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Treatment Analysis and Overall Survival Outcomes of Patients with Bilateral Vestibular Schwannoma

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Abstract

Objectives: To investigate the clinical presentation, treatment breakdown, and overall survival (OS) outcomes of patients with NF2-associated bilateral vestibular schwannoma (NVS).

Methods: The 2004–2016 National Cancer Database was queried for patients with a diagnosis of VS. The "Laterality" code was utilized to stratify patients into sporadic unilateral vestibular schwannoma (UVS) and NVS.

Results: Of the 33,839 patients with VS, 155 (0.46%) were coded for NVS with an average age and tumor size of 37.4±20.5 years and 23.5±18.2 mm. Patients underwent observation (45.3%), surgery (29.3%), and radiotherapy (20.0%), and had a 5.8% 5-year mortality rate. Compared to UVS, NVS was negatively associated with receiving surgery (40.2% *vs.* 29.3%, p=0.02) while watchful observation was more prevalent (30.1% *vs.* 45.3%, p=0.001). In NVS, undergoing surgery was associated with larger tumor size (34.5±21.2 *vs.* 17.8±13.3 mm, p=0.001) and shorter diagnosis-to-treatment time (49.1±60.6 *vs.* 87.0±78.5 days, p=0.02), radiotherapy was associated with older age (44.4±18.9 *vs.* 35.2±20.6 years, p=0.02) and longer diagnosis-to-treatment time (85.9±77.9 *vs.* 53.9±65.5 days, p=0.04), and observation was associated with smaller tumor size (17.8±15.9 *vs.* 28.0±19.2 mm, p=0.01). Kaplan-Meier log-rank analysis demonstrated similar 10-year OS between NVS and UVS patients (p=0.58) without factoring the earlier age of presentation. Furthermore, there were no temporal changes in presentation/management of NVS, and OS was not dependent on the received treatment (p=0.30).

Conclusions: This is the first study utilizing a national cancer database to investigate a large NVS cohort. With younger age, larger tumors, and more conservative management, NVS's OS was not treatment-dependent and was similar to sporadic UVS, though the latter should not be interpreted as similar life expectancies due to the much earlier presentation.

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Conflicts of Interest: None

Keywords

Bilateral Vestibular Schwannoma; Unilateral Vestibular Schwannoma; Neurofibromatosis; NF2; National Cancer Database

INTRODUCTION

With a prevalence of 1 in approximately 60,000, neurofibromatosis type 2 (NF2) is a rare autosomal dominant disorder with the unique propensity for developing multiple meningiomas, ependymomas, and schwannomas.[1, 2] NF2 patients are usually diagnosed around ages 20–30 with a complete disease penetrance by age 60, where risk factors include having first degree relatives with NF2, acquiring vestibular schwannoma (VS) or meningioma at a young age, or developing multiple spinal tumors.[3–5] Whether the Wishart type with an early rapid course of tumor growth or Gardner type with a late and more benign course,[4] bilateral VSs are one of the most well-known hallmarks of NF2 seen in 90–95% of patients.[3] When considering active or passive treatment of bilateral, large, or adherent VSs in patients with NF2, hearing preservation, facial nerve function, and growth rate are regarded as key concerns.[6–9]

Similar to sporadic unilateral VS (UVS) in the general population, NF2-associated VS (NVS) are mainly managed via observation, surgery, or stereotactic radiosurgery. However, compared to UVS, NVS have a higher tendency to grow in lobular patterns and adhere to nerves or structures.[3, 10, 11] The complex bilateral configuration and unique biological behavior can also lead to higher rates of regrowth, facial nerve damage, or hearing loss.[6, 12, 13] These along with the younger age at presentation provide additional challenges for neurotologists and neurosurgeons in navigating the type and timing of treatment.[3, 10, 14] With such a multifaceted complexity, NF2 is commonly managed via an interdisciplinary approach by multiple specialists.[15, 16] Though emerging studies continue to shed light on the diagnosis and management of NVS, there remain discussions regarding treatment decision-making and long-term outcomes.[17] As such, we utilized the National Cancer Database (NCDB) to collect patients treated for bilateral VS, most likely due to NF2 by definition,[18] in order to compare their presentation, management, treatment trends, and overall survival (OS) outcomes with patients presenting with UVS.

