Head and Neck Cancer: The Pain Experience

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Pain Management in 2018: Tug-of-War
Pain Control: The Arguments in Favor

- Aggressive pain control may prevent progression to chronicity
- Review
  - Ji RR et al. Neuroinflammation and Central Sensitization in Chronic and Widespread Pain Anesthesiology, 2018
Impact of Uncontrolled Pain:

• Physical:
  – Chronic activation of the HPA axis and increased sympathetic tone
  – Central sensitization with the development of symptom complex that impact QOL (fatigue, depression, Neurocognitive impairment, ect…)
  – Decreased function (family role, work, AIDLs, ADLs)

• Emotional:
  – Total mood disorder with suicidal ideation and attempt
  – Spiritual distress with existential crisis

• Social:
  – Alterations in family interactions
  – Alters support structures with loss of social contacts
  – Financial impact due to medical expenses and loss of work
Pain in Head and Neck Population: Conceptualization

- **Tumor Related:**
  - Primary or recurrent disease
    - Well described syndromes that herald a malignant process

- **Treatment Related:**
  - Modality Specific
    - Surgery
      - Typical acute and chronic post-operative pain
      - Distinct syndromes unique to HNC patients: example - First bite syndrome
    - Radiation
      - Acute toxicities: Mucositis and Dermatitis
      - **Late toxicities: Mucosal sensitivity** and Oseoradionecrosis
    - Chemotherapy
      - Acute toxicities: Mucositis or jaw pain
      - Late toxicities: Peripheral neuropathy
  - **Modality Non-specific:**
    - Infection (such as candidiasis)
    - **Musculoskeletal Pain**
    - **Central Pain**
    - **Neuropathic Pain Syndromes**
Musculoskeletal Impairment
Soft Tissue and Skeletal Impact of Cancer and its Treatment

- Surgical
  - Extirpation of tissue leading to altered function
  - Damage to soft tissues (edema, lymphedema and fibrosis), nerves, vascular supply and bone
- Radiation
  - Acute edema, lymphedema and fibrosis leads to loss of integrity and function of tissues within the radiation field
- Treatment induced sarcopenia
  - Muscle mass loss with associated weakness
- Fatigue
  - Decreased capacity for activity with associated deconditioning
- Postural changes
  - Multidimensional in etiology
  - Can exacerbate musculoskeletal issues
  - Impact swallowing and increasing aspiration
  - Decrease respiratory capacity – restrictive lung disease
Extracellular matrix deposition

Direct DNA damage

Fibroblastic recruitment

Local inflammation

Fibrosis

Host - Genetic predisposition

Systemic inflammation and associated systemic symptoms

Lymphatic system structural damage

Interstitial fluid accumulation

Local Inflammation

Lymphangiogenesis

Lymphedema

Clinical Manifestations

Firm skin and soft tissues without swelling

Firmness of Skin and Underlying Tissues

Palpable skin thickening without visible swelling

Reducible tissue swelling

Fibrofatty, non-reducible tissue swelling

Clinical Manifestations

Radiation, surgery, & tumor

Soft Tissue Damage
**Background: Prevalence Mixed Surgical and Radiation Population**

![Pie chart showing prevalence of lymphedema types]

- **None**: 25%
- **External**: 7%
- **Internal**: 30%
- **Both**: 38%

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Prospective, Longitudinal Trial: Prevalence Over Time

- **End-of-Treatment:**
  - 91.6% (76 of 83) of the patients had late-effect external lymphedema
  - 93.1% (67 of 72) had late-effect internal lymphedema
  - 83.1% (69 of 83) had late-effect fibrosis.

- **Lymphedema across the trajectory:**
  - 100% had some indication of external lymphedema, internal lymphedema, or fibrosis between 3- and 18-months post-treatment.
Biomarker Analysis:

- For each biomarker a two-group solution demonstrated the best fit for the data.
- Tested the likelihood that patients in a biomarker group were in a specific lymphedema/fibrosis group.
- Biomarker AUC and lymphedema/fibrosis trajectory.
Examples:

- **Il-6**:
  - Regulates adipose tissue
  - Plays a role in human lymphedema
  - Active in collagen production

- **Il-1β**
  - Pro-inflammatory cytokine that is up-regulated by radiation
  - Associated with radiation induced skin fibrosis

