Preoperative diagnosis of vagal and sympathetic cervical schwannomas based on radiographic findings

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OBJECTIVE Vagus nerve and sympathetic chain cervical schwannomas (VNCSs and SCCSs) are benign nerve sheath tumors that arise in the head and neck. Despite similar presentations that make accurate preoperative diagnosis more difficult, the potential for morbidity following resection is significantly higher for patients with VNCS. Therefore, the authors analyzed a retrospective case series and performed a comparative analysis of the literature to establish diagnostic criteria to facilitate more accurate preoperative diagnoses.

METHODS The authors conducted a blinded review of imaging studies from retrospectively collected, operatively confirmed cases of VNCS and SCCS. They also performed a systematic review of published series that reported patient-specific preoperative imaging findings in VNCS or SCCS.

RESULTS Nine patients with VNCS and 11 with SCCS were identified. In the study cohort, splaying of the internal carotid artery (ICA) and internal jugular vein (IJV) did not significantly predict the nerve of origin (p = 0.06); however, medial and lateral ICA displacement were significantly associated with VNCS and SCCS, respectively (p = 0.01 and p = 0.003, respectively). Multivariate analysis demonstrated that ICA and IJV splaying with medial ICA displacement carried an 86% probability of VNCS (p = 0.001), while the absence of splaying with lateral ICA displacement carried a 91% probability of SCCS (p = 0.006). The presence of vocal cord symptoms or peripheral enhancement significantly augmented the predictive probability of VNCS, as did Horner's syndrome or homogeneous enhancement for SCCS.

A review of the literature produced 25 publications that incorporated a total of 106 patients, including the present series. Splaying of the ICA and IJV was significantly, but not uniquely, associated with VNCS (p < 0.0001); multivariate analysis demonstrated that ICA and IJV splaying with medial ICA displacement carries a 75% probability of VNCS (p < 0.0001), while the absence of such splaying with lateral ICA displacement carries an 87% probability of SCCS (p = 0.0003).

CONCLUSIONS ICA and IJV splaying frequently predicts VNCS; however, this finding is also commonly observed in SCCS and, among the 9 cases in the present study, was observed more often than previously reported. When congruent with splaying, medial or lateral ICA displacement significantly enhances the reliability of preoperative predictions, empowering more accurate prognostication.

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KEY WORDS vagal schwannoma; cervical sympathetic schwannoma; imaging; radiology; CT scan; MRI; oncology

Schwannomas are benign neoplasms arising from myelinating Schwann cells. Although they occur throughout the body, up to 45% are found in the head and neck, with many arising in the parapharyngeal space as either vagus nerve cervical schwannoma (VNCS) or sympathetic chain cervical schwannoma (SCCS).

Given their benign course and anatomically accommodating location, many of these tumors present incidentally or as painless neck masses; the presence of vagus
nerve symptoms or Horner’s syndrome defines the nerve of origin (NOO) but they are infrequently observed in practice. Surgery is typically recommended; however, the potential operative consequences vary considerably. There is a risk of highly morbid vocal cord paralysis and dysphagia with VNCS resection, mandating preoperative counseling of patients regarding the potential for additional operations to restore laryngeal function or for feeding tube placement. In contrast, the complications associated with SCCS resection are more benign and generally limited to first bite syndrome or Horner’s syndrome, which are better tolerated.

To improve patient counseling for these potential outcomes, prior studies have attempted to establish radiographic criteria that identify the NOO. In particular, separation of the internal carotid artery (ICA) from the internal jugular vein (IJV) has been identified as a consistent and accurate indicator of VNCS. However, clinical experience suggests more variability. Therefore, the goal of this study was to analyze these radiographic criteria both in a 20-patient cohort with a surgically confirmed NOO and in the published literature.

Methods

After institutional review board approval was obtained, the study cohort was compiled by searching institutional pathology reports from 1993 to 2015 using diagnosis and site codes. Inclusion criteria were anatomically confirmed NOO and access to clinical history and preoperative imaging. Patients with a history of anterior cervical surgery or head and neck cancer were excluded.

