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Residual Tumor Volume Guides Post-Surgical Treatment Paradigm and Need for Salvage Radiotherapy in Vestibular Schwannoma Management

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Abstract

Background and Objectives: Vestibular schwannomas (VS) are slow-growing tumors of the vestibular nerve. Gross total resection (GTR) is recommended for large tumors (> 4cm), brainstem compression, cranial neuropathy, and hydrocephalus. In select complex cases at our high-volume skull base center, subtotal resection (STR) is pursued for various clinical factors. These patients may require adjuvant radiotherapy (ART) if residual tumor progresses. We sought to evaluate tumor control following STR of VS and identify risk factors of future ART need.

Methods: A single-center retrospective review (2009–2019) identified patients with VS with complete data who underwent STR without prior treatment. Tumor volumes were extracted from contrast-enhanced T1-weighted volumetric MRI by semi-automated segmentation using 3D Slicer. Clinical and procedural data, including House-Brackmann scores at discharge and 90-day follow-up, were reviewed. Postoperative tumor volumes and progression-free survival (PFS) were calculated. Multivariate logistic regression assessed risk factors for ART.

Results: Among 1119 VS patients, 38 (3.4%) patients underwent STR. Of the STR patients, 15 (39.5%) required ART. Preoperative volumes did not differ significantly. In STR-alone patients, the average residual volume was 15.26±3.54%, while in STR+ART patients the average residual volume was 37.53±12.33% ($p<0.001$). The smallest residual requiring ART was 23.4%, while the largest residual not requiring ART was 20.6%. Median PFS among ART patients was 29.67 months. On multivariate analysis, percent residual volume independently predicted ART need (AOR 1.28, CI 1.06-2.29, **p=0.002**).

Conclusion: STR is viable in select complex VS cases. Residual VS volume ≥20.6% may confer increased risk of progression and necessitate ART. Close postoperative surveillance over 2-3 years is warranted.

Introduction

Vestibular schwannomas (VS) are slow-growing Schwann cell tumors of the vestibulocochlear nerve and the most common cerebellopontine angle tumor in adults, typically presenting with sensorineural hearing loss, imbalance, or tinnitus.[1,2] Their incidence has risen to 3–5 per 100,000 person-years, largely due to improved MRI detection and screening for asymmetric hearing loss.[3,4] Treatment can be categorized into four groups: observation, irradiation, surgery, or a combination thereof. Treatment generally includes observation, irradiation, surgery, or combinations thereof. Tumor size remains the strongest predictor of growth and guides initial management: lesions < 1.5 cm are typically observed, < 2.5 cm considered for radiosurgery, and > 4 cm for surgical resection, though thresholds vary across institutions.[5,6] Surgery is also indicated for tumors causing brainstem compression, cranial neuropathy, or hydrocephalus.[7,8]

Surgical risk correlates with tumor size. Serviceable hearing (pure-tone average ≤ 50 dB HL, word-recognition ≥ 50%) is lost in 30–60% of cases < 1.5 cm and up to 95% when > 2.5 cm.[9–12] Similarly, the

risk of facial nerve weakness or paralysis, defined as House-Brackmann ≥ 3) after surgical resection in tumors < 1.5 cm is about 10% whereas it has been reported as high as approximately 30% in those with VS > 2.5cm.[13–15] Consequently, many surgeons favor subtotal resection (STR) over near-total or gross-total resection to preserve function, accepting a risk of residual disease. However, residual tumor may regrow, prompting adjuvant radiotherapy (ART), which introduces additional risks such as radiation necrosis and long-term toxicity.[16] Despite size-based guidelines for initial treatment, no standardized paradigm exists for managing subtotally resected tumors, and ART use remains surgeon-dependent. This study therefore aimed to identify risk factors predicting the future need for ART after STR.

