A Machine-Learning Approach to Differentiating Benign and Malignant Peripheral Nerve Sheath Tumors

A MULTICENTER STUDY

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Outline

- **Background:**
  - Benign and Malignant PNST
  - Current Clinical Workflow

- **Methods:**
- **Results**
- **Future Directions**

**Goal:** Develop a binary classifier using MRI information, providing early diagnosis of Benign and Malignant peripheral nerve sheath tumors (PNSTs)
Benign and Malignant PNST

Peripheral Nerve Sheath Tumors (outside the brain and spine)

- **Benign (BPNSTs)**
  - Schwannoma
  - Neurofibroma
  - Perineuroma
  - Hybrids
  - Ganglioneuroma

- **Malignant (MPNSTs)**
MPNSTs – Can’t Miss Diagnosis

- Natural History
  - 5-year survival 30-50%
  - 50% of all MPNSTs occur in Neurofibromatosis (NF1)
  - 5-10% of NF1 patients will develop MPNSTs

- Pathophysiology
  - Malignant Transformation
  - Neurofibroma → Malignancy
  - Invasion and metastasis → morbidity & surgical difficulty
Surgical Morbidity – Complex

**MPNST, Surgical Goal:** complete resection – *total resection is curative* – with minimal disruption of nerve function

Surgical Challenges
- Greater nerve fiber invasion
- Neighboring tissue invasion
- Needs wide excisional margins
- Must avoid seeding
- Expect repeat surgery
Surgical Morbidity – Simple

**BPNSTs** are surgically simpler
- Local involvement
- Low recurrence potential

**Schwannoma:**
- Tumor of supporting Schwann cells
- Single nerve fiber
- Tumor displaces uninvolved fascicles

**Neurofibroma:**
- Tumor of the endoneurium
- Single or multiple nerves
- Possible functional implications
A Need for Early Diagnosis by Imaging

Accurate imaging can aid surgical planning to maximize quality of life
- Resect MPNSTs earlier
- Avoid unnecessary surgery

Imaging Options
- MRI: qualitative and semantics
- PET: SUV > 3.5
- Gold Standard: Surgical Biopsy

Wasa et al. - MRI Criteria
With 2 of 4 – 61% sens, 90% spec

1. Diameter > 5 cm
2. Peripheral tumor enhancement
3. Perilesional edema
4. Intra-tumoral cyst
Radiographic Ambiguity

MRI T1 with Gad Fat Sat commonly available

- Neck – NF1
- Right Thigh – MPNST
- Left Thigh – MPNST
- Right RP – MPNST
Additional Tools: PET, Derlin et al.

PET – less available

SUVmax ≥ 3.5
- 100% Sensitive
- 54.5% Specific
- 47.4% PPV

MRI comparison
- 66.7% sensitive
- 90% specific
- 75% PPV
Outline

**Goal**: Develop a binary classifier (MPNST vs BPNST) with MRI

- Background:
- **Methods**:
  - Segmentation
  - Clinical data collection
  - Feature
    - Extraction
    - Selection
    - Optimization
  - Prediction Analysis
- Results
- Future Directions
Workflow

- **Input**: MRI T1-gad with Fat Suppression
  - Most available

- **Output**: Classification probability and label
  - MPNST or BPNST

**Goal**: develop a binary classifier for Malignant versus Benign peripheral nerve sheath tumors (PNSTs) with MRI
Radiomics Workflow

- Image segmentation
- Clinical data collection
- Feature
  - Extraction
  - Selection
  - Optimization
- Prediction Analysis

**Goal:** develop a binary classifier for Malignant versus Benign peripheral nerve sheath tumors (PNSTs) with MRI
Images and Segmentation

- Imaging Segmentation
  - 171 Benign
  - 95 Malignant
  - SHC, Uni. Utah, Mayo

- Clinical data collection

- Feature
  - Extraction
  - Selection
  - Optimization

- Prediction Analysis
Clinical Features

- Chart review
- Red Flag symptoms of MPNSTs/infiltrative tumors

<table>
<thead>
<tr>
<th></th>
<th>Benign (N = 171)</th>
<th>Malignant (N = 95)</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>Age, yrs. (SD)</td>
<td>45.5 (15.3)</td>
<td>43.3 (18.2)</td>
<td>0.320</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>75 (44%)</td>
<td>54 (57%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Female</td>
<td>96 (56%)</td>
<td>41 (43%)</td>
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<tr>
<td>Spontaneous Pain</td>
<td>41 (24%)</td>
<td>71 (75%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Motor Deficit</td>
<td>45 (26%)</td>
<td>31 (33%)</td>
<td>0.275</td>
</tr>
<tr>
<td>NF1</td>
<td>38 (22%)</td>
<td>41 (43%)</td>
<td>&lt;0.001</td>
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<tr>
<td>NF2</td>
<td>10 (6%)</td>
<td>0 (0%)</td>
<td>0.016</td>
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<tr>
<td>Schwannomatosis</td>
<td>5 (3%)</td>
<td>0 (0%)</td>
<td>0.164</td>
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</table>

