30)
Gender	
Men	175 (49.6%)
Women	178 (50.4%)
Mean Current Age (Standard Deviation)	60 (12)
Mean Age Of Case At Diagnosis (SD)	53 (12)
Tumor Location	
Right	175 (49.6%)
Left	178 (50.4%)
Previous Craniotomy	30 (8.5%)
Previous Radiation Treatment	3 (0.9%)
Median Time From Diagnosis to Treatment (Months)	3 (0-265)
Median Time From Treatment To Questionnaire (Months)	63 (18-141)
Surgery For Tumor Progression	
Repeat Gamma Knife	2
Microsurgery	1

3.2.3 Questionnaire

A functional outcomes questionnaire was developed. The survey assessed the patient's perception of their current hearing status in both the tumor and the non-tumor ear, tinnitus, balance disorder symptoms, and vertigo. Patients were also queried over their overall satisfaction with the procedure and if they would recommend the procedure to somebody else. We also administered the SF-36 in order to further assess health related quality of life.

3.2.4 Statistical Analysis

Descriptive statistics were used to display demographic data. Medians, Means, standard deviations, and overall proportions were used when appropriate. Pearson's Correlation Coefficient, student's t-tests, and ANOVA were used where appropriate in order to explore relationships between variables. All data were analyzed using PASW Statistics 18, Release Version 18.0.0 (© SPSS, Inc., 2009, Chicago, IL, www.spss.com)

3.2.5 SF-36 Analysis

SF-36 questionnaire data were analyzed according to the SF-36v2 user's manual[37]scoring criteria. Summary scores for physical and m ental health (PCS and MCS respectively) were also obtained according to the scoring criteria for ease of interpretation and overall comparison. Normalized t-scores were obtained for each of the eight scales as well as the summary scores. The data were normalized to the 1998 SF-36 US population norms as outlined in the user's manual. This normalized data are presented for a more meaningful interpretation of the data. It allows for easy comparison to US population norms and facilitates comparisons made across subgroups. It also eliminates excess variability of standard deviations and equates the central tendencies across scales. The US population norms demonstrate a mean of 50 and a standard deviation of 10 for each of the eight scales as well as the two summary scores.[37]Student's t-tests were performed on summary scores between the patients while stratifying according to functional status in order to determine significant

differences in summary scores according to functional status. One-sample t-tests were performed between patients and 1998 US population norms in order to determine statistically significant differences between mean scores in each of the eight scales and the two summary scores as well as a stratified analysis by age grouping. The One-sample t-tests used the population mean of 50 for test comparisons of overall score and the corresponding age group means for the stratified analysis as published by the SF-36.[37]

3.2.6 Effect Size Scoring

It was determined that a minimal clinically significant difference in SF-36 scores would follow Cohen's formulation of effect size (ES) scoring. This was done by dividing the difference in mean scores by the standard deviation of the patient's score. The general accepted ranges were represented as 0.20 to 0.50 for a "small" effect size, 0.50 to 0.80 for a "medium" effect size and greater than 0.80 would be "large". This usually translates to a mean score difference of around 2 to 5 points for a clinically significant difference. .[38-40]Because the 1998 US population norms carry a mean scale score of 50 and a standard deviation of 10, the normalized data can be interpreted as having an effect size change of 0.10 for every one point difference in mean score when comparing to the population norms.[37]

3.3 RESULTS

3.3.1 Functional Outcomes

Two hundred and forty six (70.3%) patients reported that they currently do not have useful hearing in the tumor ear. For our questionnaire, we defined useful hearing as being able to use the ear at least fairly in an everyday conversation. Of interest, 334 (94.9%) patients reported retention usable hearing in the non-tumor ear. Fifteen patients (4.2%) described their hearing as either poor or deaf in both ears.

Tinnitus was reported by 163 (41.7%) patients either often or continuously. Imbalance symptoms were noted by 121 (34.4%) patients either often or continuously. Vertigo symptoms were reported by 42 (12%) patients either often or continuously.

Table 3-2 Self-reported Current Functionality

	n (%)
Hearing in Tumor Ear (Usable: Excellent/Good/Fair vs. Non-Usable: Poor/Deaf) For Use in an Everyday Conversation	
• Usable	104 (29.7)
• Non-Usable	246 (70.3)
Hearing in Non-Tumor Ear (Usable: Excellent/Good/Fair vs. Non-Usable: Poor/Deaf) For Use in an Everyday Conversation	
• Usable	334 (94.9)
• Non-Usable	18 (5.1)
Tinnitus in Tumor Ear	
• Never/Rarely	190 (53.8)
• Often/Continuous	163 (41.7)
Tinnitus in Non-Tumor Ear	
• Never/Rarely	334 (94.6)
• Often/Continuous	19 (5.4)
Tinnitus in Both Ears	
• Never/Rarely	314 (89)
• Often/Continuous	39 (11)
Balance Problems	
• Never/Rarely	231 (65.6)
• Often/Continuous	121 (34.4)
Vertigo or Dizziness	
• Never/Rarely	308 (88)
• Often/Continuous	42 (12)
Are You Satisfied With Your Current Overall Functionality and Activity Level?	
• Yes	318 (91.1)
• No	31 (8.9)
Would You Recommend The Gamma Knife Radiosurgery Procedure for a Friend or Family Member With Your Type of Tumor?	
• Yes	337 (96.8)
• No	11 (3.2)
Additional surgeries	
• Repeat Gamma Knife Radiosurgery	2(0.6)
• Unspecified in Self-Report	5(1.4)

3.3.2 Overall Satisfaction

Three hundred eighteen patients (91.1%) reported that they were satisfied with their current level of functioning and 337 (96.8%) noted that they would recommend the Gamma Knife Radiosurgery procedure to a friend or relative if they were to develop an acoustic neuroma (Table 3-2).

3.3.3 SF-36 Outcomes

The SF-36 scores were compared to 1998 US population norms. Our patients reported outcomes that either matched or exceeded outcomes noted for 1998 US population norms. The vitality category was both statistically and clinically significant with a “small” effect size of 0.29 ($p<0.0001$).Body pain, social functioning, and m ental health categories were statistically better than the population norms ($p<0.0001$, $p=0.008$, $p=0.009$ respectively) but they did not meet a clinically significant effect size of at least 0.2 (Table 3-3). The Mental Health Summary Score was significantly higher than population norms (mean score difference 1.72, $p=0.001$) but again, it was not clinically significant.

