Evaluating Perineural Spread to the Intratemporal Facial Nerve on Magnetic Resonance Imaging

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objectives. To determine the sensitivity and specificity of magnetic resonance imaging (MRI) for the detection of perineural spread (PNS) along the intratemporal facial nerve (ITFN) in patients with head and neck cancers.

Study Design. Case series with chart review.

Setting. Tertiary care center.

Subjects and Methods. We included 58 patients with head and neck malignancies who underwent sacrifice of the ITFN between August 1, 2002, and November 30, 2015. Demographics, preoperative facial nerve function, prior oncologic treatment, and timing between MRI and surgery were recorded. Histopathology slides and preoperative MRI were reviewed retrospectively by a neuropathologist and a neuroradiologist, respectively, both blinded to clinical data. The mastoid segment of the facial nerve (referred to as the descending facial nerve [DFN]) and stylomastoid foramen (SMF) were evaluated separately. A grading system was devised when radiographically assessing PNS along the DFN.

Results. Histopathologic evidence of PNS was found in 21 patients (36.2%). The sensitivity and specificity of MRI in detecting PNS to the DFN were 72.7% and 87.8%, respectively. MRI showed higher sensitivity but slightly lower specificity when evaluating the SMF (80% and 82.8%, respectively). Prior oncologic treatment did not affect the false-positive rate ($P = .7084$). Sensitivity was 100% when MRI was performed within 2 weeks of surgery and was 62.5% to 73.3% when the interval was greater than 2 weeks. This finding was not statistically significant (SMF, $P = .7076$; DFN, $P = .4143$).

Conclusion. MRI shows fair to good sensitivity and good specificity when evaluating PNS to the ITFN.

Keywords

perineural spread, perineural invasion, facial nerve, imaging, mastoid, temporal bone

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Perineural growth is a recognized adverse characteristic of head and neck malignancies. The incidence of this finding varies between studies and is dependent on tumor histology. The rate of perineural growth for squamous cell cancers (SCCs) of the head and neck has been reported between 14.2% and 63.2%.¹⁻⁵ Certain salivary gland tumors are also known to show this phenomenon, most commonly adenoid cystic carcinomas, but other histologic types such as adenocarcinomas and mucoepidermoid carcinomas also demonstrate this behavior.⁶

A distinction is made between microscopic perineural invasion (PNI) seen in unnamed small nerves and perineural spread (PNS). The latter corresponds to the macroscopic propagation of tumor cells within the perineural space of large, usually named, nerves. PNS may be detected on radiologic investigation while PNI can only be discovered on histopathologic examination.⁷⁻⁸ The most commonly affected large nerves are the trigeminal (cranial nerve [CN] V) and facial (CN VII) nerves.⁹

Neural and perineural involvement have been associated with decreased disease-free survival rates and overall poorer outcome.¹⁰⁻¹¹ Local recurrence rates are markedly increased, up to 4-fold, with the presence of PNI.⁵ Moreover, nerve dysfunction caused by PNS can result in paresthesia and paralysis, significantly affecting quality of life.¹²

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The presence of PNS is a clinical finding that can have significant repercussions on the treatment plan. It is an important element to consider when determining surgical candidacy and the extent of resection. PNS to the intratemporal facial nerve (ITFN) from cutaneous or parotid malignancies typically requires a mastoidectomy and facial nerve sacrifice in addition to resection of the primary tumor.

Of the studies examining the role of magnetic resonance imaging (MRI) to detect PNS in head and neck cancers, only 6 have included patients with facial nerve involvement. These studies have included few patients with PNS specifically to the facial nerve, the largest one reporting only 13 such subjects. Moreover, only 1 report presented information detailed enough to calculate both the sensitivity and specificity for PNS to the facial nerve. The primary objective of our study was to determine the sensitivity and specificity of MRI for the detection of PNS along the ITFN in patients with head and neck cancers. Secondarily, we aimed to determine if prior oncologic treatment or timing between preoperative MRI and surgery had any effects on the false-positive and false-negative rates.

**Methods**

After obtaining institutional review board approval (UT MD Anderson Cancer Center, IRB# DR08-0802), we performed a retrospective case review of all the patients who underwent a mastoidectomy or temporal bone resection with intratemporal facial nerve resection between August 1, 2002, and November 30, 2015, at our tertiary care center. A total of 58 patients were identified based on the following inclusion criteria: (1) patients having undergone sacrifice of the ITFN as part of the surgical treatment for a head and neck malignancy, (2) sufficient information available in the chart regarding the exact site of nerve resection, (3) available preoperative MRI of sufficient quality, and (4) available histopathologic slides for review.