METHODS

Due to the lack of identifying subject information and publicly accessible nature of the database, this study was exempted from institutional review board approval. The NCDB which is sponsored by the American College of Surgeons and the American Cancer Society collects data from affiliated U.S. hospitals to encompass approximately 70% of the new cancer diagnoses.[19] The 2004–2016 NCDB was queried for patients with a diagnosis of VS using *International Classification of Disease for Oncology, Third Edition* primary site codes C72.4 (acoustic nerve) and histology codes 9560 (acoustic neuroma) and 9570 (neuroma). The “Laterality” code was utilized to stratify patients into UVS and NVS. This code specified that lesions must “not code metastatic sites as bilateral involvement”. Tumors specified as “Right”, “Left”, or “Unilateral unknown” were included as UVS, whereas

tumors with unknown laterality were excluded from the analysis (N=686). We categorized NCDB patients treated for unilateral VS, likely due to sporadic non-NF2 origin, as UVS, and those coded for bilateral VS presentation as NVS. Cases with a reported tumor size of >100 mm were excluded to avoid possible reporting errors, and the NCDB-reported NVS tumor sizes were assumed to belong to the larger tumors. Of note, survival analysis was on OS and not disease-specific or recurrence-free survival. Charlson/Deyo score, which is an NCDB-reported measure of overall health status, was binarized as score 0 (no comorbidities) and score 1–3 (existing comorbidities). To assess for temporal trends in diagnosis or treatment, patients were categorized into three groups according to their respective year of presentation: 2004–2007, 2008–2011, or 2012–2016.

Treatment was categorized as surgery, radiotherapy, and watchful observation. These treatment classifications were from NCDB-specific variables and in accordance with previously published NCDB studies of VS patients.[20–23] Statistical analysis was mostly performed using PASW Statistics 18.0 software (SPSS Inc., Chicago, IL) with a threshold of $p<0.05$ considered statistically significant. Continuous and categorical variables were compared using two-tailed unpaired *t*-test and chi-squared tests of independence, respectively. Univariate and multivariate cox proportional-hazard models were constructed to evaluate the association between several demographic or clinical factors and survival. Kaplan-Meier log-rank tests, analyzed via the statistical programming language R (version 3.6.1; The R Foundation for Statistical Computing; Vienna, Austria) and RStudio (version 1.2.1335; RStudio; Boston, MA) for visualization, were used to compare survival outcomes between UVS and NVS as well as between treatment types within each cohort.

RESULTS

Of the 33,839 patients with a diagnosis of VS, 155 (0.46%) were coded for NVS. This cohort's average age and tumor size were 37.4±20.5 years and 23.5±18.2 mm, respectively, and consisted of 52.9% females and 10.3% with Charlson/Deyo score 1–3. Observation, surgery, and radiotherapy was the primary treatment modality in 45.3%, 29.3%, and 20.0% of patients, respectively, and 5- and 10-year overall mortality rates were 5.8% and 10.4%. Patient presentations, treatments, and survival outcomes of NVS are presented and compared to those with UVS in Table 1. Compared to UVS, NVS presented with larger tumors (23.5±18.2 *vs.* 18.0±12.6, $p<0.001$). Though overall mortality rates were similar, the treatment breakdowns were significantly different: NVS underwent surgical operation less frequently (29.3% *vs.* 40.2%, $p=0.02$) but were watchfully observed more often (45.3% *vs.* 30.1%, $p=0.001$), both of which remained statistically significant in multivariate analysis when factoring for age and tumor size as confounders ($p<0.001$). Of note, radiotherapy rates were similar on univariate ($p=0.05$) and multivariate analysis ($p=0.74$).