Table 3-3 Effect Size

Sf-36 Scale	Case/US Population Effect Size
Physical Functioning	0.03
Role Physical	0.05
Body Pain	0.18[14]
General Health	0.10
Vitality	0.29[15]
Social Functioning	0.13[14]
Role Emotional	0.06
Mental Health	0.13[14]

[14] Statistically significant at $p<0.05$ according to one-sample t-test comparing to a mean of 50

[15] Both statistically and clinically significant

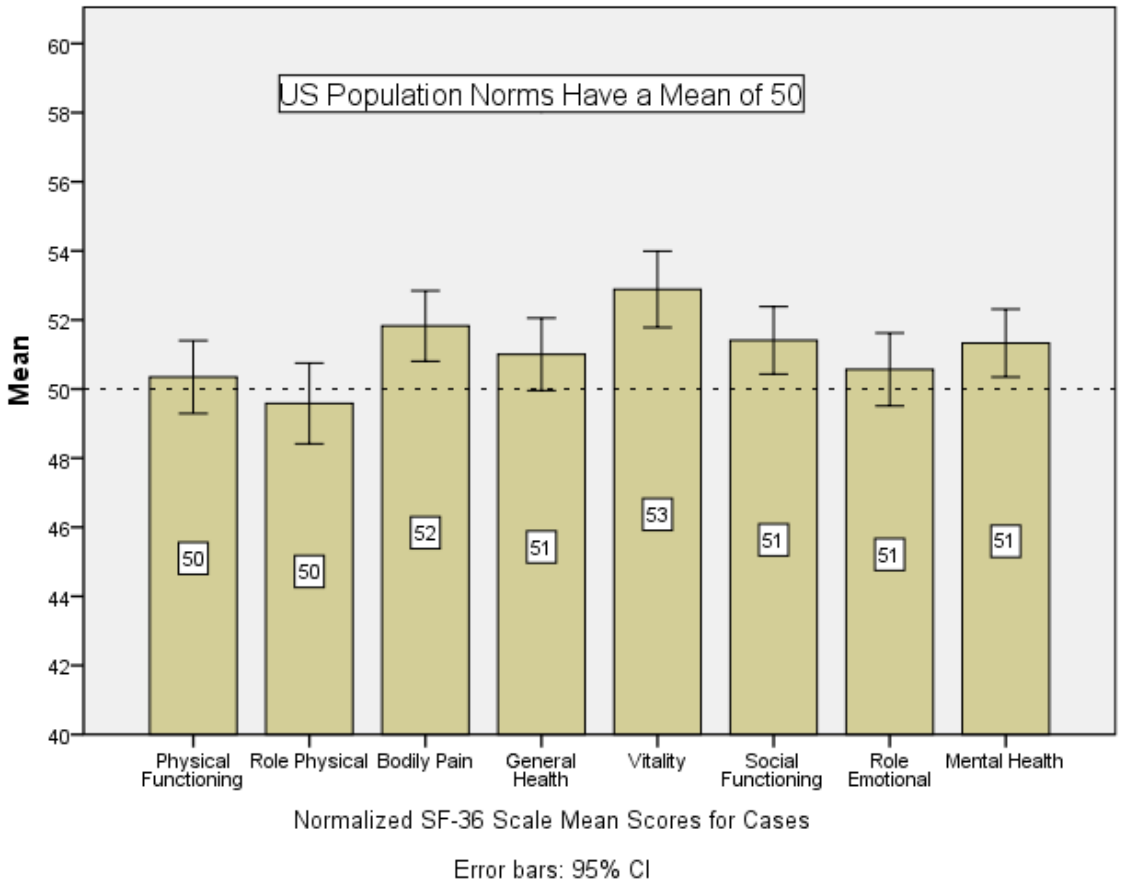

Figure 3-1 Normalized SF-36 Scores For Patients With 95%CI. Scores Represent The Eight Domains Measured And Are Compared To A Normalized Mean Of 50

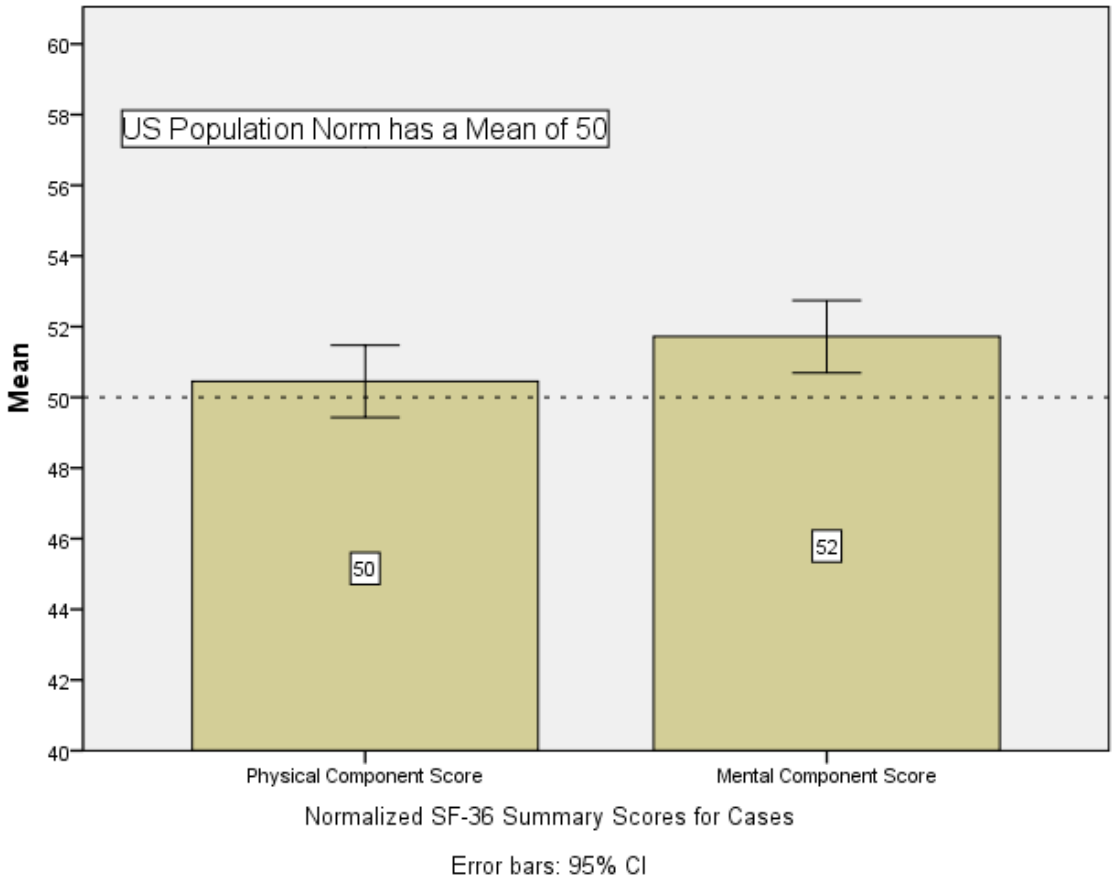

Figure 3-2 Normalized SF-36 Scores For Patients With 95%CI. Scores Represent The Overall Physical And Mental Summary Compared To A Normalized Mean Of 50

Summary scores were not significantly different between men and women (mean difference of PCS 0.82 p=0.43, MCS 1.55 p=0.14) in our cohort. We found a significant difference in PCS mean scores stratified by age groupings that showed them lowering with age (ANOVA p<0.0001) but no significant difference was found in MCS age groups

(ANOVA p=0.37). The SF-36 US population norms for PCS and M CS were also published as stratified by age groupings[37]and these were compared to our patient's age groups. Our patients did the same or better than US norms in all age groups. Our patients had statistically significant better scores than US norms in the following age groups: 25-34 MCS=52.46 p=0.027, 45-54 PCS=53.30 p =0.001, 55-64 PCS=52.08 p<0.0001, 65-74 PCS=47.45 p<0.021, 75+ PCS=45.04 p=0.001.