The patients’ medical charts were reviewed and the following information was gathered: demographics, surgical history, prior oncologic treatment, preoperative facial nerve function, timing between preoperative MRI and surgery, tumor histology, primary tumor site, and segments of the facial nerve that were resected. Facial nerve function was assessed in clinic using the House-Brackmann (HB) grading system.

**Imaging**

Magnetic resonance imaging for each patient was reviewed by an experienced radiologist (L.E.G.), blinded to the diagnosis, imaging report, surgical results, and any original annotations redacted prior to review. Although MRI slice thickness modified during the period of investigation from 5 to 3 mm, all studies included axial T1 and T2-weighted pre-contrast sequences and axial, coronal, and sagittal T1-weighted sequences with fat suppression after administration of intravenous gadolinium-based contrast.

To our knowledge, there is no widely recognized grading or scoring scale for facial nerve enhancement on MRI. A grading scale was therefore devised for this study. It was based on enhancement and symmetry of the descending (mastoid) segment of the facial nerve (DFN), plus noting whether the stylomastoid foramen (SMF) was normal or abnormal (based on abnormal enhancement and/or loss of the normal T1 fat-related signal hyperintensity). Please see Figure 1 for examples of each grade.

The following Radiographic Facial Nerve Grading Scale (RFNGS) was used:

1. Normal-appearing, symmetrically non- or mildly enhancing descending nerve, not enlarged, no likelihood of tumor involvement
2. Slight asymmetry in size and/or enhancement, low likelihood of tumor involvement but not unequivocally normal
3. Asymmetric widening and/or excessive enhancement of the descending facial nerve segment on the side of tumor, worrisome for tumor involvement

**Histopathologic Examination**

A detailed histopathological review of the resected tumors and facial nerve was undertaken. Hematoxylin and eosin–stained microscopic slides were reexamined for perineural invasion by a head and neck pathologist (DB) blinded to clinical and radiologic information. A broad definition of PNI characterizes it as tumor cell invasion in, around, and through the nerves. Finding of tumor cells within any of the 3 layers of the nerve sheath (epi-, peri-, endoneurium) represents PNI.

**Statistical Analysis**

Based on comparisons between readings of MRI films and blinded readings by a clinical pathologist, true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) values were determined. Those values were used to calculate the following parameters:

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}} \times 100.$$  

$$\text{Specificity} = \frac{\text{TN}}{\text{FP} + \text{TN}} \times 100.$$  

$$\text{False-Negative Rate} = \frac{\text{FN}}{\text{TP} + \text{FN}} \times 100.$$  

$$\text{False-Positive Rate} = \frac{\text{FP}}{\text{TN} + \text{FP}} \times 100.$$  

Positive Predictive Value $= \frac{\text{TP}}{\text{TP} + \text{FP}} \times 100$  

Negative Predictive Value $= \frac{\text{TN}}{\text{TN} + \text{FN}} \times 100$.

Accuracy $= \frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}} \times 100$.

Comparisons of these parameters of the various imaging and functional measures vs blinded “gold-standard” readings by a clinical pathologist were assessed by Pearson $\chi^2$ or, where there are fewer than 10 subjects in any cell of a 2 × 2 grid, by the 2-tailed Fisher exact test. These statistical tests were performed with the assistance of the Statistica (Version 13; TIBCO Statistica, Palo Alto, California) software package.

**Results**

**Patient Demographics and Clinical Characteristics**

Among the 58 patients that we identified, 21 (36.2%) showed evidence of PNS to the ITFN and 37 did not have PNS. All the patients with PNS showed involvement at the SMF, and 12 patients showed spread to the DFN. Nineteen of the 21 patients with facial nerve PNS (90.5%) showed PNI in the primary tumor. Of the 37 patients without PNS, 23 (62.2%) showed PNI in the primary tumor and 14 (37.8%) did not (Figure 2).

The demographics of patients without and with PNS are shown in Table 1. The most commonly encountered tumor histology was squamous cell carcinoma, representing 42.9% of tumor types in patients with PNS and 21.6% in those without PNS. Tumor histology is shown in Table 2 for patients without and with PNS.

![Figure 2](https://example.com/figure2.png)

Figure 2. Distribution of patients by confirmed histologic presence of PNS along the ITFN and PNI in the main specimen. DFN, descending facial nerve; ITFN, intratemporal facial nerve; MRI, magnetic resonance imaging; PNI, perineural invasion; PNS, perineural spread.
Histopathologic Findings

Several patterns of PNI and PNS were observed: complete or incomplete encirclement of the nerve, sandwiching, “onion-skin” lamination, tangential contact of tumor cords, and neural permeation. A variety of architectural tumor patterns were noted: solid or sheet-like, tumor islands, thick and thin cords, or diffusely arranged individual tumor cells. The nonsolid patterns appeared to be more invasive and tended to track along the nerve, as opposed to the solid patterns of tumor that “flowed” around the nerve. Figure 3 shows histopathologic examples of PNI.