In the cohort with NVS, receiving surgical treatment was associated with larger tumors (34.5±21.2 *vs.* 17.8±13.3 mm, $p=0.001$) and fewer days from diagnosis to treatment (49.1±60.6 *vs.* 87.0±78.5 days, $p=0.02$), though age ($p=0.36$), insurance type ($p=0.34$), and Charlson/Deyo comorbidity scores ($p=0.94$) were not significantly different. Undergoing radiotherapy in this cohort was associated with older age (44.4±18.9 *vs.* 35.2±20.6 years, $p=0.02$) and longer duration between diagnosis and treatment (85.9±77.9 *vs.* 53.9±65.5

days, p=0.04), but tumor size (p=0.47), insurance type (p=0.46), and Charlson/Deyo comorbidity scores (p=0.46) were not different. Lastly, the only variable significantly associated with undergoing observation in NVS was smaller tumor size (17.8±15.9 *vs.* 28.0±19.2 mm, p=0.01). Kaplan-Meier log-rank analysis demonstrated a similar 10-year OS probability, from the time of diagnosis, between NVS and UVS (p=0.58) (Figure 1A). When considering survival probability based on undergoing different treatment modalities, patients with UVS had significantly different survival outcomes (p<0.001) favoring active treatment (Figure 1B), but treatment modality did not make a significant OS difference in NVS (p=0.30) (Figure 1C).

When categorizing patients according to the diagnosis year, there were no temporal changes in clinical presentations or treatment patterns in the cohort with NVS, contrary to the UVS population which had significant temporal changes in diagnosis (e.g., smaller tumor and older age at diagnosis) and management (increasing observation at the expense of active treatment) (Table 2). Multivariate cox proportional-hazards model of subjects with NVS showed no association between month-dependent OS survival and diagnosis age (OR=1.01, 95% CI 0.91–1.11, p=0.83), tumor size (OR=0.89, 95% CI 0.71–1.11, p=0.30), time from diagnosis to treatment (OR=1.00, 95% CI 0.98–1.02, p=0.90), and treatment choice (OR=1.33, 95% CI 0.08–21.94, p=0.84).

DISCUSSION

By querying a large cohort of patients with UVS and NVS from a national cancer registry, this manuscript depicts the current state of patient presentations, treatment decision making, OS outcomes, and temporal changes between the two cohorts and on a national level. It was observed that NVS were mostly treated by observation followed by surgery, and compared to UVS, had younger age, larger tumors, and more conservative management patterns. We observed that receiving surgery for NVS was associated with a faster decision-making process while patients with radiotherapy had a significantly higher diagnosis-to-decision timeline, and that tumor size was positively and negatively associated with undergoing surgery and observation, respectively. Though there existed various temporal changes in the UVS presentation and treatment, no significant patterns were observed among the NVS population. Furthermore, though USV's OS probability was observed to be treatment-dependent, NVS had similar treatment-associated OS rates.

NF2 is a rare autosomal dominant genetic syndrome caused by the mutation of *NF2 tumor suppressor gene* with full disease penetration by 60 years of age.[3, 4] Given bilateral VS is the most common manifestation of this rare disorder and observed in >90% of patients, presenting symptoms can include hearing loss, tinnitus, dizziness/imbalance, and visual or peripheral nerve dysfunction.[1, 3, 24] Moreover, this population's NVS are commonly associated with other tumors of the brain and spinal cord, requiring comprehensive management strategies.[25] In contrast, sporadic UVS tumors with a lifetime risk of 1 in 1,000 affect one vestibular nerve and are without a strong hereditary component.[5, 26] As observed in this report and consistent with the literature, patients with NVS are usually younger with larger lesions.[4, 27, 28] In spite of the differences between the clinical presentations of NVS and UVS, the overall management of these tumors share many similarities.[3, 29] However,

evaluating the treatment approaches and long-term outcomes of both patient populations remain areas of active research, warranting continuous investigations.