Methods

Cohort Identification

After IRB approval, a prospectively maintained single-center database was retrospectively reviewed for consecutive primary vestibular schwannoma cases from 2009–2019. A waiver of patient consent was approved by the IRB due to the retrospective nature of the study. Inclusion required surgical management with subtotal resection (STR, 51–90% tumor removal) as documented in operative reports. Exclusion criteria were prior VS treatment, NF2-related schwannomatosis, partial resection (10–50%), or near-total/gross-total resection (> 90%).[17,18] Patients with partial resection were excluded, as partial resection reflected distinct surgical intent in which surgeons preemptively plan to leave residual tumor. Therefore, this patient minority describes a different treatment course, surgical strategy, and goals of resection.[19] All included patients had ≥ 5 years of follow-up.

Tumor size was determined from T1-weighted contrast-enhanced MRI in three orthogonal planes pre- and post-operatively. Follow-up MRI occurred immediately post-resection and at 6 months. Tumor volumes were extracted by semi-automated segmentation and masks were generated using the 3D Slicer software.[20] Residual volume was expressed as a percentage of preoperative volume for normalization. Koos grades were recorded to describe extrameatal extent of the tumor and provide context for the tumor's location.[21] Tumor consistency was noted radiographically and intra-operatively. Audiologic data, when available, were classified using American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) 1995 criteria. Serviceable hearing was defined as either at least a 50% speech discrimination score (SDS) and pure tone audio (PTA) less than 50 dB, corresponding to AAO-HNS Class A and B. Facial nerve function was graded by House-Brackmann (HB) score at discharge and 90-day follow-up.

At our institution, the decision to offer ART was determined based on radiographic progression, which was classified according to the accepted definitions as an increase in tumor size, evidenced by a new contrast enhancement in any dimension, over two consecutive MRI scans.[22–24] We also defined recurrence by new symptom presentation; however, none of our patients demonstrated VS-associated symptoms prior to a second MRI confirming progression. Progression-free survival (PFS) was measured

from surgery to first radiographic progression; overall survival was recorded at 5 years, after which patients were censored.

Statistical Analysis

Statistical analyses were performed in R version 4.4.2. Continuous variables were presented as mean ± SD if normally distributed by Kolmogorov-Smirnov test. Univariate analysis compared demographic, clinical, radiographic, and procedural variables using Pearson $\chi 2$ tests or Fisher's exact tests for categorical data and two-tailed t-tests or Wilcoxon tests for continuous data, as appropriate.

A multivariate logistic regression model with Firth correction was used to identify independent predictors of receiving ART. Variables were selected based on clinical relevance (age, sex, tumor volume) or univariate p-value < 0.10. Variables were defined as uncommon if they represented less than 5% of the total cohort sample and were accordingly excluded. As sparse data would affect the stability and accuracy of the multivariate model, this threshold was chosen in line with best practices for ensuring model convergence and reducing bias in rare-event settings. All variables were tested for collinearity prior to inclusion. For model simplicity, House-Brackmann scores were dichotomized into acceptable (I–II) vs. poor (III–VI), and Koos grades into no brainstem contact (I–II) vs. brainstem contact (III–IV). An alpha criterion of $p < 0.05$ was used as the threshold for significance.

Results

Among 1119 VS patients with complete data, 329 (29.4%) patients received surgery, of which 38 (11.6%) patients had a subtotal resection (STR). Within the total cohort, 256 patients received primary radiotherapy, and 534 patients were serial observed for a radiographically confirmed VS. Among surgical patients, 280 (85.1%) had near/gross-total resection and 4 (1.2%) had partial resection. Of the 38 STR patients, 15 (39.5%) later required adjuvant radiotherapy (ART), while 23 (60.5%) did not **(**Fig. 1**)**. The average age of patients at surgery was 47.24 ± 13.41 years, and the overall cohort was 57.9% female. No significant differences were identified between cohorts in race, sex, or age at surgery. The comparison between the STR + ART and STR only cohorts is summarized in Table 1.