Descending Facial Nerve

Proper evaluation of the DFN was feasible in 52 of 58 patients. Of the 6 patients not included in our calculations, 2 did not have the descending segment included in the surgical specimen. The other 4 DFNs could not be properly evaluated on MRI due to mastoid opacification or extensive infiltration of the temporal bone by tumor.

Two different sets of calculations were performed for the DFN. In the first set, grade 1 of the RFNGS was considered normal and grades 2 to 3 abnormal. For this set, MRI showed a sensitivity of 72.7% and a specificity of 87.8% for the detection of PNS along the DFN. The second set of calculations considered grades 1 and 2 as normal. In that case, sensitivity was found to be 45.5% and specificity 100%.

MRI slice thickness was 3, 4, and 5 mm for 27, 5, and 20 patients, respectively. Slice thickness had no statistically significant impact on sensitivity or specificity.

Stylomastoid Foramen

The SMF could be fully evaluated in 49 patients. Nine patients were excluded: the SMF was not specifically biopsied at the time of surgery in 7 cases, and MRI assessment was equivocal in 2 instances. On histopathology, PNS was found at the SMF in 21 patients. In 2 additional cases, histopathologic examination revealed the presence of tumor in

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Table 1. Demographics of Patients without and with PNS to the ITFN.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients without PNS (n = 37 Patients)</th>
<th>Patients with PNS (n = 21 Patients)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>55.5 ± 20.7</td>
<td>63.0 ± 18.7</td>
<td>.1794</td>
</tr>
<tr>
<td>Male/female ratio, No.</td>
<td>27/10</td>
<td>14/7</td>
<td>.6121</td>
</tr>
<tr>
<td>Prior surgery, No. (%)</td>
<td>14 (37.8)</td>
<td>12 (57.1)</td>
<td>.1554</td>
</tr>
<tr>
<td>Prior parotidectomy, No. (%)</td>
<td>13 (35.1)</td>
<td>8 (38.1)</td>
<td>.8216</td>
</tr>
<tr>
<td>Prior radiotherapy, No. (%)</td>
<td>9 (24.3)</td>
<td>4 (19.0)</td>
<td>.6433</td>
</tr>
<tr>
<td>Prior chemotherapy, No. (%)</td>
<td>6 (16.2)</td>
<td>1 (4.8)</td>
<td>.1981</td>
</tr>
<tr>
<td>Days between MRI and surgery, median (range)</td>
<td>20 (1-237)</td>
<td>27 (3-67)</td>
<td>.2939</td>
</tr>
</tbody>
</table>

Abbreviations: ITFN, intratemporal facial nerve; MRI, magnetic resonance imaging; PNS, histologically positive perineural spread to the facial nerve; SD, standard deviation.

Table 2. Tumor Histology in Patients without and with PNS.

<table>
<thead>
<tr>
<th>Tumor Histology</th>
<th>Patients without PNS (37 Patients) No. (%)</th>
<th>Patients with PNS (21 Patients) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>8 (21.6)</td>
<td>9 (42.9)</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>5 (13.5)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>5 (13.5)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Carcinoma ex pleomorphic</td>
<td>4 (10.8)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>4 (10.8)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>2 (5.4)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>1 (2.7)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Basosquamous</td>
<td>1 (2.7)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Carcinoma with squamous differentiation</td>
<td>1 (2.7)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 (2.7)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>1 (2.7)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Poorly differentiated carcinoma</td>
<td>1 (2.7)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>1 (2.7)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td>1 (2.7)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Sebaceous carcinoma</td>
<td>1 (2.7)</td>
<td>1 (4.8)</td>
</tr>
</tbody>
</table>

Abbreviation: PNS, perineural spread.
the surrounding soft tissues adjacent to the SMF without frank PNS. MRI evaluation of the SMF was considered abnormal for these 2 instances; both were considered false positives.

Evaluation of the SMF on MRI showed a sensitivity of 80% and a specificity of 82.8%. MRI slice thickness was 3, 4, and 5 mm for 22, 4, and 23 patients, respectively. Slice thickness had no statistically significant impact on sensitivity or specificity.

**Tympanic Facial Nerve**

The tympanic segment was biopsied in 6 patients and was positive for tumor in all instances. MRI evaluation of the tympanic segment was considered abnormal in 2 cases, normal in 3, and could not be performed in 1 patient.