Through utilizing the NCDB, we observed that compared to UVS, NVS were less likely to undergo surgery and more likely to be carefully observed. Similarly, Sahu *et al.* reported a tendency for observing NVS, where active treatment was pursued for hearing preservation or relieving symptomatic mass effect.[27] It is recommended that surgical resection be considered as the first line therapy for large tumors that are likely to compress the facial nerve or brainstem.[25] This was reflected in our analysis of the NVS cohort, where surgical treatment was associated with larger tumor size but age was not a significant factor. For some patients with large bilateral tumors and prominent symptomatic burdens, surgical resections can be supplemented with supplementary hearing rehabilitation methods (e.g., cochlear implant, auditory brainstem implant, speech rehabilitation) for communication.[27, 30, 31] Consistent with our observed rates of watchful observation in NVS, an expert review by Blakeley *et al.* reported that observation is often the initial approach followed by surgery when necessary (e.g., >3cm or compression of vital structures), and radiosurgery in NVS remains controversial even though it is increasing in popularity in treating idiopathic UVS.[25] The hesitancy among some NF2-treating clinicians for utilizing radiation can be attributed to possible radiation-associated secondary malignancies, though it may still be an appropriate approach for patients who refuse or are poor candidates for surgery.[32] As such, it was interesting to observe that in the NCDB cohort, radiation was essentially used at the same rate between the two cohorts, despite its more limited acceptance for NVS. Despite different presentations and treatment breakdowns, we observed similar overall survival rates between the two cohorts, though this can be influenced by the disproportionate sample cohorts and potential biases pertinent to national databases.[33, 34]

Multiple recent reports have shed light on a temporal trend toward conservative management of VS,[21, 22, 35] which was confirmed by this study in only the UVS and not the NVS cohort. In addition to the short duration of the temporal analysis (2004–2016), this can be due to the already established emphasis on the initial observation of NVS as well as the overall comprehensive and multi-faceted management. Moreover, it was observed that time from diagnosis to treatment was also increased over time in UVS but not NVS. In NVS, a longer time from diagnosis to treatment was positively associated with receiving radiation therapy and negatively associated with undergoing surgery. The latter can be due to the symptomatic and urgent nature of some cases associated with eventual surgical resection, and the former can be influenced by insurance delays, specialist seeking, and a lack of consensus on the efficacy of radiotherapy for NVS.[25] Of note, there is an emerging and novel medical treatment for NVS, namely bevacizumab therapy, which can decrease tumor growth and provide symptomatic and quality of life improvement.[36–38] Though this was not investigated in this study due to the limited reporting by NCDB, this warrants continuous research to elucidate bevacizumab's role in the comprehensive management of NVS.

Although we observed no statistical difference in the 10-year OS probabilities of UVS and NVS, this should not be interpreted as similar life expectancies between the two cohorts. Previous studies have reported a relatively short life expectancy for NVS, which can be associated with earlier onset, late diagnosis, number of meningiomas.[1, 39–41] The NCDB

which was utilized in this study can elucidate OS, however, disease-specific survival analysis may be more appropriate for comparing UVS and NVS. This is because many sporadic UVS may be diagnosed incidentally in relatively older age, not warranting treatment and dying unrelated of the disease, but causing a similar 10-year OS projection to NVS. Even though the observed 5- or 10-year mortality rates and 10-year OS probability were similar between UVS and NVS, this may certainly not translate to similar overall life expectancies when factoring in the much earlier presentation of NVS.

Though we took diligent care in the study design, data extraction, and statistical analysis and interpretation, this study contains noteworthy limitations. First, this study relies on the assumption that NCDB subjects with bilateral VS presentation had NVS by definition, and that patients coded as UVS did not in-fact have hereditary NVS. This was supported by our demographics and tumor characteristic analyses showing NVS's larger tumor size and younger age at presentation, which is reflective of the existing literature.[3, 27, 28, 42–45] However, it is very possible that many patients with NVS who only received treatment for one tumor were not appropriately coded into the database as having bilateral VS. Furthermore, even though NF2 is also an important pediatric topic, since the pediatric population have separate cancer registry databases, this manuscript's data contained mostly adults. Secondly, utilization of a de-identified national database limited us to the data provided, precluding potentially important information such as genetic testing, family or physical history, and VS-specific symptoms (headache, hearing loss, tinnitus) or outcomes (e.g., hearing preservation, tumor recurrence) beyond the scope of NCDB's documentation. The database also provides one variable for tumor size, thus NVS could not be characterized and analyzed for both tumors. Patients who underwent multiple treatments (e.g., surgery followed by radiotherapy) were only classified per the initial treatment for survival analysis, but future studies are encouraged to analyze various treatment combinations and the influence of sequence or timeline on outcomes. Finally, the analyzed 10-year timeline and relatively low number of BVS subjects was possibly not enough to assess temporal changes in diagnosis or treatment patterns. Despite these limitations, this manuscript provides valuable information by investigating a large cohort of NVS and comparing their presentation, treatment, OS outcomes, and trends in management with UVS.