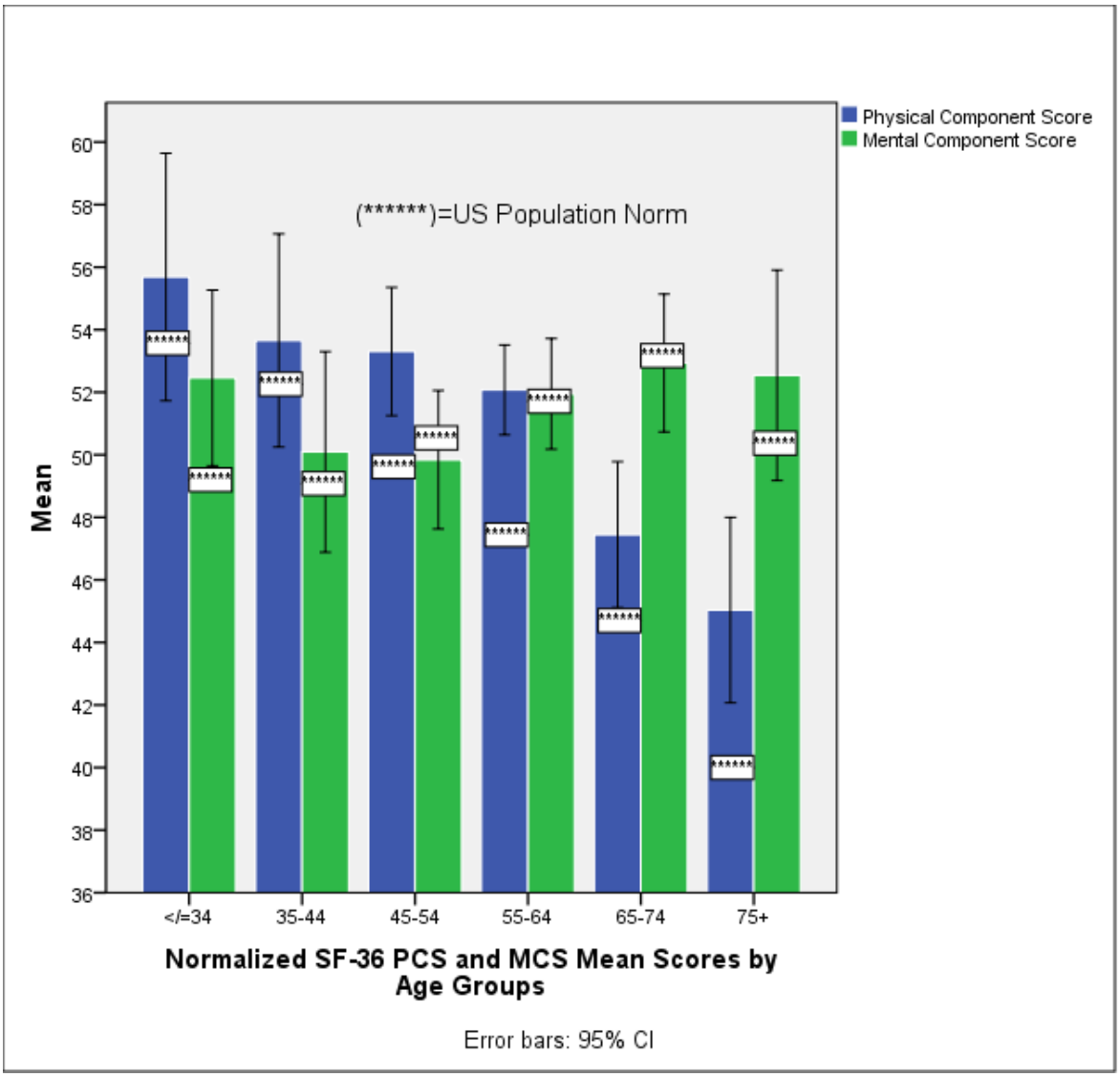

Figure 3-3 Normalized SF-36 Scores With 95%CI Stratified By Age Group. Scores Represent The Overall Physical And Mental Summary Scores In Each Age Group. The Line Of Asterisks [****] In Each Bar Represents The Varying Normalized Mean For Each Age Group For Comparison

No significant correlation was found between the length of time from treatment and the summary scores (Pearson's correlation coefficient: PCS -0.054 p=0.32, MCS 0.07 p=0.194).

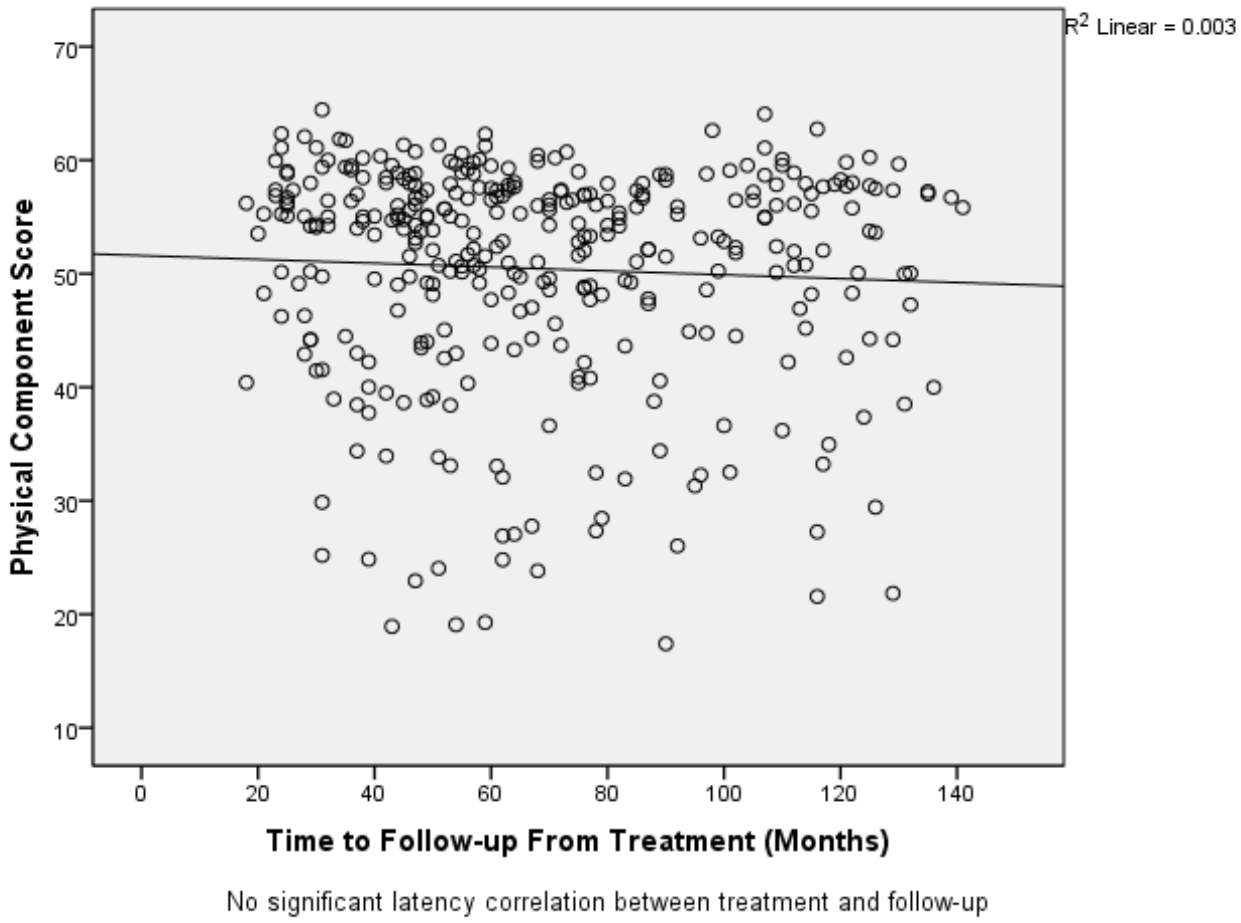

Figure 3-4 Scatter Plot With Best-Fitted Line Demonstrating No Significant Correlation Between Time From Follow Up To Physical Component Summary Score (PCS Correlation Coefficient -0.054 P=0.32)

