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

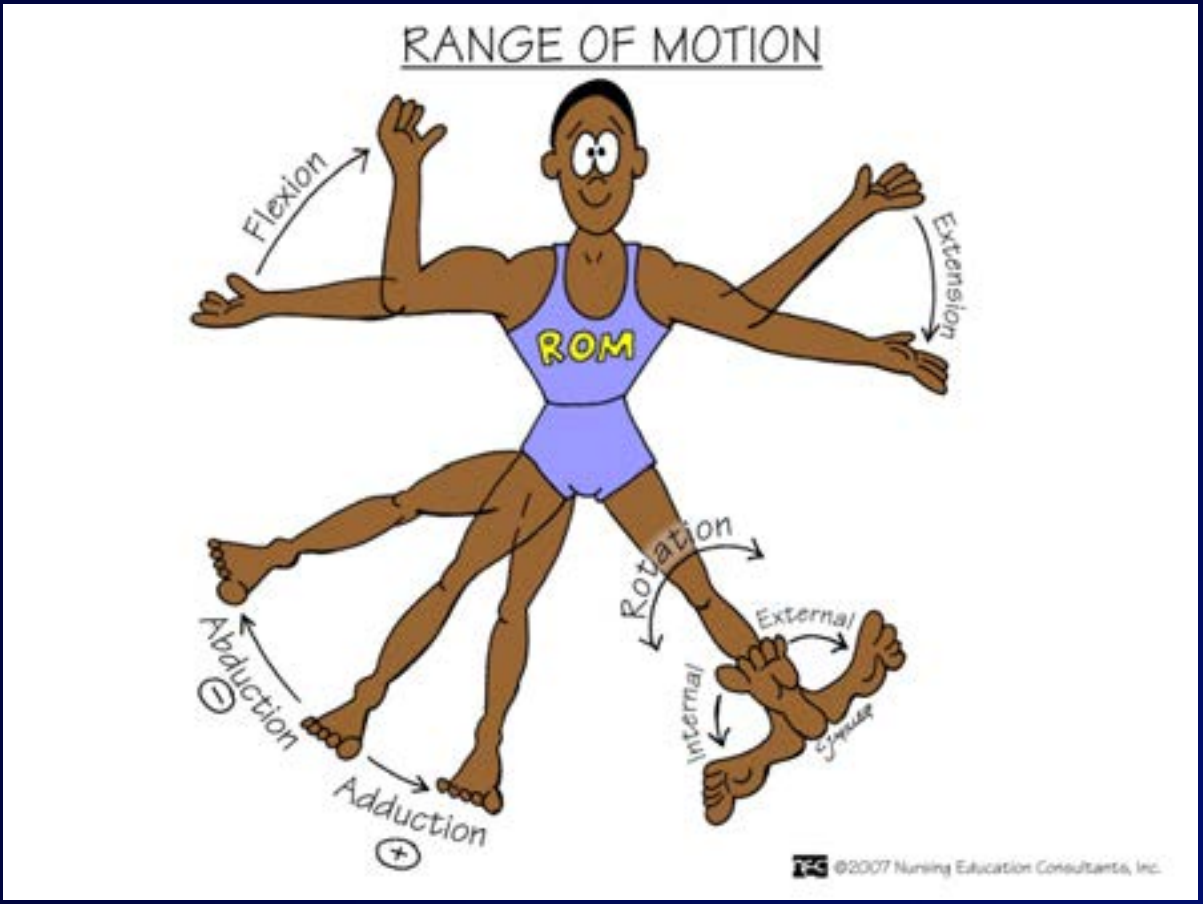
Impact of Uncontrolled Pain:

- 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

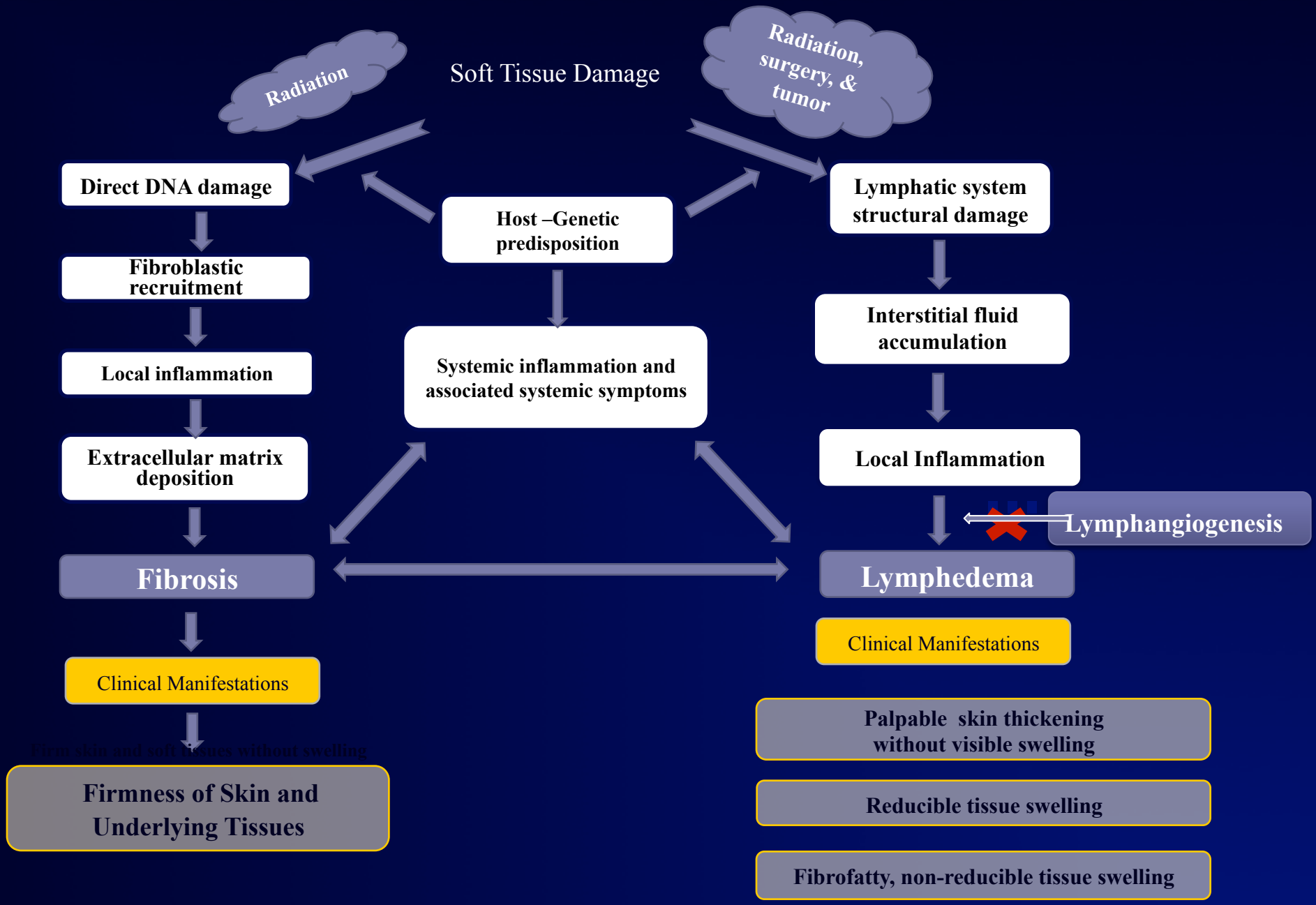
- Tumor Related:
  - Primary or recurrent disease
    - Well described syndromes that herald a malignant process
- Treatment Related:
  - Modality Specific
    - Surgery
      - Typical acute and chronic post-operative pain
      - Distinct syndromes unique to HNC patients: example - First bite syndrome
    - 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