Table 1
Univariate Analysis of Vestibular Schwannoma Patients Requiring vs. Not Requiring Salvage Radiotherapy after Subtotal Resection

Sex (%)	**Overall (n = 38)**	**No ART (n = 23)**	**ART (n = 15)**	**p-value**
				0.222
Female	22 (57.9)	11 (47.8)	11 (73.3)	
Male	16 (42.1)	12 (52.2)	4 (26.7)	
Age at surgery (years) (mean (SD))	47.24 (13.41)	49.90 (14.45)	43.15 (10.92)	0.184
Race (%)				0.526
Asian	4 (10.5)	3 (13.0)	1 (6.7)	
Black/African American	3 (7.9)	1 (4.3)	2 (13.3)	
Native Hawaiian or Other Pacific Islander	1 (2.6)	0 (0.0)	1 (6.7)	
Not Specified	9 (23.7)	6 (26.1)	3 (20.0)	
Other	3 (7.9)	1 (4.3)	2 (13.3)	
White	18 (47.4)	12 (52.2)	6 (40.0)	
BMI at Diagnosis (mean (SD))	25.88 (5.24)	25.72 (5.13)	26.12 (5.59)	0.736
Laterality of tumor (%)				0.310
Left	24 (63.2)	16 (69.6)	8 (53.3)	
Right	14 (36.8)	7 (30.4)	7 (46.7)	
Cystic tumor (%)	14 (36.8)	11 (47.8)	3 (20.0)	0.163
Estimated Tumor Volume (mm^3) (median (IQR))	9174 (10062)	10,680 (15873)	8,625 (5067)	0.757
Largest tumor dimension (mm) (mean (SD))	28.83 (11.65)	30.17 (13.24)	27.50 (10.18)	0.681
Koos grade (%)				0.364
1	3 (7.9)	3 (13.0)	0 (0.0)	
2	3 (7.9)	1 (4.3)	2 (13.3)	
3	9 (23.7)	6 (26.1)	3 (20.0)	
4	23 (60.5)	13 (56.5)	10 (66.7)	
Surgical approach (%)				0.145

Sex (%)	Overall (n = 38)	No ART (n = 23)	ART (n = 15)	p-value
				0.222
Middle Fossa	2 (5.3)	0 (0.0)	2 (13.3)	
Suboccipital	31 (81.6)	19 (82.6)	12 (80.0)	
Translabyrinthine	5 (13.2)	4 (17.4)	1 (6.7)	
Postoperative Residual Tumor Volume (mm^3) (mean (SD))	2,998.87 (3108.95)	2,851.57 (3198.68)	3,224.74 (3062.07)	0.723
% Residual Tumor Volume (mean (SD))	24.05 (13.66)	15.26 (3.54)	37.53 (12.33)	**< 0.001**
Perioperative Complications (%)	3 (7.9)	2 (8.7)	1 (6.7)	0.975
Postoperative House- Brackmann Score (mean (SD))	3.13 (1.47)	3.17 (1.61)	3.07 (1.28)	0.939
90-Day House-Brackmann Score (mean (SD))	2.45 (1.48)	2.48 (1.53)	2.40 (1.45)	0.926
Progression-Free Survival	42.36 (28.72)	60.00 (0.00)	30.86 (32.04)	**< 0.001**
5-year Overall Survival (%)	38 (100.0)	23 (100.0)	15 (100.0)	1.000

Univariate Analysis

The average preoperative tumor volume across the entire patient cohort was 13040.50 ± 16313.96 mm^3. Between cohorts, preoperative tumor volumes were not significantly different (17869.41 ± 216.84 mm^3 vs. 8211.58 ± 6163.62 mm^3, p = 0.757). Cystic degeneration and Koos grade were also comparable. Of 25 patients with audiologic data, 9 (36%) presented with serviceable hearing. Perioperatively, the complication rate was not different between cohorts (8.7% vs. 6.7%, p = 0.975). Two patients experienced intraoperative hemorrhage not requiring blood transfusion, and one patient experienced a vertebral artery injury.