Red Flag symptoms of MPNSTs/infiltrative tumors:
- Pain
- Rapid growth
- Neurological deficits
Feature Extraction

- Quantitative Imaging Feature Pipeline (Stanford, Napel)
- Upload NifTI segmentations
- Pyradiomics Package: 900 standardized features
Feature Selection – Preliminary Model

1. LASSO
   - 70:30 Train Test Split
   - R, glmnet-package
   - 10x Cross Validation
   - 1000 cycles

2. Preliminary model
   - 80% selection
   - 21 Features (from 900)
     › 19 Textural
     › 2 Clinical

3. Error Reduction

1. 900 Initial Features
   - First Order Statistics (19 features)
   - Shape-based (3D) (16 features)
   - Shape-based (2D) (10 features)
   - Gray Level Cooccurrence Matrix (24 features)
   - Gray Level Run Length Matrix (16 features)
   - Gray Level Size Zone Matrix (16 features)
   - Neighbouring Gray Tone Difference Matrix (5 features)
   - Gray Level Dependence Matrix (14 features)

2. 21 Selected Features
   1. Intercept
   2. log-sigma-5-mm-3D_glim_RunLengthNonUniformity
   3. wavlet-HLS_glim_MaximumProbability
   4. wavlet-HLS_glim_RunVariance
   5. original_shape_MaximumCircumference
   6. original_glim_RunEmphasis
   7. original_shape_Maximum2DCircumference
   8. log-sigma-5-mm-3D_glim_GrayLevelNonUniformity
   9. Energy
   10. log-sigma-5-mm-3D_interborder_Skewness
   11. log-sigma-5-mm-3D_interborder_Max
   12. wavlet-HLS_glim_LargeAreaLargeGrayLevelEmphasis
   13. log-sigma-3-mm-3D_interborder_Energy
   14. wavlet-HLS_interborder_Energy
   15. log-sigma-3-mm-3D_interborder_TotalEnergy
   16. original_interborder_TotalEnergy
   17. wavlet-HLS_interborder_TotalEnergy
Feature Selection – Optimized Model

- Imaging Segmentation
- Clinical data collection

- Feature
  › Extraction
  › Selection
  › Optimization
    • caret package
    • 21 features, ranked

- Prediction Analysis
Goal: Develop a binary classifier (Malignant/Benign) with MRI

- Background:
- Methods:
- Results
  - 1. Texture + Clinical
  - 2. Texture Only
  - 3. Clinical Only
  - 4. Comparison to Human
- Future Directions
1. Clinical + Texture: AUCs

**Receiver Operating Curve for Training Set**

- Sensitivity (True Positive Rate)
- AUC = 0.940

**Receiver Operating Curve for Test Set**

- Sensitivity (True Positive Rate)
- AUC = 0.845
2. Comparison to Human Readers

- Two of each training level
  - Two trials
    - 1. Imaging + Clinical
    - 2. Imaging only
  - Imaging:
    - T1W, post-gad, fat-sat +
    - T2W or proton-density images, when available

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<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
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<td>0.775</td>
<td>0.538</td>
<td>0.752</td>
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<tr>
<td>PN Surgery Fellow</td>
<td>0.625</td>
<td>0.814</td>
<td>0.648</td>
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<tr>
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<td>0.821</td>
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<td>0.575</td>
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<td>0.839</td>
<td>0.676</td>
<td>0.588</td>
<td>0.896</td>
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<td>0.684</td>
<td>0.742</td>
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<td>AUC</td>
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Conclusions and Limitations

- Radiomics Classifier Outperforms Human readers

- Radiomics
  - Sensitivity 0.676
  - Specificity 0.882

- Humans
  - Sensitivity 0.839
  - Specificity 0.686

- Imaging Availability
  - Axial view only
  - T1W only
  - Acquisition technique: fat saturation, contrast quality

- Patient heterogeneity: brachial plexus, arm, wrist

- Segmentation vs Semantics
Semantics not captured by segmentations

BPNST: Neurofibroma
  - Target sign

BPNST: Schwannoma
  - Split fat sign

MPNST
  - Absent split fat sign

MPNST
  - Perilesional edema

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