A senior neuroradiologist (J.M.M.) who was blinded to the clinical data reviewed all imaging studies. The following tumor features were captured: ICA and IJV splaying, ICA and external carotid artery (ECA) splaying, IJV compression, ICA displacement, parapharyngeal fat pad displacement, MRI signal and enhancement patterns, tumor size, and tumor vascularity. Splaying was primarily defined as any separation of the ICA and IJV or the ICA and ECA. Displacement was identified on axial images and defined as > 1 cm of medial or lateral shift, as measured from the center of the vessel of interest to a sagittal line drawn through its expected location. Contralateral structures were used for reference. Vascular compression was defined as a > 1 mm decrease in luminal diameter. Tumor size and volume were measured using the greatest diameter in the anteroposterior, superoinferior, and transverse planes. MRI signal intensity patterns on T1 and T2 sequences were classified as hyper-, hypo-, or isointense to nerve tissue. The T2 target sign was defined as a distinct mass showing a biphasic pattern, with a higher intensity peripherally and a lower intensity centrally on T2-weighted images. Enhancement patterns following gadolinium administration were classified as homogeneous, heterogeneous, or peripheral.

A systematic review of the literature was conducted using PubMed, MEDLINE, Embase, Evidence-Based Medicine Reviews, Web of Science, and Scopus. Key words and medical subject headings (MeSH) terms, which were searched alone and in combinations, included schwannoma, neurilemmoma, neuroma, vagus nerve, 10th cranial nerve, sympathetic chain, and cervical. Initial search results after deduplication yielded 280 unique English-language articles, 53 of which described preoperative radiographic features of VNCS or SCCS; these were reviewed in detail. Twenty-five of these publications described patient-specific imaging findings (106 unique patients), and 2 directly compared preoperative imaging findings between VNCS and SCCS (21 unique patients).

Our study cohort was analyzed in isolation for significant associations between patient outcomes and NOO. Comparative analysis of pooled data extrapolated from the literature was then conducted using 2 models. Both pooled analyses were derived by combining results of our study cohort with those from published case series and reports that described individual patient data (Supplemental Tables 1 and 2). In the first model, which we refer to as the “literature review,” only those studies directly comparing NOO in both VNCS and SCCS were included and analyzed with respect to their shared outcome—ICA and IJV splaying. The second model, which we refer to as the “pooled cohort,” included all studies that reported outcomes for individual patients with either VNCS or SCCS and was tested with respect to all anatomical study outcomes. Statistical analyses included the Student t-test, chi-square test, Fisher exact test, multivariate analysis, and derived receiver operating characteristic curves. All statistical testing was completed using JMP 10.0.0 (SAS Institute Inc., 1989–2007). A p value < 0.05 was considered significant.

Results

Patient Search, Population Overview, and Clinical Data

Our preliminary chart review yielded 1132 unique patient records, 43 of which had documented findings consistent with possible VNCS or SCCS. Subsequent review of the operative reports identified 27 tumor patients with anatomically confirmed NOO (12 with VNCS and 15 with SCCS). Of these patients, 20 had preoperative radiographs available for review (9 with VNCS and 11 with SCCS).

Distributions by sex, age, presence of neurofibromatosis Type 2, and medical comorbidities were comparable by NOO (Table 1). Dysphagia and/or vocal fold paralysis and Horner’s syndrome were uniquely and significantly associated with VNCS and SCCS, respectively, but each was observed in only 4 of 9 and 3 of 11 patients; most patients presented incidentally or with a neck mass.

Imaging

Neither ICA/IJV nor ICA/ECA splaying was significantly associated with VNCS or SCCS (p = 0.06 for both; Table 2 and Figs. 1 and 2). Medial and lateral ICA displacement were significantly associated with VNCS (p = 0.01) and SCCS (p = 0.003), respectively. Homogeneous enhancement was isolated to SCCS, and peripheral enhancement was significantly associated with VNCS (p = 0.07 and p = 0.03, respectively).