- **TNF-α**
  - Produced as a response to radiation
  - Correlates with pulmonary fibrosis
### Biological Correlatives: AUC

<table>
<thead>
<tr>
<th></th>
<th>External LE</th>
<th></th>
<th>Internal LE</th>
<th></th>
<th>Fibrosis</th>
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<tbody>
<tr>
<td></td>
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<td>MS</td>
<td>P-value</td>
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<td>MS</td>
<td>P-value</td>
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<td>AUC</td>
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<td>IL-10</td>
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<td>4.76</td>
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<td>IL-1β</td>
<td>0.11</td>
<td>0.57</td>
<td>&lt;0.001</td>
<td>0.11</td>
<td>0.54</td>
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<td>0.38</td>
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<tr>
<td>IL-6</td>
<td>12.8</td>
<td>24.0</td>
<td>0.001</td>
<td>12.3</td>
<td>23.4</td>
<td>0.002</td>
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<td>18.4</td>
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<tr>
<td>IL-8</td>
<td>127.4</td>
<td>141.2</td>
<td>0.041</td>
<td>127.8</td>
<td>135.9</td>
<td>0.651</td>
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<td></td>
<td>131.8</td>
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<tr>
<td>MMP-9</td>
<td>0.90</td>
<td>1.21</td>
<td>0.03</td>
<td>1.01</td>
<td>1.22</td>
<td>0.443</td>
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<td></td>
<td></td>
<td>1.01</td>
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<td>TGF-β2</td>
<td>11162</td>
<td>12138</td>
<td>0.303</td>
<td>14968</td>
<td>11293</td>
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<tr>
<td>TNF-α</td>
<td>17.5</td>
<td>25.7</td>
<td>&lt;0.001</td>
<td>21.6</td>
<td>22.5</td>
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<td></td>
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<td></td>
<td>19.8</td>
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<tr>
<td></td>
<td>External LE</td>
<td>Internal LE</td>
<td>Fibrosis</td>
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<td>IL-10</td>
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<td><img src="image2.png" alt="Graph" /></td>
<td><img src="image3.png" alt="Graph" /></td>
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<tr>
<td>IL-12p70</td>
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<td><img src="image5.png" alt="Graph" /></td>
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<td><img src="image8.png" alt="Graph" /></td>
<td><img src="image9.png" alt="Graph" /></td>
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<td>IL-6</td>
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<td><img src="image12.png" alt="Graph" /></td>
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<tr>
<td>IL-8</td>
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<td><img src="image15.png" alt="Graph" /></td>
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</tr>
</tbody>
</table>
• Correlation between TNF-α trajectory and the severity of external LE and fibrosis
Impact:
Why do we care about LEF?
Lymphedema Symptom Intensity and Distress Survey-Head & Neck (LSIDS-H&N sample)

Instructions: Please read each of the symptoms and circle yes or no to indicate whether you have had this symptom over the past week. If you circle yes, please indicate the severity of this symptom and the bother of this symptom.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes/No</th>
<th>Severity</th>
<th>Bother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling uncomfortable in your head or neck</td>
<td>Yes</td>
<td>Slight</td>
<td>Slight</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Heaviness</td>
<td>Yes</td>
<td>Slight</td>
<td>Slight</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Tightness</td>
<td>Yes</td>
<td>Slight</td>
<td>Slight</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Firmness or hardness of your skin</td>
<td>Yes</td>
<td>Slight</td>
<td>Slight</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Stiffness</td>
<td>Yes</td>
<td>Slight</td>
<td>Slight</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>
Manifestations: LSIDS-H&N
Most Common Complaints

- Feeling *uncomfortable* in head and neck
- Tightness
- Firm or hard skin
- Stiffness
- Tenderness
- Limited movement
- Problems swallowing
- Voice changes
- Something stuck in throat
- Feeling tired
- People staring at me