Postoperatively, absolute residual tumor volume did not significantly differ between patients who received STR alone and patients who received STR and subsequent ART (2,851.57 mm^3 vs. 3,224.74 mm^3, p = 0.723). For the entire cohort, the postoperative residual tumor volume was 24.05 ± 13.66% of the preoperative volume for the entire cohort. Residual tumor volume as a percentage of the original tumor volume was significantly different between the STR alone vs. the STR + ART cohort (15.26 ± 3.54% vs. 37.53 ± 12.33%, p < 0.001). The smallest residual requiring ART was 23.4% of preoperative tumor volume, while the largest residual not requiring ART was 20.6% of preoperative tumor volume. Overall

survival at 5 years in both cohorts was 100%, but progression-free survival was significantly decreased in the STR + ART cohort (60.00 vs. 30.86 months, $p < 0.001$).

Facial Nerve Outcomes

Given the concern for new-onset or worsened facial palsy associated with more aggressive VS resection, we examined whether facial nerve function was negatively affected in the cohort that had less residual tumor percent volume after STR. On univariate analysis, no differences were identified in postoperative House-Brackmann grades for STR patients upon discharge (3.17 ± 1.61 vs. 3.07 ± 1.28, $p = 0.939$) or on 90-day follow-up (2.48 ± 1.43 vs. 2.40 ± 1.45, $p = 0.926$). This remained nonsignificant on multivariate analysis, suggesting that increased debulking did not worsen facial nerve outcomes.

Multivariate Analysis

Since percent residual tumor volume was a perfect classifier and led to complete separation, multivariate logistic regression using Firth correction was utilized to calculate adjusted odds ratios. Only percent residual tumor volume was a significant predictor of increased odds for requiring ART (AOR 1.28, CI 1.06–2.29, **p = 0.002**). This is summarized in Table 2.

Table 2
Multivariate Analysis of Risk for Tumor Progression Requiring Adjuvant Radiotherapy

% Residual Tumor Volume	**AOR or β-value (CI)**	**p-value**
	1.28 (1.06, 2.29)	**0.002**
Male sex	0.71 (< 0.01, 94.91)	0.970
Age at surgery	0.99 (0.46, 1.39)	0.942
Koos Grade 3 or 4	2.32 (0.01, 122.04)	0.681
Preoperative Estimated Tumor Volume	1.00 (0.99, 1.01)	0.892
Postoperative House-Brackmann I-II	0.60 (< 0.01, 7.19)	0.752
AOR = Adjusted odds ratio, CI = Confidence interval		

Characterization of the Salvage Radiotherapy Patient Cohort

Among patients requiring ART after STR, the mean age at radiotherapy was 44.9 ± 11.1 years. PFS averaged 30.9 months, with 100% 5-year overall survival. Four patients (26.7%) developed RT-related complications: radiation necrosis, new-onset headaches suspected to be secondary to nerve damage, facial spasms, and localized skin/ear pain. Three (20%) patients required reoperation for near/gross total

resection of recurrent disease despite ART. Their postoperative House Brackmann grades were HB III, III, and IV. This is summarized in Table 3.

Table 3
Characteristics of Vestibular Schwannoma Patients Receiving Adjuvant Radiotherapy

RT-Specific Factors	ART Patients (n = 15)
Progression-Free Survival (months) (mean (SD))	30.86 (32.04)
Patients Requiring Reoperation After ART (%)	3 (20.0)
Post-RT Complications (%)	4 (26.7)
Average Age at RT (years) (mean (SD))	44.87 (11.12)