In our study cohort, ICA/IJV splaying with medial ICA displacement carried an 86% probability of correctly predicting VNCS (p = 0.001; Table 3). Lack of ICA/IJV
splaying and the presence of lateral ICA displacement carried a 91% probability of correctly predicting SCCS (p = 0.006). The addition of clinical symptoms indicating VNCS or SCCS increased these probabilities to 90% and 93%, respectively (p = 0.003 and p = 0.002). Incorporating peripheral or homogeneous tumor enhancement into the multivariate model increased the predictive probability to 97% in VNCS and 99% in SCCS for tumors meeting 3 radiographic criteria (p = 0.002 and p = 0.001, respectively). The combination of all radiographic criteria plus congruent clinical symptoms approached 100% probability of correctly predicting NOO (p = 0.002).

Tumor location with respect to the carotid bifurcation, displacement of the parapharyngeal fat pad, vascularity, and vascular narrowing were not significant. Tumor size did not differ significantly between the groups.

A previously undescribed finding of scattered contrast puddling within the tumor mass was observed in more than 80% of all tumors visualized on CT imaging, without a significant difference in prevalence between VNCS and SCCS (Fig. 3 and Table 2). Intraoperative photographs demonstrating a transcervical approach are provided for reference, highlighting relationships between the vagus nerve, sympathetic chain, ICA, and IJV in a typical patient with SCCS (Fig. 4).

**Comparative Analysis**

Furukawa et al. and Saito et al. have authored the only prior reports in which preoperative radiographic findings in patients with VNCS and SCCS were compared directly, and ICA/IJV splaying was their only shared outcome. The literature review group we compiled, which contains results from the Furukawa and Saito studies combined with our data, revealed a significant association between ICA/IJV splaying and VNCS (p < 0.0001; Table 4). This finding echoes previously published results.

The pooled cohort was analyzed with respect to all anatomical study outcomes. ICA/IJV splaying was significantly associated with VNCS (p = 0.001; Table 4), as was medial ICA displacement (p < 0.0001); lateral ICA displacement was significantly associated with SCCS (p < 0.0003). Multivariate analysis using pooled cohort data demonstrated that the combination of ICA/IJV splaying and medial ICA displacement carried a 75% probability of correctly predicting VNCS (p < 0.0001; Table 5). Absence of ICA/IJV splaying and the presence of lateral ICA displacement carried an 87% probability of correctly predicting SCCS (p = 0.0003).
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Discussion

More than half of the patients with VNCS and SCCS are asymptomatic or present with nonspecific symptoms, and while most cases are amendable through curative resection, the contrast in potential postoperative consequences is dramatic. With this clinical landscape in mind, previous authors have attempted to define reliable guidelines for predicting the NOO to more accurately counsel patients regarding anticipated risks. The mandate to improve prognostication is especially relevant in our practice and many like it, as gross-total resection is the standard of care.

In 1996, Furukawa et al. analyzed 9 patients using ultrasound and concluded that VNCS splays the ICA and IJV, whereas SCCS does not. This criterion has since been reevaluated by multiple authors with mixed results. Hoo et al. reported on a series of 4 patients with VNCS, only 3 of whom were accurately identified using Furukawa’s criteria. Saito explicitly tested ICA/IJV splaying in a population with VNCS and SCCS and observed that ICA/IJV splaying accurately predicted NOO in 86% of the patients with VNCS. However, the finding was not universally observed—it incorrectly predicted the NOO in 1 patient with SCCS. To account for these exceptions to Furukawa’s rule, Saito recommended a modification for large VNCSs in which posterior vessel displacement may reduce the degree of splaying and lead to misdiagnosis.