CONCLUSION

This was the first study to utilize a large national cancer database to investigate patients presenting with bilateral VS likely due to NF2, and to compare their treatment experience and OS outcomes with unilateral VS. Presenting at younger age and larger lesions, NVS were mostly managed by watchful observation, and receiving surgery was associated with larger tumors and timely decision-making process. Though patients with UVS have had a temporal change towards conservative treatment and different OS rates per treatment, there was no temporal changes in diagnosis/treatment or treatment-dependent OS among NVS.

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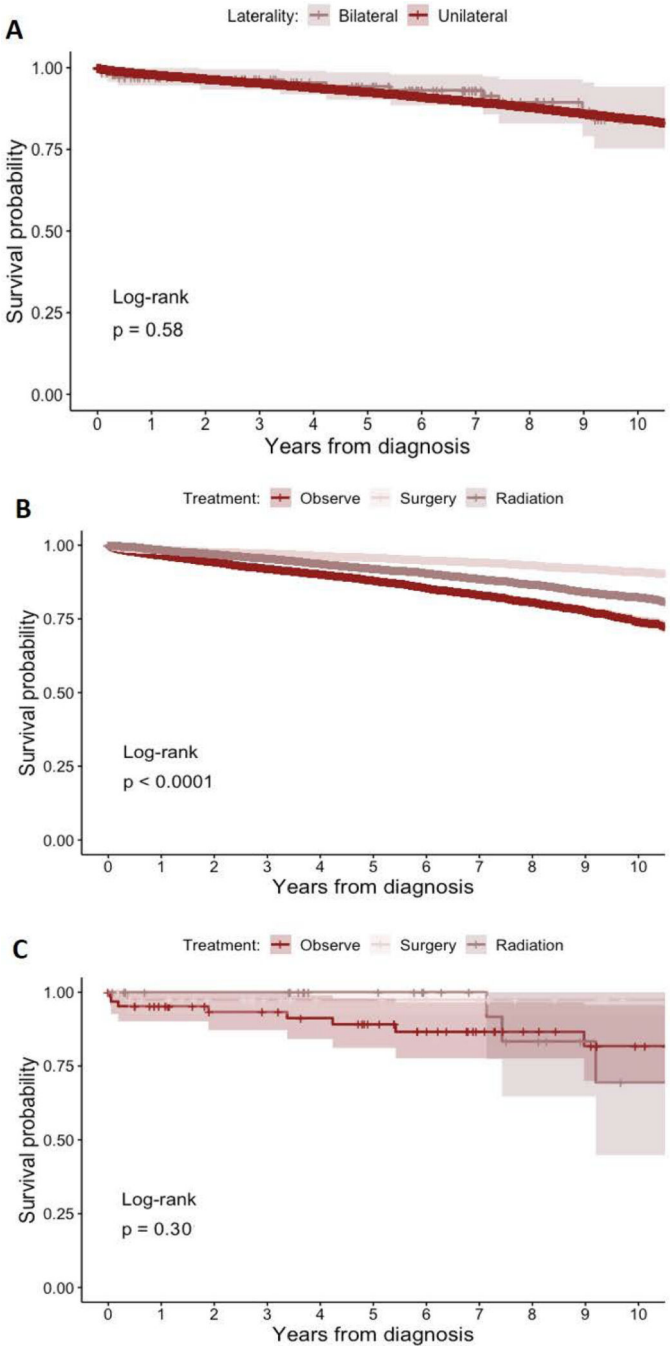

Figure 1.