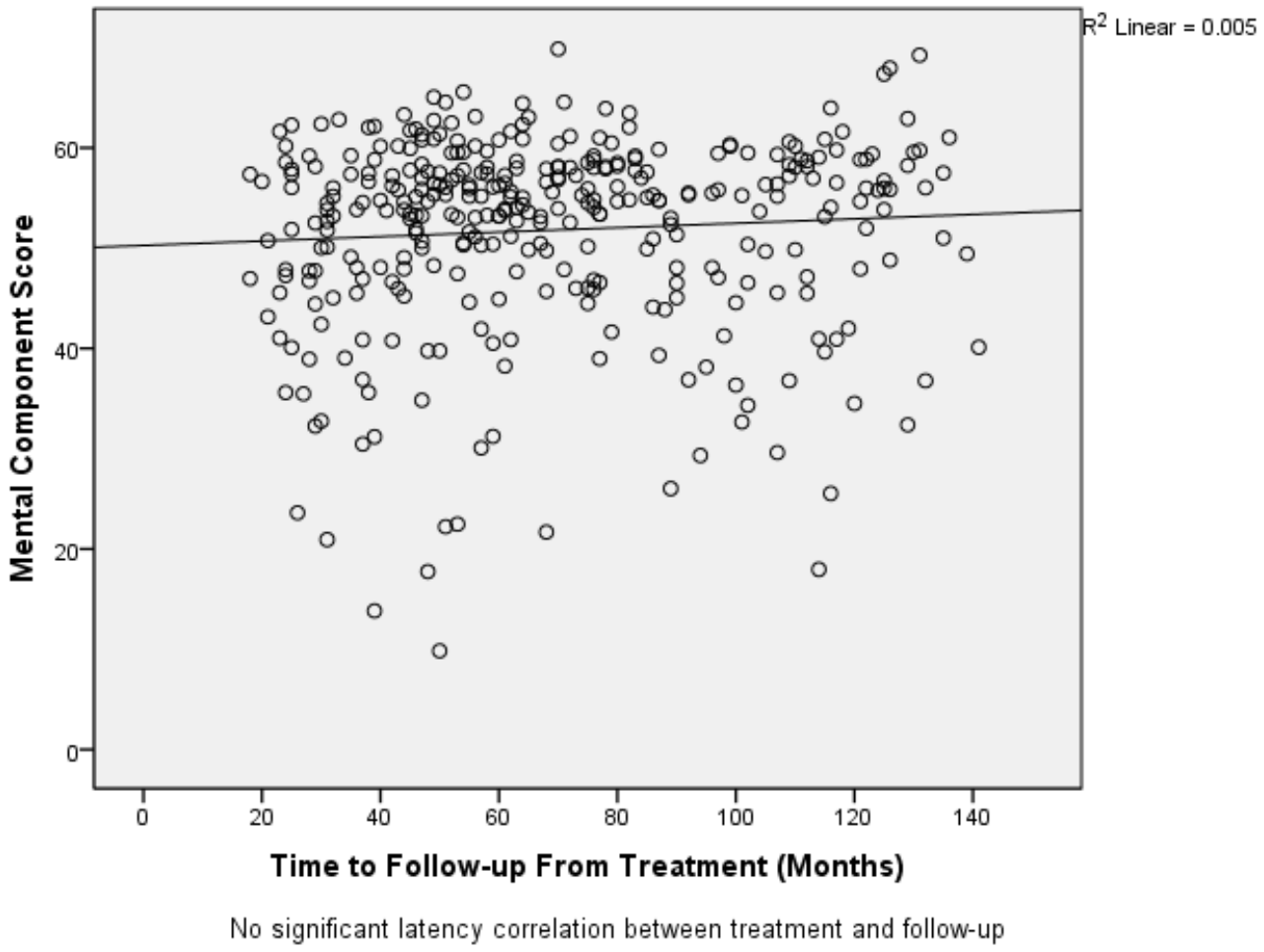

Figure 3-5 Scatter Plot With Best-Fitted Line Demonstrating No Significant Correlation Between Time From Follow Up To Mental Component Summary Score (MCS Correlation Coefficient 0.07 P=0.194)

Mean SF-36 summary scores stratified by functional differences demonstrated significant differences in hearing, balance, and vertigo. Non-functional hearing in the

tumor ear showed a significantly lower PCS (-2.79, effect size -0.27, p=0.014) but no significant difference in MCS. Regular imbalance and vertigo problems was significantly associated with lower PCS and MCS (imbalance *PCS* -6.41 ES -0.56; vertigo PCS -9.53 ES -0.73; imbalance *MCS* -4.06 ES -0.36; vertigo MCS -7.65 ES -0.71, p<0.0001). No significant differences were found for tinnitus.

Table 3-4 Functional Status Effect on Summary Scores

	Physical Summary Score			Mental Summary Score		
Functional Status	Mean Difference	Effect Size	P Value	Mean Difference	Effect Size	P Value
Hearing In Tumor Ear: Non-Functional Vs. Functional	-2.79	-0.27[16]	0.01	-0.18	-0.02	0.87
Tinnitus In Tumor Ear: Continuous/Often Vs. Rarely/Never	-1.87	-0.19	0.10	-0.4	-0.04	0.68
Imbalance Continuous/Often Vs. Rarely/Never	-6.41	-0.56[16]	<0.001	-4.06	-0.36[16]	<0.001
Vertigo Continuous/Often Vs. Rarely/Never	-9.53	-0.73[16]	<0.001	-7.65	-0.71[16]	<0.001

[16] Clinically significant effect size

3.4 DISCUSSION

Patients with acoustic neuromas are presented with various management options that range from continued observation (wait and scan), microsurgical removal by one of several surgical approaches, or stereotactic radiosurgery using one of several methodologies. Since 1987 we have evaluated the long term role and outcomes of Gamma knife radiosurgery in an increasing experience. In our observational cases, we have noted that most (>80%) patients demonstrate clinical worsening and image defined tumor growth within a period of 5- 10 years. Since our experience also confirms that hearing preservation is better when patients undergo SRS earlier[41-43]In order to evaluate both potential etiological factors in the development of acoustic neuromas as well as to survey long term outcomes, we developed a specially designed survey to assess both factors. The present study was designed to define the outcomes of acoustic neuroma patients who underwent GK SRS in the second ten year interval of our evolving evaluation of SRS using the Leksell Gamma knife (AB Elekta, Stockholm, Sweden). We compared these results to standard population outcome norms using data provided by the SF-36 scoring manual.