Other authors have adapted Furukawa’s rule to the analysis of other adjacent structures, looking for characteristic patterns that would predict VNCS or SCCS. Torita et al. and Anil and Tan studied ICA/ECA splaying as a potential marker of SCCS, but it was observed in only 33% of patients, with Anil and Tan documenting a fifth case of ICA/IJV splaying in SCCS. Other researchers have explored displacement of the ICA or the parapharyngeal fat pad with broadly similar results, that is, inconsistent and infrequently observed trends, all in very small series or case reports.

In the present study, we examined these criteria using 3 models: 1) in isolation in the study cohort, 2) in a limited literature review comprising our own patients alongside those documented in the 2 other head-to-head analyses of VNCS and SCCS, and 3) in a pooled cohort incorporating all radiographic reports of VNCS and SCCS.

Study Cohort

Our study cohort, which almost doubles the size of the largest prior series, demonstrates significantly more variability between VNCS and SCCS than previously described. Although ICA/IJV splaying was observed in 67% of patients with VNCS, it was also frequently absent. An additional 3 instances of ICA/IJV splaying were identified in patients with SCCS, and the prevalence of splaying was not significantly different between VNCS and SCCS. Similarly, although ICA/ECA splaying has been reported...
in SCCS and not in VNCS, our results showed that it occurs at a higher prevalence in VNCS (67% for VNCS vs 27% for SCCS), a difference that is not significant (p = 0.06). Perhaps most importantly, lateral and medial ICA displacements were identified for the first time as statistically significant predictors of NOO (p = 0.003 lateral and p = 0.01 medial ICA displacement).

We observed a novel pattern in tumor enhancement profiles, with peripheral enhancement isolated to VNCS (a significant association) and homogeneous enhancement isolated to SCCS (a finding that may demonstrate significance in a larger study). Taken together with ICA/IJV splaying and NOO-defining clinical symptoms, these findings provide substrate for a powerful multivariate model that will allow providers to accurately quote probabilities of correctly identifying the NOO preoperatively (Table 3). Of note, although the probabilities for accurate predictions approach 100% in the presence of anatomy-defining clinical symptoms, they do not reach it. This is attributable to a model effect that reflects an inherent dif-

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**TABLE 3. Multivariate analysis for study cohort**

<table>
<thead>
<tr>
<th>ICA/IJV Splaying</th>
<th>Medial ICA Displacement</th>
<th>Lateral ICA Displacement</th>
<th>Dysphagia/Vocal Cord Paralysis</th>
<th>Horner’s Syndrome</th>
<th>Peripheral Enhancement</th>
<th>Homogeneous Enhancement</th>
<th>VNCS*</th>
<th>SCCS*</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>86%</td>
<td>—</td>
<td>0.001</td>
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<tr>
<td>No</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>91%</td>
<td>—</td>
<td>0.006</td>
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<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>90%</td>
<td>—</td>
<td>0.003</td>
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<tr>
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<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>93%</td>
<td>—</td>
<td>0.002</td>
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<tr>
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<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>97%</td>
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<td>—</td>
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<td>—</td>
<td>—</td>
<td>99%</td>
<td>—</td>
<td>0.001</td>
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<tr>
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<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>100%</td>
<td>—</td>
<td>0.002</td>
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<tr>
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<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>100%</td>
<td>—</td>
<td>0.002</td>
</tr>
</tbody>
</table>

— = not applicable.

* Percentages reflect probability of accurately predicting NOO given the imaging findings.

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**FIG. 3.** Angiographic correlation of CT puddling. Digital subtraction angiogram, common carotid artery injection, demonstrates mild increased vascularity (white arrows) from the ascending pharyngeal branch with puddling (white arrowheads), consistent with a schwannoma (A–C). Anterior displacement of the ECA and ICA can be seen. Coronal (D), sagittal (E), and axial (F) CT angiograms demonstrate CT puddling centrally (black arrows). This sign should be helpful in differentiating these lesions from paraganglioma, which is significantly more hypervascular in the early phase of CT angiography and potentially eliminates the need for preoperative angiography.
ference between anatomical and statistical realities; even though vocal cord symptoms and Horner’s syndrome were observed exclusively in VNCS and SCCS, respectively, the small number of observations of each statistically allows for the remote possibility of a configuration in which these symptoms would be observed in the “wrong” tumor, despite the anatomical impossibilities.