**Labyrinthine Segment and Geniculate Ganglion**

The labyrinthine segment of the facial nerve and the geniculate ganglion were biopsied in 2 patients. Histopathology was positive for tumor in 1 case, which was not detected on MRI.

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**Clinical Preoperative Facial Nerve Function**

Sensitivity and specificity were also calculated for the preoperative clinical evaluation of facial nerve function on physical examination. Probability calculations for the preoperative facial nerve function were performed in 37 patients who had not undergone a parotidectomy prior to their oncologic resection. When the HB score of 1 was considered normal, the sensitivity was 92.3% and specificity was 25%. If HB scores of 1 and 2 were considered normal, the sensitivity dropped to 64.3%, and the specificity was 47.8%.

**Table 3** shows all the statistical measures for MRI evaluation of the DFN and SMF and for the clinical preoperative facial nerve function.

**Effects of Prior Treatment**

Prior oncologic treatment, including surgery, radiotherapy, and chemotherapy, did not have any statistically significant impact on the false-positive or false-negative rates for the evaluation of the ITFN on MRI.
Time Between Preoperative MRI and Surgery

Sensitivity of MRI for detection of PNS was 100% for both the SMF and DFN when imaging was performed ≤ 14 days prior to surgery. If a delay of more than 14 days was present between imaging and surgery, sensitivity was 73.3% for the SMF and 62.5% for DFN (SMF, \( P = .7076 \); DFN, \( P = .4143 \)).

Discussion

The present study shows that MRI has a fair to good sensitivity and good specificity for detecting PNS to the ITFN. Compared to imaging, preoperative clinical evaluation of the facial nerve has more limited diagnostic utility. While it had a high sensitivity in our cohort, it lacked specificity for ITFN involvement even in patients not previously operated on.

While several studies have examined the role of imaging in PNS of head and neck cancers, a limited number of reports have included patients with facial nerve invasion. Only Baulch et al.13 provide sufficiently detailed information to calculate the sensitivity and specificity of MRI for detection of PNS specifically to the facial nerve. For their 13 facial nerve cases, they obtained a sensitivity of 78% and specificity of 75%. Our study, which includes the largest number of patients with facial nerve biopsies, shows a similar sensitivity, varying between 72.7% and 80%, as well as a higher specificity of 82.8% to 87.8%.

Table 4 summarizes the data of prior studies that examined the value of MRI for detection of perineural spread in head and neck malignancies. Only studies that had patients with facial nerve involvement are included in the table. Imaging review of the facial nerves had several challenges. In some patients, motion or pulsation artifact made difficult discrimination of the DFN segment. In other patients, identification of the nerve was difficult if there was mastoid air cell opacification; in these cases, a grade of 3 was assigned even if the more superior aspect of the nerve was not apparent asymmetric.

Timing between preoperative MRI and surgery is an important consideration. Gandhi and Sommerville19 have recommended that imaging should be obtained within 1 month of surgery in patients with cutaneous cancers of the head and neck. They noted that while the normal progression of PNS to the skull base may be unpredictable, our data do not show any statistically significant differences in sensitivity or specificity when looking at different time points. This lack of detectable difference is possibly due to small numbers of false negatives and true positives in our cohort. To our knowledge, the importance of timely imaging for PNS diagnosis in head and neck cancers has not been well described previously. Baulch et al.13 reported a similar number of days between preoperative MRI and surgery, with an average of 25 days and a range of 1 to 63 days prior to surgery. If a delay of more than 14 days was present between imaging and surgery, sensitivity was 73.3% for the SMF and 62.5% for DFN (SMF, \( P = .7076 \); DFN, \( P = .4143 \)).

### Table 4

<table>
<thead>
<tr>
<th>Study</th>
<th>Total (VII), No.</th>
<th>Imaging Modality</th>
<th>TN, No.</th>
<th>TP, No.</th>
<th>FN, No.</th>
<th>FP, No.</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>FPR, %</th>
<th>FNR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nemzek et al.14</td>
<td>19 (2)</td>
<td>MRI</td>
<td>NA</td>
<td>18</td>
<td>1</td>
<td>NA</td>
<td>95</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Williams et al.15,16</td>
<td>29 (3)</td>
<td>MRI</td>
<td>NA</td>
<td>15</td>
<td>14</td>
<td>NA</td>
<td>52</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Lee et al.16</td>
<td>38 (11)</td>
<td>MRI, CT, PET</td>
<td>NA</td>
<td>30</td>
<td>8</td>
<td>NA</td>
<td>79</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Gandhi et al.18</td>
<td>30 (7)</td>
<td>MRI</td>
<td>NA</td>
<td>30</td>
<td>0</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hanna et al.17</td>
<td>38 (7)</td>
<td>MRI</td>
<td>11</td>
<td>14</td>
<td>0</td>
<td>2</td>
<td>100</td>
<td>85</td>
<td>88</td>
<td>100</td>
<td>15</td>
<td></td>
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<td>CT</td>
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<td>1</td>
<td>88</td>
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<td>73</td>
<td>73</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; FN, false negative; FP, false positive; FNR, false-negative rate; FPR, false-positive rate; MRI, magnetic resonance imaging; NA, not available; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; TN, true negative; TP, true positive.