Several published studies have evaluated the outcomes of Gamma Knife Radiosurgery and indicate that this management strategy is associated with long term improvement in outcomes, especially in comparison to outcomes reported after microsurgical management.[44-50]All such studies have certain limitations. Since there is no widely used acoustic neuroma specific questionnaire, there is no uniformity in health related quality of life measurement tool. A recent publication by Schaffer, BT. 2010 showcased what may be the first attempt at validating an acoustic neuroma-specific

quality of life measurement tool.[51]Many published studies are underpowered to obtain significant results and most of their outcome data were less than four years.

Table 3-5 Gamma Knife Radiosurgery Quality of Life Outcomes

Author	Follow Up (Years)	Quality of Life Measurement Tool	N	Results
Myrseth E, et al 2005	1.5-13	GBI[17], SF-36[18],	168	GK[19] fared better than MS[20] on both measures. Combined SF-36 scores were lower than Norwegian population norms. Stratified GK scores were not reported.
Myrseth E, et al 2009	2	Sf-36, GBI	88	Prospective look at GK improved from baseline on GBI.
Pollock B, et al 1995	2-4	Functional outcome rating scale	87	GK Resumed regular activities sooner than MS post-op. GK did better than MS on functional scale but did not reach significance.
Pollock B, et al 2006	1-5	HSQ[21]	82	GK had no prospective decline. MS had significant prospective decline.
Regis J, et al 2002	3	Functional evaluative questionnaire	210	GK had better functional outcomes compared to MS
Roijen L. Van, et al 1997	2	"Health and Labor Questionnaire" (employment productivity), SF-36, EuroQol	145	GK had better outcomes than MS. GK was more cost-effective than MS.
Sandooram D, et al 2004	2-5	GBI	165	GK and MS did worse than successful observation but observed tumors were about half the size of treated ones. GK results did not reach significance.
Timmer FC, et al 2009	0.17-4.6	Sf-36, GBI	97	GK SF-36 results were similar to Dutch population norms. GBI did not have significant difference.

[17] Glasgow Benefit Inventory

[18] Short Form-36 Questionnaire

[19] Gamma Knife

[20] Microsurgery

[21] Health Status Questionnaire

Our study evaluated 353 acoustic neuroma patients at a median of 5.25 years after undergoing radiosurgery. The present study is the first to compare outcomes after Gamma Knife Radiosurgery for acoustic neuroma to age matched US population norms. A study in the Netherlands also showed that acoustic neuroma patients' SF-36 scores were comparable to their Dutch population norms.[52]A Norwegian study compared Norwegian SF-36 population norms to patients who underwent Gamma Knife Radiosurgery for an acoustic neuroma.[48]The Norwegian study looked at combined SRS/microsurgery data and did not report stratified SRS scores. These combined treatment outcomes showed that patients did the same or slightly worst than their country's population norms. Loyd et al. evaluated outcomes in United Kingdom acoustic neuroma patients who underwent a watch and scan strategy and compared them with UK SF-36 population norms. His observation cohort did significantly worse than UK population norms.[53]A Dutch cross-sectional study looked at baseline SF-36 scores upon initial diagnosis of acoustic neuroma and compared them with Dutch population norms.[54] These recently diagnosed patients who had not undergone any treatment yet also did poorer compared to Dutch population norms.

The answers to the functional questions that we included in the questionnaire have yielded data that on face value could seem to conflict with published data related to objective testing such as audiograms in patients eligible for hearing preservation after SRS. In the present report 70% of patients reported that they did not have serviceable hearing in their tumor side. This series included patients who were deaf or had unserviceable hearing at the time of SRS (Gardner Robertson Class III-V) as well as patients who had serviceable hearing prior to SRS (Gardner Robertson Class I or II).

We have reported that serviceable hearing can be maintained in as many as 70% of patients who have serviceable hearing at the time of radiosurgery.[55,56]The present study was a s elf reported outcome study that did not include objective hearing test measurements. We did find that patients with non-functional hearing in their tumor ear had a significantly lower PCS, but this carried only a small effect size of -0.27 and no significant difference was found in the MCS.

Tinnitus is a commonly reported symptom of patients with acoustic neuromas but it is impossible to measure objectively. Patients with acoustic neuromas report that tinnitus may be unilateral or bilateral. The impact of tinnitus is variable among patients and its presence does not easily correlate with a patient's level of discomfort.[57-59] In this study we did not find any significant association between tinnitus and SF-36 summary score changes. Our findings agree with previous studies including Loyd et al, 2010[53,60] who also failed to find a significant correlation between summary scores and the tinnitus handicap index. Other tinnitus studies have shown that approximately 80% of patients who suffer from chronic tinnitus did not seek treatment for it.[57]In this study we found that the presence of tinnitus resulted in no consistent impact on activities of daily living.

Symptoms of a bal ance disorder or vertigo are similarly difficult to measure objectively. We also have noted wide variability related to the impact of such symptoms among acoustic neuroma patients. Our questionnaire found that our acoustic neuroma patients who reported balance or vertigo problems had significantly lower PCS and MCS scores of "medium" clinical significance. This finding has been previously shown in studies where quality of life impairment was correlated with the presence of imbalance or vertigo. [53,60]

Despite the reported symptoms of hearing loss, tinnitus, and balance disorders, 91% of our patients report that they were satisfied with their overall level of functioning. This high level of satisfaction seems to correlate with their above average performance on the SF-36 questionnaire. Unlike our high levels of SF-36 performance in patients who underwent Gamma Knife Radiosurgery, Loyd et al. 2010's[53]watch and scan cohort showed that their physical component and summary scores of the SF-36 were significantly lower than the normal population. As described above, they attributed a proportion of this to balance symptoms. In addition they were unable to assess the impact of hearing dysfunction due to the small number of "observation only" patients that actually retained hearing.

Our patients were found to have similar or better results on their SF-36 summary scores compared to the US population and this finding held up even against age-group stratification. They are able to maintain their quality of life over the long term as shown by the lack of any significant correlation between summary scores and latency from treatment.

Our well maintained level of health related quality of life is likely attributable to several factors. Gamma Knife SRS is a non-invasive management strategy designed to obtain tumor control, maintain cranial nerve function, and avoid the relatively rare but significant risks of microsurgical removal. Long term tumor control rates vary from 90 - 98% of patients.[42,55,56]This contrasts in our experience with the >80% likelihood of tumor progression over 10 years if a "wait and scan" approach is adopted.

3.5 CONCLUSION

Overall, patients at an average of five years after undergoing Gamma Knife Radiosurgery for an acoustic neuroma reported retention of a high quality of life that matches or exceeds quality of life of US population norms. Such patients tend to report that they are satisfied with their current of function and would recommend Gamma Knife Radiosurgery to a family member or a friend if they were to develop an acoustic neuroma. Although symptomatic hearing loss and balance or vertiginous disorders were reported to impact negatively on quality of life, the effect is only of “small” or “medium” clinical significance in comparison to US population norms.