Overall, our findings provide a more clear, contemporary, and reliable adaptation of Furukawa’s rule, which we believe will prove useful in preoperative patient counseling as we continue to refine our diagnostic abilities. Our results did not demonstrate a threshold in tumor size beyond which our diagnostic criteria were valid; however, this is probably because of the small size of our study population and the fact that all the tumors were large (Table 2). Saito’s modified criteria for large tumors with posterior vessel displacement applied to only 1 patient from our series. In this individual, the ICA and IJV were noted to travel in proximity without appreciable separation, correctly diagnosing SCCS. This finding is encouraging; however, given that this outcome could not be extrapolated from other prior reports and incorporated into the comparative analysis, its generalizability remains in question.

With respect to surgical strategy, all tumors in this series were approached with the goal of gross-total resection. Such resection was achieved in 19 (95%) of 20 patients, and nerve sacrifice was required in 56% of the patients with VNCS and 82% of the patients with SCCS. Only 1 patient underwent intentional debulking to preserve vagal function, which was elected intraoperatively in a 30-year-old patient with a 2-cm tumor that was noted to have broad splaying of nerve fibers across the capsule. This case provides an especially salient example of how our criteria will enhance preoperative patient counseling, as more definitive preoperative identification of the NOO would have empowered explicit discussion of the risks and benefits of leaving the small tumor’s pseudocapsule after debulking versus the long-term sequelae of vagus nerve dysfunction in a young man.

A final noteworthy feature of the study cohort is the characterization of an otherwise undescribed accumulation of contrast material within the tumor mass on enhanced CT scans, which we have termed “CT puddling” (Fig. 3). Angiographic studies of schwannomas have provided inconsistent reports, but none has directly described CT puddling in the setting of contrast-enhanced CT scans or in cervical schwannomas specifically. Although this

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**TABLE 4. Comparative analysis: literature review and pooled cohort***

<table>
<thead>
<tr>
<th>Model</th>
<th>VNCS (%)</th>
<th>SCCS (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literature review: ICA/IJV splaying†</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Furukawa et al., 1996</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saito et al., 2007</td>
<td>6 (86)</td>
<td>1 (20)</td>
<td>0.02</td>
</tr>
<tr>
<td>Present study, 2015</td>
<td>6 (67)</td>
<td>3 (27)</td>
<td>0.06</td>
</tr>
<tr>
<td>Literature review (combined analysis)</td>
<td>17 (81)</td>
<td>4 (20)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

| Pooled cohort: anatomic outcomes†         |         |          |         |
| ICA/IJV splaying                          | 25 (83) | 23 (47)  | 0.001   |
| ICA/ECA splaying                          | 6 (38)  | 25 (39)  | 0.9     |
| Anterior ICA displacement                  | 9 (64)  | 28 (65)  | 0.9     |
| Posterior ICA displacement                 | 0 (0)   | 2 (5)    | 0.4     |
| Lateral ICA displacement                   | 0 (0)   | 20 (52)  | 0.0003  |
| Medial ICA displacement                    | 9 (60)  | 1 (3)    | <0.0001 |
| Anterior fat pad displacement              | 5 (56)  | 14 (61)  | 0.8     |
| Medial fat pad displacement                | 3 (33)  | 3 (13)   | 0.2     |

* Boldface type indicates statistical significance.
† Percentages reflect portion of total tumors from that NOO group for whom the outcome in question was reported.