Total number of evaluated nerves or patients (number of facial nerves included in the study).

Blind: radiologist blinded to clinical information.

Only those patients with histopathologic assessments are included in this table.
days; however, they did not comment on the impact of imaging delay on diagnostic accuracy. This finding would have obvious importance for the patient and surgeon. Obtaining preoperative imaging close to the day of surgery may influence preoperative planning and counseling, since nerves showing enhancement might contain perineural spread and require sacrifice resulting in complete facial paralysis.

A high level of suspicion for PNS must be kept even when the presenting cancer histology is not one of the usual suspects, such as SCC or adenoid cystic carcinoma. As shown by our data and discussed by Carlson et al, other types of cancers can also invade the facial nerve, such as salivary ductal carcinoma, acinic cell carcinoma, or mucocutaneous carcinoma. While some authors have described significant delays before clinical manifestations of PNS, others have noted that symptoms of PNS usually precede imaging findings. Our data show a higher sensitivity for preoperative clinical assessment of the facial nerve using the HB grading scale compared to MRI. However, one cannot solely rely on physical evaluation to determine the presence of PNS along the ITFN due to the very low specificity of this assessment method. This low specificity is explained, at least in some patients, by tumor invasion of distal branches without accompanying proximal spread within the temporal bone. It is therefore important to share with patients the limitations of the physical examination and the risks of false negatives on imaging when discussing surgical treatment plans and obtaining informed consent.

Microscopic PNI and clinical PNS are believed to represent a spectrum of tumoral invasion starting in small nerves and spreading to larger named nerves. In our patient population, PNI in the main specimen was more commonly found on histology than PNS to the ITFN (respectively, 72.4% vs 36.2%). In patients without PNS to the facial nerve, more than half had microscopic PNI. Interestingly, 2 patients with confirmed PNS did not have evidence of PNI in their primary tumor. This finding reflects the challenges described by others in detecting PNI.

Limitations of this study include its retrospective nature and relatively small number of patients. Our study may not have been sufficiently powered to show statistically significant differences in sensitivity and specificity when examining prior oncologic treatments or timing of imaging. Based on the observed true-positive and false-negative rates, a sample size of 120 would be necessary to detect a significant difference in sensitivity at the level of the DFN. To detect a difference at the SMF, the size would need to be 198. Operative and pathology reports needed to be reviewed to determine the exact sites of nerve biopsy. This information may have been prone to subjective interpretation in some instances. Moreover, the study spans a period of 13 years during which imaging technologies and protocols have evolved.

Nonetheless, our report shows several strengths. It represents the largest study on the value of MRI for detection of PNS specifically to the facial nerve. Radiologic images and histopathologic slides were independently reviewed by a neuroradiologist and a neuropathologist, both of whom have significant experience in their respective fields, and both were blinded to any other clinical data. Finally, the design of our study allowed for the calculation of all test parameters, not only sensitivity, as was the case in most previous studies.

Conclusion

MRI shows fair to good sensitivity and good specificity when evaluating PNS to the ITFN. While clinical assessment of facial nerve function using the HB scale shows a high sensitivity, it severely lacks specificity. The impact of timing on the accuracy of preoperative imaging requires further investigation.

Author Contributions

Marc-Elie Nader, designed the project, acquired demographic data, analyzed and interpreted data, drafted and critically revised the article; Lawrence E. Ginsberg, designed the project, acquired and interpreted radiographic data, drafted parts of the article in regards to radiologic methods, findings and discussion, and critically revised the article; Dianna B. Roberts, performed statistical analysis, drafted parts of the article in regards to statistical methods, critically revised the article; Paul W. Gidley, designed the project, acquired demographic data, interpreted data, critically revised the article.

Disclosures

Competing interests: Marc-Elie Nader, shareholder of Amgen, Cardinal Health, Johnson & Johnson, Medtronic, Pfizer; Paul W. Gidley, shareholder of Eli Lily, Amgen, Merck, Medtronic, Pfizer.

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References