Discussion

Vestibular schwannomas are the most common adult cerebellopontine angle neoplasms.[4] Gross total resection (GTR) has historically been the standard for definitive treatment, with literature supporting that maximally safe resection minimizes recurrence risk.[25,26] In select circumstances, however, gross total resection may not be preferable.[17,27,28] At our high-volume center, we choose subtotal rather than near total or gross total resection when certain specific intraoperative findings signal an unacceptable risk to neurological function. These findings are: (1) absence of a safe dissection plane between the tumor and the facial nerve, (2) tumor invasion of the brainstem, (3) adverse changes in intraoperative neurophysiological monitoring, and (4) limited visualization due to cerebellar swelling, a highly vascular tumor, vascular encasement that cannot safely be addressed or other general neurosurgical conditions (Fig. 2). In these situations, the intra-operative decision to deliberately leaving a small tumor remnant maximizes cranial nerve preservation while still achieving reliable disease control—a strategy well supported in the literature.[29–31] Postoperative radiation was offered if there was radiographic evidence of tumor growth on two consecutive MRIs.[19] This study offers additional evidence to the growing body of literature identifying postoperative residual tumor percentage, as a predictor of tumor recurrence or progression after vestibular schwannoma resection.[19,27,32] In this series of 1119 VS cases, percent residual volume was significantly higher in the STR + ART than STR alone, independent of demographics, preoperative volume, or outcomes. The largest tumor fraction that did not require ART was 20.6% of the preoperative tumor volume. Prior studies have similarly identified volume of residual disease as an independent predictor of VS recurrence: single-center studies have reported residual disease as a direct measure of the largest postoperative tumor dimension or volume on MRI.[20,25,33] To date, no study has defined a threshold for percent residual volume above which there is a significant risk of recurrence. By identifying a volume cutoff for ART, this study helps to clarify current treatment practices and potentially suggests indications for earlier incorporation of ART in the post-surgical treatment paradigm, improving safety, efficacy, and PFS.

Importantly, greater resection did not worsen facial nerve outcomes: both groups averaged HB III at discharge and HB II at 3 months. Preservation of the facial nerve is a key surgical goal, and a key intraoperative factor determining whether the VS should be aggressively or subtotally resected. Large tumors may lead to facial palsy by inflicting stretch injury, which in combination with poor vascularization leads to thinning of the nerve and dysfunction.[34] Intraoperative limitations notwithstanding, achieving at least 79.4% resection by volume maintained facial function while improving tumor control. This threshold aligns with studies of other skull base lesions: Wanna et al demonstrated that in STR for jugular paragangliomas, obtaining less than 20% residual tumor volume was associated with tumor control over a 45-month follow-up period.[35] Surgeons should consider aiming to achieve this volumetric threshold without concern for compromising function. In cases of postoperative progression, ART or stereotactic radiosurgery (SRS) may be offered. Of note, the ART decision was made based on radiographic progression, as defined as an increase in tumor size, as evidenced by a new contrast enhancement in any dimension, over two consecutive MRI scans.[22–24] None of the patients in this cohort experienced significant concurrent symptom progression or recurrence by the time of ART referral. This may reflect a strength of the postoperative surveillance strategy for subtotally resected VS, which enabled earlier radiographic detection before clinical progression.[36] Single-center studies have suggested that postoperative facial nerve function is primarily determined by preoperative tumor volume and prior VS treatment rather than residual tumor volume, but more studies are needed to confirm this safety profile.[19,37]

As percentage is a relative measurement of residual volume, the reason why tumors appeared to not progress when less than 20.6% of initial tumor volume remained is unclear and likely multifactorial. VS is slow-growing and often benign. This may represent a true threshold and suggest that meaningful sustained progression is unlikely to occur. It is possible that there are so few actively dividing tumor cells remaining in the residual tumor that the tumor is effectively devitalized; any growth, even if it continues, is likely imperceptible and would not be identified for several years.[38] It may be that the vascular supply of the tumor is no longer sufficient to support continued growth in residual disease.[27,32,33] Histopathological examination of cystic VS has noted that the tissue is sparsely cellular; with sufficient devascularization during debulking, this heterogeneous tissue may be prone to ischemia and lead to tumor control. Single-cell studies have highlighted Schwann-endothelial cell interactions in VS progression.[39,40] However, some studies have noted that proliferative activity of the tumor cells may contribute to future regrowth even after near-total resection.[41] Underlying genetic syndromes such as neurofibromatosis 2 cannot be ignored, as this may confer additional proliferative potential and treatment resistance to seemingly inert residual disease. Future studies should assess patients with longer follow-up to assess the extent of survival benefit and risk of progression.