## Symptom Prevalence Differences ($p < 0.05$)

<table>
<thead>
<tr>
<th>Frequency of Symptoms</th>
<th>LE (%) (N=23)</th>
<th>No LE (%) (N=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Altered Sensation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness of the face/neck skin</td>
<td>34.8</td>
<td>8.7</td>
<td>0.032</td>
</tr>
<tr>
<td>Heaviness of the face/neck skin</td>
<td>21.7</td>
<td>0.0</td>
<td>0.018</td>
</tr>
<tr>
<td>Warmth of the face/neck skin</td>
<td>17.4</td>
<td>0.0</td>
<td>0.036</td>
</tr>
<tr>
<td>Pain without head/neck movement</td>
<td>17.4</td>
<td>0.0</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Neck – Shoulder Musculoskeletal/Skin Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling in face</td>
<td>17.4</td>
<td>0.0</td>
<td>0.036</td>
</tr>
<tr>
<td>Swelling in neck</td>
<td>21.7</td>
<td>0.0</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Head and Neck-Specific Functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problems swallowing mashed food</td>
<td>39.1</td>
<td>9.1</td>
<td>0.019</td>
</tr>
<tr>
<td>Trouble breathing</td>
<td>26.1</td>
<td>0.0</td>
<td>0.009</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>21.7</td>
<td>0.0</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Systemic Symptom</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel worse when flying in airplane</td>
<td>25.0</td>
<td>0.0</td>
<td>0.017</td>
</tr>
</tbody>
</table>
Assessment of musculoskeletal impairment in head and neck cancer patients

- Goal: Assess long term symptom burden in HNC patients treated with surgical resection and flap reconstruction with emphasis on neck, shoulder, jaw disability and pain

- Study design:
  - Cross sectional study of 29 HNC patient treated with resection and either a free flap or pectoral flap repair
  - Tools:
    - Subjective measures: NDI, SPDI, VHNSS
    - Objective measures: CROM and ICD

- Results:
  - 69% experience neck disability
  - 35% experience shoulder pain
  - Decreased CROM was noted in all directions
  - Digital photography identified shoulder misalignment in 93%, head tilt in 89% and postural deviations in 68%

Soft Tissue Complications: A Composite Cause of Pain
Radiation Induced Oro-Mandibular Dystonia

- Characterized by masseter muscle pain, cramping and spasm
  - Similar presentation to sternoclydomastoid cramping
  - May present simultaneously with trismus
- Pathophysiology is unknown
  - EMG data suggested related to nerve or motor neuron etiology
  - MRI data showing radiation induced lesions in pons and medulla oblanga suggest a central process
- Botulinum toxin therapy may effectively palliate this syndrome

Myofascial Pain In Post Treatment Head and Neck Cancer Patients:

• Patient Population:
  – 167 patients completed treatment for HNC

• Results:
  – 96 (57.4%) reported pain
  – 20 (11.9%) reported myofascial pain
  – Trapezius was most commonly affected (80% of those affected)
  – Pain level ≥ 4 in 43 patients (44.8% reporting pain)
  – Risk factors from multivariate analysis:
    • Hypopharyngeal primary OR 6.35; (95% CI 1.58-25.56)
    • Neck dissection OR 3.43; CI 1.16-10.17

Trigger Points within the Head and Neck Region
Transition: Acute to Chronic Pain Syndrome

• Tumor and treatment result in a pro-inflammatory state with elevated levels of cytokines and chemokines
• Transduction of signal to the central nervous system with resultant neuroinflammation
• Peripheral and central neuroinflammation results in activation of glial cells in spinal cord and brain
• Promotes widespread pain through central sensitization
Central or Inflammatory Pain:

• Defined:
  – Central disturbance in pain processing

• Mechanism:
  – Generalized central augmentation or amplification of sensory stimuli
  – Attenuation of descending anti-nociceptive pathways
Central Pain:

- **Characteristics:**
  - Diffuse/multifocal hyperalgesia and allodynia
  - Not in distribution of known tissue damage
  - Associated with other systemic symptoms
  - Responds to neuroactive compounds directed at neurotransmitters involved in pain transmission

- **Predisposition:**
  - Genetic predisposition
    - 1st degree relatives with fibromyalgia are at 8-folder greater risk for FM
  - Environmental stressors may trigger development of central pain states
    - Early life emotional trauma, physical trauma, infections, and emotional stress
Criteria for the Diagnosis of Fibromyalgia: Modified 2010 American College of Rheumatology Criteria

1. Pain location inventory (PLI): Select from the 28 locations where you have experienced persistent pain during the past 7 days. Your score will be between 0 and 28.