Kaplan Meier curves comparing 10-year OS between **A)** NVS *vs.* UVS patients regardless of treatment (p=0.58), **B)** undergoing surgery, radiation, or observation in UVS (p<0.001), and **C)** undergoing surgery, radiation, or observation in NVS patients (p=0.30). Of note, these represent overall survival and not disease-specific or recurrence-free survival.

Table 1.

NVS and UVS Patients' Demographics

Variable	NVS (N=155)	UVS (N=33,684)	*p* Value
Age, mean in years ± SD	37.4 ± 20.5	55.6 ± 14.7	**<0.001**
Sex, female (%)	82 (52.9)	17,882 (53.1)	0.96
Tumor size mean ± SD, mm	23.5 ± 18.2	18.0 ± 12.6	**<0.001**
Charlson/Deyo score 1–3 (%)	16 (10.3)	3,986 (11.8)	0.56
Diagnosis to treatment days, mean ± SD	67.6 ± 72.3	73.1 ± 107.6	0.85
2-Year Mortality * (%)	5 (3.4)	943 (3.0)	0.81
5-Year Mortality * (%)	7 (5.8)	1726 (6.6)	0.65
10-Year Mortality * (%)	12 (10.4)	2502 (13.0)	0.99
Follow-up months, mean ± SD	67.3 ± 45.1	61.1 ± 42.4	0.07
Treatment *: Observation (%)	68 (45.3)	9,818 (30.1)	**0.001**
Treatment *: Surgery (%)	44 (29.3)	13,118 (40.2)	**0.02**
Treatment *: Radiotherapy (%)	30 (20.0)	9,679 (29.7)	0.05
Treatment *: Chemotherapy (%)	5 (3.3)	19 (0.1)	**<0.001**

For tumor size of NVS, size of the larger tumor was recorded.

*Percentages reflect different denominators compared to total N, due to the number of available data for each specific element.

P values calculated via chi-square (categorical values) and independent sample *t*-tests (nominal values).

NVS: NF2-associated bilateral vestibular schwannoma; UVS: unilateral vestibular schwannoma

Table 2.

Comparison of diagnostic factors and treatment decisions for patients with NVS and UVS diagnosed between 2004–2007, 2008–2011, and 2012–2016

Variable	VS Type	2004–2007 (N=59 *vs.* 8846)	2008–2011 (N=56 *vs.* 10427)	2012–2016 (N=40 *vs.* 14411)	*p* Value
Mean age at Dx, years (SD)	NVS	38.0 ± 21.5	34.8 ± 20.0	40.0 ± 20.5	0.46
	UVS	54.6 ± 14.5	55.5 ± 14.6	56.2 ± 14.8	**<0.001**
Mean tumor size, mm (SD)	NVS	22.4 ± 19.6	24.8 ± 19.6	23.1 ± 13.5	0.87
	UVS	18.3 ± 12.5	18.0 ± 12.7	17.8 ± 12.6	**0.04**
Days from Dx to Tx (SD)	NVS	74.5 ± 65.1	68.6 ± 79.0	57.0 ± 75.2	0.68
	UVS	66.2 ± 124.4	72.8 ± 115.7	78.4 ± 84.6	**<0.001**
Treatment: Surgery (%)	NVS	17 (28.8)	16 (28.6)	16 (40.0)	0.45
	UVS	4164 (47.1)	4275 (41.0)	5490 (38.1)	**<0.001**
Treatment: Radiation (%)	NVS	15 (25.4)	14 (25.0)	8 (20.0)	0.80
	UVS	3103 (35.1)	3337 (32.0)	3987 (27.7)	**<0.001**
Treatment: Observation (%)	NVS	27 (45.8)	24 (42.9)	17 (42.5)	0.85
	UVS	1696 (19.2)	2959 (28.4)	5163 (35.8)	**<0.001**

P values calculated via chi-square (categorical values) and independent sample *t*-tests (nominal values).

NVS: NF2-associated bilateral vestibular schwannoma; UVS: unilateral vestibular schwannoma; Dx: diagnosis; Tx: treatment