Among 15 patients requiring ART, 27% experienced radiotherapy-related complications, and 20% required reoperation. These findings underscore the complexity of management of residual VS post-STR and the trade-off between early ART and overtreatment. Previous studies have noted that adjuvant SRS after VS resection was associated with longer PFS than salvage SRS.[25] However, salvage microsurgery after SRS

is challenging due to radiation-induced tissue distortion or a loss of defined arachnoid planes for safe resection with associated poorer cranial nerve outcomes.[8] As this cohort received ART as a salvage approach, patients may not have been optimized candidates for radiotherapy. For example, though they were not more prevalent, cystic tumors have been suggested to demonstrate higher rates of growth, adherence to surrounding structures, postoperative morbidity, and radiosurgery resistance compared to solid tumors.[42,43] Thus, timely identification of high-risk residuals remains key.

Finally, rigorous postoperative MRI surveillance is critical. Current practices for postoperative monitoring involve the usage of serial MRI to monitor changes in tumor size.[44] Patients who have undergone GTR have a more relaxed surveillance schedule, with an MRI within the first 12 months and scans at intervals between 1–3, 5 years, and 10 years. However, for STR patients the literature suggests annual MRI scans up to 5 years, followed by biennial scans up to 10 years.[45] Maximizing safe extent of resection coupled with structured imaging follow-up provides the best balance of tumor control and functional preservation.

Limitations

This study has several limitations. Being single-center may restrict generalizability due to population and institutional practice differences. Its retrospective design introduces potential biases in follow-up and data capture. Although all patients were followed for ≥ 5 years, recurrence beyond that interval may be underestimated. Hearing outcomes were reported using the older AAO-HNS method in accordance with the scale utilized by our institution at the time of clinical decision-making for consistency.

The small ART subgroup limits statistical power for detecting differences in recurrence, complications, and long-term ART efficacy. Absence of a standardized radiotherapy regimen also introduces heterogeneity: it is possible that different outcomes may have occurred with other modalities like single-dose stereotactic radiosurgery (SRS) or 3–6 fraction hypofractionated stereotactic radiotherapy (hFRST). To maximally improve survival outcomes, future studies should explore this topic. Early postoperative MRI may overestimate residual volume due to artifacts including leptomeningeal, perineural, and dural enhancement or residual blood products.[33,46] Our study did not examine the genetic or molecular profile of resected tumors: it is possible that some tumors in our cohort exhibited regrowth not due to surpassing a residual tumor volume threshold, but rather due to genetic drivers of recurrence.

Conclusion

Vestibular schwannomas are challenging in their management and follow a complex treatment algorithm. Subtotal resection of vestibular schwannoma can be a viable strategy to debulk the tumor without compromising critical structures in the cerebellopontine angle. This study demonstrates that ≥ 79.4% resection provides durable tumor control in treatment-naïve VS without worsening facial nerve outcomes. Percent residual tumor volume is an independent predictor of the need for future salvage radiotherapy, and did not significantly impact postoperative facial nerve function. This data suggests

that optimal care requires maximizing safe resection and implementing structured surveillance to identify progression early and deliver ART when indicated.

Declarations

Competing Interests:

There are no relevant financial or non-financial interests to disclose.

Ethics

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the IRB of the Icahn School of Medicine at Mount Sinai.

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Author Contribution

Conceptualization: AD, JYZ, RKSMethodology: AU, AD, JYZ, RKSData curation: AD, JYZ, EM, AR, MDFormal data analysis and investigation: AU, ADOriginal draft preparation: AU, AD, EMReview and editing of the manuscript: AU, AD, JYZ, EM, AR, MD, CS, GW, JB, RKSProject supervision: GW, JB, RKS

Data Availability

All data generated for the purposes of this study are available from the corresponding author upon reasonable request.