<table>
<thead>
<tr>
<th>Location</th>
<th>Right knee</th>
<th>Left hand</th>
<th>Right arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td></td>
<td>Right knee</td>
<td>Left hand</td>
</tr>
<tr>
<td>Left upper back</td>
<td>Left jaw</td>
<td>Right ankle</td>
<td>Left hip</td>
</tr>
<tr>
<td>Right wrist</td>
<td>Left lower back</td>
<td>Front of chest</td>
<td>Right foot</td>
</tr>
<tr>
<td>Left thigh</td>
<td>Right hand</td>
<td>Left shoulder</td>
<td>Right upper back</td>
</tr>
<tr>
<td>Right jaw</td>
<td>Left knee</td>
<td>Right hip</td>
<td>Left arm</td>
</tr>
<tr>
<td>Right lower back</td>
<td>Mid-upper back</td>
<td>Left ankle</td>
<td>Right thigh</td>
</tr>
<tr>
<td>Left wrist</td>
<td>Right shoulder</td>
<td>Mid-lower back</td>
<td>Left foot</td>
</tr>
</tbody>
</table>

2. 10-item Symptom Impact Questionnaire (SIQR) symptoms: For each of the following 10 questions, check the one box that best indicates the intensity of the following common symptoms over the last 7 days. (Total the score by adding the degree of severity 0 – 10 for each symptom (0-100) and divide the sum by 2 to obtain the SIQR symptom score)

<table>
<thead>
<tr>
<th>Symptom</th>
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<th>2</th>
<th>3</th>
<th>4</th>
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<th>6</th>
<th>7</th>
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<td>Energy</td>
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<td>Stiffness</td>
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<tr>
<td>Sleep</td>
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<td>10</td>
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<tr>
<td>Memory problems</td>
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<td>10</td>
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<tr>
<td>Tenderness to touch</td>
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<td>10</td>
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<td>Balance problems</td>
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<td>Sensitivity</td>
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<td></td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

A patient fulfilling the following guidelines has a high likelihood of having FM
1. The symptoms and pain locations have been persistent for at least the last 3 months
2. Pain location score is > 17
3. SIQR symptom score is > 21
Prevalence of Chronic Systemic Symptoms
VHNSS 2.0-GSS

VHNSS General Symptom Survey

- Unexplained Fatigue
- Fatigue limits Activity
- Problems falling Asleep
- Problems staying Asleep
- Unexplained Sweating
- Cold
- Hot
- Memory Trouble
- Joint/Muscle Aches
- Sad
- Anxiety

Legend:
- None
- Mild
- Moderate/Severe
Neuropathic Pain

I took a pain pill....

Why are you still here??
Mucosal Sensitivity:

- Develops in patients with clinically significant radiation mucositis
- Manifestation:
  - Burning mucosal pain
  - Worsened with dryness, spiced or acid foods
- Postulated Mechanism:
  - Sensitization of peripheral nociceptors secondary to pro-inflammatory cytokines released by tissues
- Characteristics:
  - Can last for protracted periods of time
  - **May alter food choices indefinitely**
  - Does not respond well to opioids
  - May respond to topical agents such as lidocaine (acts on Na+ channels) or ketamine (NMDA inhibitor)
## VHNSS vs 2.0
### Tool Development Data

<table>
<thead>
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<th>Question</th>
<th>Number of Patients</th>
<th>≥ 1</th>
<th>≥ 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning in lining of throat or mouth</td>
<td>69</td>
<td>46.4</td>
<td>23.2</td>
</tr>
<tr>
<td>Sensitive to hot, spicy or acid food</td>
<td>67</td>
<td>80.6</td>
<td>58.2</td>
</tr>
<tr>
<td>Sensitive to dryness</td>
<td>69</td>
<td>85.5</td>
<td>60.9</td>
</tr>
<tr>
<td>Changes in food intake</td>
<td>67</td>
<td>61.2</td>
<td>43.3</td>
</tr>
<tr>
<td>Prevents teeth brushing</td>
<td>63</td>
<td>17.5</td>
<td>11.1</td>
</tr>
</tbody>
</table>
Metallic Taste Phantoms and Mucosal Sensitivity:

- **Methods:**
  - 100 5-yr HNC survivors treated with RT compared to 100 matched controls
  - **Measures:**
    - Single item taste question – presence of metallic taste for no reason
    - co-morbid disease, tumor characteristics, QOL, oral pain, depression, anxiety and tobacco use
  - **Results:**
    - 43% of patients reported oral pain
    - Hierarchical regression analysis testing for predictors of spontaneous pain
    - FACT-HN score (0 = .05) the metallic taste (p = .01) predicted for spontaneous pain.
    - 62% of patients with spontaneous pain had metallic taste

- **Hypothesis:**
  - Taste alterations and oral pain are both pathophysiologically linked by underlying neural damage

Logan HL, Pain, 2008
Oral Pain in Head and Neck Cancer:

- Logan HL, J Pain: 2010
  - Current smokers report higher spontaneous and function oral pain as well as pain related interference (p value’s < .001)

- Mercer ME, Physiology and Behavior, 1997
  - Ingestion of sweet food is associated with increased pain tolerance
    - Thought to be due to stimulation of opioid activity
Brachial Plexus-Associated Neuropathy after High-dose Radiation in HNC

- **Population:**
  - 330 pts treated with RT for HNC
    - 155 (47%) primary RT; 175 (53%) Adjuvant RT
  - Median time from completion 56 months

- **Results:**
  - 12% reported neuropathic symptoms:
    - Ipsilateral pain 50%
    - Numbness/tingling 40%
    - Muscle atrophy 25%

- **Predictors:**
  - Neck dissection (p<0.01)
  - Radiation dose (p<0.001)

Tolerance of the Brachial Plexus to High-Dose Reirradiation

- **Freedom from plexopathy:**
  - **Low risk:**
    - > 2 years between treatment courses and Dmax < 96 Gy
  - **Intermediate-risk:**
    - <2 years between treatment courses or Dmax > 95 Gy
  - **High Risk:**
    - Both < 2 years between treatment courses and Dmax > 95 Gy

Chen AM, IJROBP, Vol98, Issue 1, 2017, 83-90
Trigeminal Nerve Involvement:

- Both sensory and motor components
- Clinical presentation varies based on site of involvement
  - Peripheral:
    - Pain, paresthesia and analgesia in the distribution of involved nerve
  - Central:
    - Example: cavernous sinus involvement
    - Ophthalmoplegia, mydriasis, proptosis and CV III, V1, V2 and VI deficits.
- Increasing incidence with increase in number of patients with squamous cell cancers involving pre-auricular lymph nodes
Glossopharyngeal Neuralgia: Cranial Nerve IX

- Mixed function including motor and sensory to the tongue and pharynx
- Pain located in the pharynx, soft palate base of tongue and ear.
Occipital Neuralgia:

- Pain located in the lower neck, occipital region and retro-orbital
Syndromes associated with Skull Base Tumors

• Orbital Syndrome:
  – Frontal headache, diplopia, proptosis and CNVI hyesthesia
• Parasellar syndrome (cavernous sinus syndrome)
  – Frontal headache, diplopia, and CNVI hyesthesia
• Middle fossa syndrome
  – Facial pain or numbness
• Jugular foramen syndrome
  – Hoarseness, dysphagia, paralysis of CN 9-12
• Occipital condyle syndrome
  – Unilateral occipital pain and unilateral tongue paralysis
Complex Cancer Pain

- Requires a multi-modal approach to care
  - Anesthesia Pain
  - Functional Neurosurgery
  - Radiology
  - Radiation Oncology
  - Medical Oncology
  - Physical Therapy
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Impact of QOL and Symptoms on Survival

- **Population:**
  - 109 HNC pts completed curative therapy

- **Results:**
  - QOL and Symptoms predicted survival

- **Survival Predictors:**
  - Physical function
  - General pain
  - Sleep disturbance

Conclusions:

• Pain is prevalent and severe in patients undergoing therapy
• Pain persists for a significant period of time after treatment is completed
• Pain is caused by a variety of mechanisms
• Pain manifests in numerous ways
• Pain is associated with decrease survival
• Growing literature indicates that adequate treatment of symptoms at various points across the trajectory may improve survival
• Aggressive multimodal care is needed to optimize symptom control, function and survival