4.0 DO ACOUSTIC NEUROMAS AFFECT HEARING IN THE NON-TUMOR EAR? A CROSS-SECTIONAL LOOK AT THE NON-TUMOR EAR OF PATIENTS UNDERGOING GAMMA KNIFE RADIOSURGERY FOR ACOUSTIC NEUROMA AND COMPARISON TO NHANES POPULATION NORMS

4.1 INTRODUCTION

Many patients with an acoustic neuroma will eventually lose their hearing in the affected ear regardless of intervention or even tumor growth.[43,61-63]This makes hearing in the unaffected ear a significant concern for the morbidity of the patient. Acoustic neuromas are known to cause unilateral hearing loss that can be demonstrated with elevated audiogram thresholds and low speech discrimination scores.

There is not much published research about the status of a patient's hearing in the non-tumor ear. This study collected audiogram information on 321 acoustic neuroma cases in order to describe hearing in the non-tumor ear of patients with vestibular schwannoma. We also compared our findings to sample data that are generalized to the US population from the National Health and Nutrition Examination Survey (NHANES). The goal of this study is to provide a description of hearing in the non-tumor ear of patients with acoustic neuroma.

4.2 METHODS

4.2.1 Survey Design

We developed a survey instrument as part of a comprehensive study which included the assessment of risk factors for development of vestibular schwannoma. This questionnaire collected potential etiological factors and included noise exposures such as occupational noise, loud hobbies, military history, and the use of hearing protection. This study received the approval of the University of Pittsburgh Institutional Review Board for Human Research and informed consent was obtained from all study participants.

4.2.2 Patient Recruitment

Patients were recruited from the University of Pittsburgh Gamma Knife Radiosurgery database. In the database there are 1475 patients who underwent Gamma Knife stereotactic radiosurgery (SRS) at the University of Pittsburgh Medical Center for a new or recurrent acoustic neuroma in the interval between August, 1987 and December 31, 2010. We selected patients who underwent SRS between the years 1997-2007. The patients were given our newly developed Acoustic Neuroma questionnaire. All patients were contacted by written letter via the United States postal service. A questionnaire was mailed along with a pre-paid return envelope. Patients had the option of filling out the questionnaire by hand or they could request an interview over the telephone with a trained recruiter or they had the option to complete it via email. The majority of patients

opted to complete their questionnaire via postal service (339, 96%), ten patients via email (3%) and four via telephone interview (1%).

A total of 822 acoustic neuroma patients were treated by SRS between 1997-2007. A total of 420(51%) patients consented to the survey and ultimately 353 (43%) patients completed all of the necessary components. A total 321 (90.9% of 353) patients had complete audiogram data and were included in the final analysis. Audiograms closest to the date of diagnosis were used for this study to best approximate a baseline reading of hearing status. Median tumor volume was 0.5cm3 (range 0.012-17.3). The Mean age of the participants was 54.72 (standard deviation ±12.46) years old at the time of diagnosis. Gender and tumor side were both equally divided (men 166 (51.71%), right side tumor 163 (50.78%)). Median interval between date of diagnosis and audiogram was 22 days (-3639 to 3769), median time from diagnosis to this questionnaire was 77.07 months (0.43-219.6).

Table 4-1 Demographics of Acoustic Neuroma Patients

Acoustic Neuromas Treated between 1997-2007	822
Patients Who Responded to Questionnaire	353(43% of 822)
Patients With Audiogram (Included in Study)	321 (91% of 353)
Age	
Mean	54.72
Std. Deviation	12.46
Gender	
Male	166 (51.7%)
Female	155 (48.3%)
Tumor Location	
Right	163 (50.8%)
Left	158 (49.2%)
Median Time From Audiogram to Diagnosis (Days)	22 (-3639 to 3769)
Median Time From Diagnosis To Questionnaire (Months)	77.07 (0.43-219.6)
Median Tumor Volume	0.5cm3 (range 0.012-17.3)

4.2.3 Audiograms

Audiometry is routinely performed in the assessment and care of patients with acoustic neuroma. Although the primary reason for audiogram assessment is generally to monitor the hearing status in the tumor ear, audiograms are performed bilaterally. For this study we collected data from audiograms that our patients had around the time of their diagnosis. A trained research assistant who was not involved in the treatment of the patients entered the data. We extracted the results from both ears and recorded hearing levels in decibels (dB) at 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hertz (Hz). We also recorded speech discrimination scores (SD) and presentation level in (dB). The data were separated into tumor ear and non-tumor ear categories. Our analysis was focused on the non-tumor ear. Pure tone averages (PTA) = (mean of 0.5, 1, and 2 KHz) were obtained to describe the hearing levels of speech. [64,65]

4.2.4 Sensorineural Hearing Loss

We defined normal hearing as hearing threshold levels under 25 (dB)[66]Hearing loss that is attributed to age or loud noise exposure is best identified in the high tones. In this study we will refer to high-tone hearing as hearing levels between 3, 4, and 6 (KHz). Moderate sensorineural hearing loss (MSNHL) is considered to be hearing levels greater than 25 (dB).[67]Severe sensorineural hearing loss (SSNHL) is defined as any measurement of 3, 4, or 6 (KHz) greater than 65 (dB)[68]

4.2.5 NHANES

The National Health and Nutrition Examination Survey (NHANES) is an effort to obtain health and nutritional data on the US population. This survey has been in place on a periodic basis since the 1960's and on a yearly basis since 1999.[69] The goal has been to obtain data that are representative of the civilian, non-institutionalized US population.[69]In the 2001-2002 sample that we used in this study, there were 13,156 persons selected for the sample, 11,039 of those were interviewed (83.9%), and 10,477 (79.6%) were examined with various tests in mobile exam centers. [70]A "half-sample" of the total sample underwent audiogram examination and data have been released on (n=2046 people).[69-71]

This dataset was chosen because it is close in time to our patient's audiograms and helps to avoid any possible secular trends. We combined the audiogram data to obtain both (PTA) and high tone hearing averages (PTA=0.5, 1, and 2 kHz; high tones=3, 4, and 6 kHz). The NHANES study did not test speech discrimination scores.

The NHANES data had a range of people ages 20 to 69 (mean age 41.91 (95%CI=41.23-42.59)). We selected our patients who were also in this age range for comparison (n=286) and created 10 year age groups for frequency matching. The NHANES sample as well as our patient sample were evenly distributed by gender (NHANES: 893 men (48.8% weighted proportion); Patients: 166 men (51.7%)) (Table 4-5).

4.2.6 Noise Exposure

Subjective exposures were obtained via self-report questionnaire. Patients were asked what proportion of time they had exposure to loud occupational noise (loud occupational noise is defined as not being able to have a conversation at speaking level[68]). Their answers were categorized to occupational noise exposure of <50% time vs. ≥50% time. Patients who reported positive exposures to occupational noise were also asked how much of the time they used hearing protection and their answers were categorized to hearing protection use <50% time vs. ≥50% time. Patients were asked if they had ever served in the military. Patients were also asked if they had ever participated in loud hobbies such as: target shooting/hunting, motorcycle/atv/race car, concert attendance, musical instrument, machine shop, gardening/lawn maintenance with power tools and how many years they participated in these hobbies. Their answers were categorized to <1 year vs. ≥1 to 5 years.