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Figures

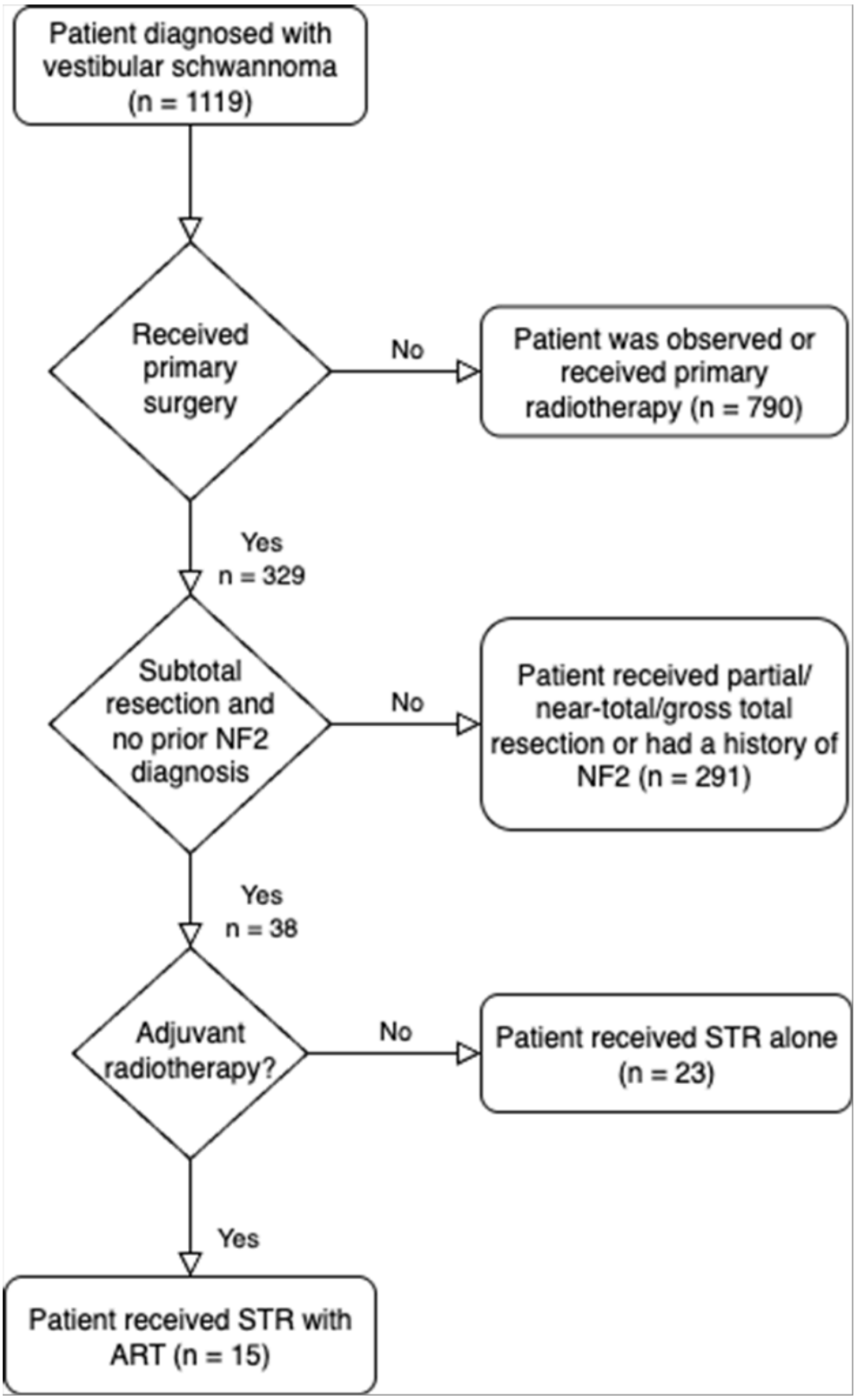


Figure 1

Patient flowchart describing patient treatment paradigm.



Figure 2

Illustration of a vestibular schwannoma suitable for subtotal resection. The tumor demonstrates 3 of the 4 factors that influenced the surgeons' decision to leave residual tumor behind: 1) absence of a safe dissection plane between the tumor and the facial nerve, 2) tumor invasion of the brainstem, and 3) limited visualization a highly vascular tumor/ vascular encasement that cannot safely be addressed or other general neurosurgical conditions. The cutout depicts a maximal residual tumor volume of 20.6% of its preoperative volume to avoid further adjuvant radiotherapy. Illustration by Ansley Unterberger, MD.