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**TABLE 5. Pooled cohort: multivariate analysis**

<table>
<thead>
<tr>
<th>ICA/IJV Splaying</th>
<th>Medial ICA Displacement</th>
<th>Lateral ICA Displacement</th>
<th>VNCS* (%)</th>
<th>SCCS* (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>75%</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>Yes</td>
<td>87%</td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>

* Percentages reflect probability of accurately predicting NOO given the imaging findings.
finding is not useful in distinguishing VNCS from SCCS, it may be valuable in differentiating schwannomas from other parapharyngeal and carotid sheath neoplasms, such as paragangliomas.

**Comparative Analysis**

Our decision to define and study 2 pooled analyses was motivated by the demands of statistical rigor, particularly in the face of retrospective data. The literature review cohort was defined by a total of 3 case series, including our study cohort, sharing a common hypothesis, primary outcome, and study design. Within this 41-patient population, ICA/IJV splaying was observed in 81% of patients with VNCS and 20% with SCCS, which proved statistically significant (p < 0.0001). This provides the best evidence to date that ICA/IJV splaying strongly suggests VNCS, but with the qualification that it is by no means a diagnostic finding or even a rare observation in SCCS.

To take the most inclusive survey of preoperative imaging in patients with VNCS and SCCS, the pooled cohort was defined by combining results from all available publications. On univariate analysis, findings in the pooled cohort reflected those of the study cohort and the literature review: ICA/IJV splaying and medial ICA displacement were significantly associated with VNCS, while lateral ICA displacement was significantly associated with SCCS. Multivariate modeling predicted a 75% probability of VNCS if both ICA/IJV splaying and medial ICA displacement were observed and an 87% probability of SCCS if there was no ICA/IJV splaying with lateral ICA displacement. These predictions potentially represent a more conservative set of guidelines for providers to use in preoperative counseling (Table 5).

Had the results of these 3 analyses not echoed one another so closely, the overall results would have been called into question, and no useful recommendations could be made. However, given the highly congruent observations, we take guarded reassurance that these findings provide meaningful insight and constitute improved criteria for diagnosing VNCS and SCCS.

Although our study represents a significant advance on prior attempts to define preoperative imaging criteria, it was subject to considerable limitations. All 3 analyses were based on retrospective data, and the number of patients available for inclusion was small. Only 2 prior studies directly compared preoperative imaging findings in patients with VNCS and SCCS, and they shared only 1 outcome, which constrained the literature review. Finally, data extracted from prior publications for inclusion in the pooled cohort were inconsistently reported, and the ability of imaging techniques to accurately visualize abnormalities has improved considerably since publication of the first included report. Despite these realities, our work represents the most inclusive, broadly reaching, and statistically powerful study to date and an essential step toward definitive diagnostic criteria.

**Conclusions**

Taken together, our findings support ICA/IJV splaying on preoperative imaging as the cornerstone of differentiating VNCS from SCCS. However, we have also demonstrated that this observation is far from universal and should be regarded with considerable skepticism. We have identified a second imaging feature, medial or lateral ICA displacement, that combined with ICA/IJV splaying, peripheral or homogeneous tumor enhancement, or characteristic clinical symptoms significantly enhances the reliability of preoperative predictions. With this in mind, our findings outline key goals for future research, including prospective study of these radiographic features. Perhaps the most immediately impactful contribution of our work is an objective framework for predicting VNCS and SCCS, which for the first time will empower surgeons to offer patients with cervical schwannoma an objective, evidence-based prediction of potential surgical morbidity.

**References**

Preoperative imaging in cervical schwannoma

Author Contributions
Conception and design: Link, Graffeo, Van Abel, Morris. Acquisition of data: all authors. Analysis and interpretation of data: Graffeo, Van Abel, Morris. Drafting the article: Graffeo. Critically revising the article: Link, Graffeo, Van Abel. Reviewed submitted version of manuscript: all authors. Statistical analysis: Graffeo. Administrative/technical/material support: Graffeo. Study supervision: Link, Van Abel.

Supplemental Information
Online-Only Content
Supplemental material is available with the online version of the article.

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.