4.2.7 Statistical Analysis

Data analysis was performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). Descriptive statistics were used to display demographic data. Medians with ranges, means with standard deviations, and overall proportions were used when appropriate. Medians were compared using the Wilcoxon Mann-Whitney U Test for non-parametric data when the data did not meet the normality assumption. Univariate analysis of categorical data was performed via Pearson's Chi-Square test. Multiple logistic regression was performed in order to obtain the log odds of association between

exposures and sensorineural hearing loss. Models were adjusted for age and gender. Occupational noise was adjusted for the use of hearing protection.

In order to account for the complex survey sampling design, NHANES data were analyzed using the SURVEYMEANS and S URVEYREG procedures in SAS. Appropriate 2 year sample weights were used for the audiogram data as provided by the Centers for Disease Control (http://www.cdc.gov/nchs/nhanes/nhanes2001-2002/AUX_B.htm). Weighted proportions, means, and confidence intervals were obtained to describe the NHANES data in order for it to be representative of the US population.[69-71]Hypotheses were tested via F-test of equal means in the SURVEYREG procedure.[72]

4.3 RESULTS

4.3.1 Audiograms

There were 321 audiograms included in this study. Audiogram threshold levels were higher in the tumor ear compared to the non-tumor ear across all frequencies and a difference is seen in (SD) scores of 26.5% (69.3% vs. 95.8%, respectively).

Table 4-2 Mean Audiometric Thresholds (dB) and Speech Discrimination (SD) Scores by Affected Ear

N=321	Frequency (Hz)								
Ear	500	1000	2000	3000	4000	6000	8000	SD (%)	SD Level (dB)
Tumor									
Mean (dB)	26.35	32.64	40.95	47.95	52.53	55.81	57.39	69.3	63.20
StDev	18.16	21.79	24.13	24.70	25.08	25.62	27.19	34.70	21.55
Non-Tumor									
Mean(dB)	14.02	14.67	17.65	23.08	28.82	33.07	35.78	95.8	55.94
StDev	10.62	11.78	14.64	18.06	21.60	22.67	24.92	9.70	20.16

4.3.2 Sensorineural Hearing Loss and Loud Noise Exposure (Univariate Analysis)

Mean age was significantly higher among patients with evidence of either (MSNHL) or (SSNHL) when compared to normal hearing (+10.8 years and +16.08 years, respectively: $p<0.0001$). Men were in greater proportion for both (MSNHL) and (SSNHL) (58.2% and 79.5%, respectively compared to normal hearing 37.1%: $p<0.001$). Military service was greater among (MSNHL) and (SSNHL) (18.7% and 52.3%, respectively compared to normal hearing 6.3%: $p<0.01$). Patients who had evidence of (MSNHL)

and (SSNHL) did not report a greater amount of loud hobbies compared to those with normal hearing (p=0.76, p=0.18, respectively).

Table 4-3 Univariate and Multivariate Regression Analysis of Loud Noise Exposures and Sensorineural Hearing Loss

Total n=321	Normal Hearing n=143(44.55)	MSNHL N=134 (41.74)						SSNHL N=44 (13.71)					
Variable	n(%)	n(%)	p-value[22]	aOR[23]	95%CI	aOR[24]	95%CI	n(%)	p-value[1]	aOR[2]	95%CI	aOR[3]	95%CI
Age at Dx													
Mean	48.31	58.39			1.07-			64.39			1.31-		
SD	10.98	10.87	<0.0001	1.11	1.14			10.84	<0.0001	1.20	1.28		
Female	90(62.9)	56(41.8)			2.03-			9(20.5)			5.44-		
Male	53(37.1)	78(58.2)	<0.001	3.59	6.33			35(79.5)	<0.0001	17.96	59.37		
Ever served in the military													
No	134(93.7)	109(81.3)			0.50-			21(47.7)			0.47-		
Yes	9(6.3)	25(18.7)	0.002	1.26	3.16			23(52.3)	<0.0001	1.71	6.17		
Any loud hobby													
<1year	44(30.8)	39(29.1)			0.54-			9(20.5)			0.32-		
≥1-5 years	99(69.2)	95(70.9)	0.76	1.01	1.88			35(79.5)	0.18	0.99	3.09		
Occupational Loud Noise													
<50%Time	127(88.8)	112(83.6)			1.01-		0.73-	29(65.9)			2.31-		1.00-
>=50%TIme	16(11.2)	22(16.4)	0.21	2.34	5.38	1.68	3.87	15(34.1)	<0.001	8.82	33.64	2.88	8.28

[22] Univariate analysis based on chi-square test

[23] Odds ratio adjusted for age and gender

[24] Odds ratio of occupational noise adjusted for hearing protection use ≥50% time (hearing protection data was only obtained for occupational noise)

4.3.3 Univariate Analysis of Occupational Noise Exposure

A greater proportion of patients who reported occupational loud noise exposure ≥50% of the time also had evidence of (MSNHL) and (SSNHL) but this only reached univariate significance for (SSNHL). ((MSNHL) 16.42% vs. 11.19% normal hearing: p=0.21, (SSNHL) 34.09% vs. 11.19% normal hearing: p<0.001) (Table 4-3).

Further analysis was performed on occupational noise exposure to look at both (PTA) and high tone hearing. Mean age was found to be similar between exposed and non-exposed groups (<50% Time; Mean age 55.04 (SD=12.20), >=50% Time; Mean age 53.11 (SD=13.72): p=0.30). The audiogram frequencies were averaged into low (speaking) tones (0.5, 1, and 2 kHz) and high tones (3, 4, and 6 kHz) and compared by occupational noise exposure. The (≥50% time occupational noise) group had a (PTA) threshold that was elevated but not significantly (difference 2.2; p=0.89) and a high tone threshold that was significantly elevated (difference 9.7; p=0.01).

Table 4-4 Audiometry of Pure Tone Average (PTA) and High Tone Thresholds by Noise Exposure

Amount of Occupational Noise Exposure		(PTA)[25]	High Tones[26]
<50% Time Mean age: 55.04 (SD 12.20)	N Mean (SD)	268 **15.09** (10.20)	268 **26.72** (18.43)
>=50% Time Mean age: 53.11 (SD 13.72)	N Mean (SD)	53 **17.26** (15.10)	53 **36.42** (24.30)
p-value[27]		0.89	0.01

[25] 500, 1000, and 2000 kHz

[26] 3000, 4000, and 6000 kHz

[27] Based on Wilcoxon-Mann-Whitney Test

4.3.4 Sensorineural Hearing Loss Regression Model

Multiple logistic regression models were built with the loud noise exposure variables adjusted for age, and gender. Age and gender were significant in both moderate and severe sensorineural hearing loss (age (MSNHL) Odds Ratio (OR) =1.11; 95%CI 1.07-1.14; (SSNHL) OR=1.20; 95%CI 1.31-1.28; gender (MSNHL) OR=3.59 95%CI 2.03-6.33; gender (SSNHL) OR=17.96 95%CI 5.44-59.37). Military service was associated with (MSNHL) and (SSNHL) but did not reach significance ((MSNHL) OR=1.26 95%CI 0.50-3.16; (SSNHL) OR=1.71 95%CI 0.47-6.17). loud hobbies did not show an association with (MSNHL) or (SSNHL). Occupational loud noise exposure did show a significant association with both (MSNHL) and (SSNHL) but when it was adjusted for hearing protection the association dampened and only retained significance in (SSNHL). ((MSNHL) OR=2.34 95%CI 1.01-5.38; hearing protection adjusted OR=1.68 95%CI 0.73-3.87; (SSNHL) OR=8.82 95%CI 2.31-33.64; hearing protection adjusted OR=2.88 95%CI 1.00-8.28) (Table 4-3).

4.3.5 Comparison to NHANES

The non-tumor hearing thresholds of our patients as well as the NHANES sample all maintained normal range hearing of <25 (dB) in the (PTA) throughout all of the age groups. Patient's (PTA) hearing had a statistically lower threshold than NHANES in the 61-69 age group (mean difference=3.24, p=0.04). Patient's high tone hearing had a statistically lower threshold then NHANES in the 41-50 age group (mean difference=4.63, p=0.01). Evidence of (MSNHL) in the high tone hearing thresholds

(>25 dB) were seen in the 51-60 and 61-69 age groups for both our patients and the NHANES sample.

Table 4-5 High Tone Hearing In Non-Tumor Ear Vs. National Average (By Age Group)

Demographics	NHANES[28]	Non-Tumor Ear
Total	(N=2046)	(N=286)
Men	893 (48.82%)	166 (51.71%)
Mean Age (95%CI)	41.91 (41.23-42.59)	52.19 (Std. Dev 10.65)
Age Groups	Mean Low Tone Audiometry[29] in Decibels (dB)	Mean High Tone Audiometry[30] in Decibels (dB)
Age <30		**Age <30**
NHANES (n used[31]=495) missing[32]=38 Mean (95%CI)	8.55 (7.74-9.37)	11.22(9.54-12.90)
Non-Tumor (N=10) Mean (StDev)	9.67 (7.73)	8.67 (9.29)
Age 31-40		**Age 31-40**
NHANES (n=401) missing 32 Mean (95%CI)	9.28(8.50-10.06)	14.61(13-16.21)
Non-Tumor (N=30) Mean (StDev)	10.83(8.91)	17.61(15.28)
Age 41-50		**Age 41-50**
NHANES (n=414) missing 27 Mean (95%CI)	11.63(10.67-12.59)	21.20(19.41-22.99)
Non-Tumor (N=70) Mean (StDev)	11.02(7.12)	16.57(12.56)
Age 51-60		**Age 51-60**
NHANES (n=332) missing 18 Mean (95%CI)	15.66(14.36-16.96)	30.54(27.75-33.33)
Non-Tumor (N=110) Mean (StDev)	13.73(8.44)	28.73(15.76)
Age 61-69		**Age 61-69**
NHANES (n=272) missing 17 Mean (95%CI)	21.04(19.10-22.99)	40.96(36.89-45.03)
Non-Tumor (N=66) Mean (StDev)	17.80(10.20)	35.25(21.01)

[28] N represents actual number of participants. Percentages are weighted to be representative of the total US population. 95% confidence intervals are given

[29] Mean of 0.5, 1, and 2 kHz

[30] Mean of 3, 4, and 6 kHz

[31] Number of observations used in the weighted PROCSURVEY output

[32] Number of observations with non-positive weights

4.4 DISCUSSION

The first reported study of contralateral hearing loss in acoustic neuroma patients was published in 1977 and demonstrated abnormal auditory brainstem responses in the non-tumor ear. [73]Such abnormal findings have been attributed to large acoustic neuromas that cause significant compression of the brainstem. [73-75] Our median tumor volume was in the small to moderate tumor range (0.5cm3 (range 0.012-17.3)) which would not cause compression of the brainstem. Another consequence of large acoustic neuromas was found in one study with abnormal caloric tests. Hyperactive contralateral responses was also attributed to brainstem compression from large acoustic neuromas.[76]

A study of electrocochleography in the contralateral ear demonstrated that 25.9% of subjects had abnormal negative summating potential to compound action potential ratios (–SP/AP).[77]This finding was not found to be related to the tumor size or audiogram thresholds. The author believed that these findings were accurate but gave a possible explanation of endolymphatic hydrop formation in the contralateral ear (which could have been caused by several factors including inner ear damage, viral infection, noise exposure, and head trauma)[77] which were not controlled for in their study.

A Dutch study by Stipkovits et al. (1998) looked at contralateral audiograms at 0.5, 1, 2, and 4 kHz and compared them to an international standard of audiogram thresholds (ISO 7029) by age. This study reported that some patients (between 20-30%) showed contralateral audiometry thresholds that were higher than the 90th percentile of the standardized thresholds at each frequency.[75]The study did not report

what the audiogram thresholds are nor did it adjust for the higher proportion of men in their analysis (53.8% men vs. 46.2% women).

Our patients maintained a high speech discrimination score of 95.84% (Gardner Robertson 1-2) in the non-tumor ear which would be classified as highly functional hearing.[78]Patients who showed evidence of abnormal audiometry such as (MSNHL) or (SSNHL) had expected factors for sensorineural hearing decline such as increasing age (which is the most common cause of sensorineural hearing loss) and the male gender which can be linked to gender specific environmental and occupational exposures as well as a military history.[79-88]These associations can be seen both in our univariate analysis and as increased risk in our regression models. We did not find any increased risk associated with the practice of loud hobbies. Some of the limitations of our subjective data on loud hobbies include: lack of more in depth analysis pertaining to frequency of hobby practice (as opposed to only asking about duration) and information on whether or not any hearing protection was used during the hobbies.

Occupational noise exposure also attributed to some of the high tone hearing loss seen in our patients. Chronic loud noise exposure is a well established risk of sensorineural high tone hearing loss.[89-92]In our comparison of occupational noise exposure we found that between groups of similar ages, there was evidence of significantly higher hearing thresholds in the high tones consistent with the reported occupational loud noise exposure (Table 4-4). We can also see the effect of occupational noise exposure adjusted for age and gender on sensorineural hearing loss in our regression models. We can even demonstrate the expected shielding effect of

hearing protection use on sensorineural hearing loss when we adjust for it in our regression models (Table 4-3).

The NHANES control group was frequency matched by age and the overall gender distribution was near 50% in both groups (NHANES=48.82% men; patients=51.7% men). Both our patient sample and the NHANES sample showed abnormal hearing thresholds in the high tones in the oldest age groups and our patients did not do worse than the NHANES sample in either of those age groups. The two groups where our patients showed statistically lower hearing thresholds most likely do not represent a clinically significant difference since both hearing levels remain within a normal hearing range <25(dB)[66] (Table 4-5).

4.5 CONCLUSIONS

Acoustic neuroma patients have a very normal level of hearing in the non-tumor ear. Despite the devastating effect that the tumor can have on hearing in the affected ear, there does not appear to be any negative effect on the contra-lateral hearing. Patients have a level of hearing in the unaffected ear that is comparable to the normal US population as seen when comparing to the NHANES sample. Evidence of sensorineural hearing loss in the non-tumor ear of our patients can be explained by established risk factors such as advanced age and loud noise exposure. Further research in this area in the form of a prospective study to look for changes in audiometry over time would be beneficial in order to better understand the effect, if any, of acoustic neuromas on the non-tumor ear as well as the effect, if any, of tumor treatment on the unaffected ear.

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