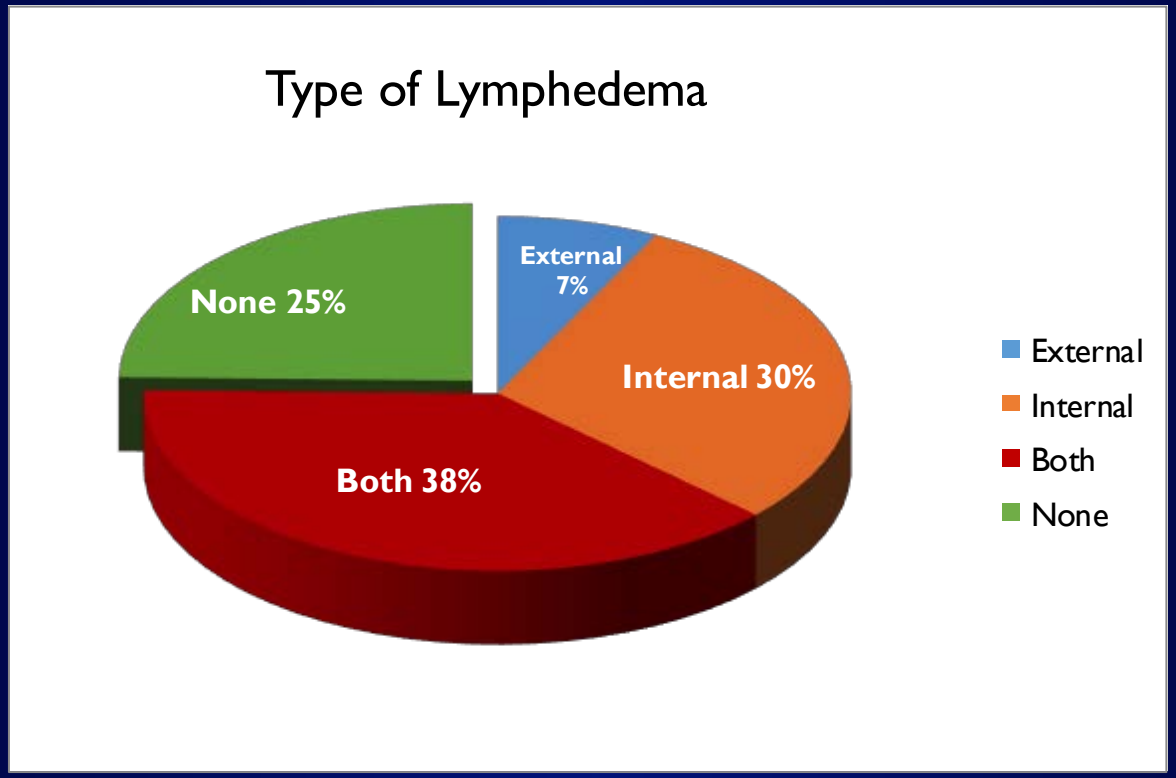


Soft Tissue and Skeletal Impact of Cancer and its Treatment

- 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


Soft Tissue Damage
Radiation
Radiation, surgery, & tumor
Direct DNA damage
Fibroblastic recruitment
Local inflammation
Extracellular matrix deposition
Fibrosis
Clinical Manifestations
Firm skin and soft tissues without swelling
Firmness of Skin and Underlying Tissues
Host –Genetic predisposition
Systemic inflammation and associated systemic symptoms
Lymphatic system structural damage
Interstitial fluid accumulation
Local Inflammation
Lymphangiogenesis
Lymphedema
Clinical Manifestations
Palpable skin thickening without visible swelling
Reducible tissue swelling
Fibrofatty, non-reducible tissue swelling

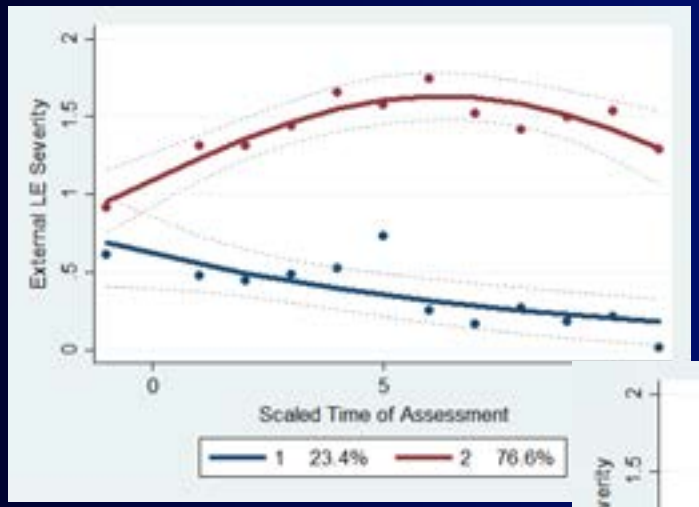
Background: Prevalence
Mixed Surgical and Radiation Population

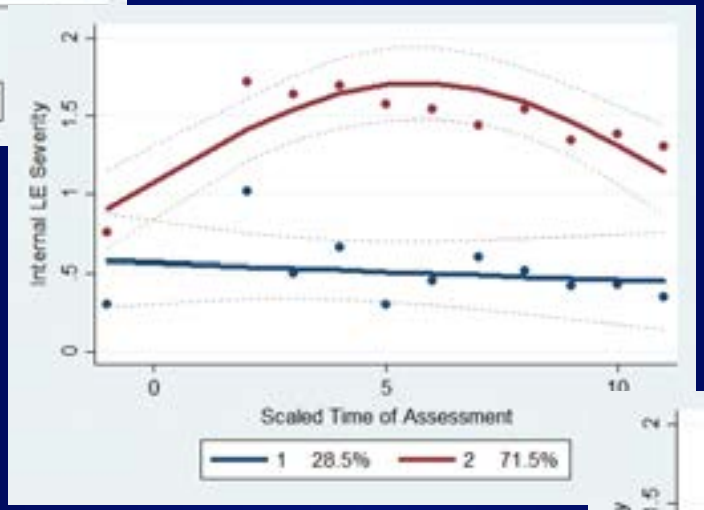


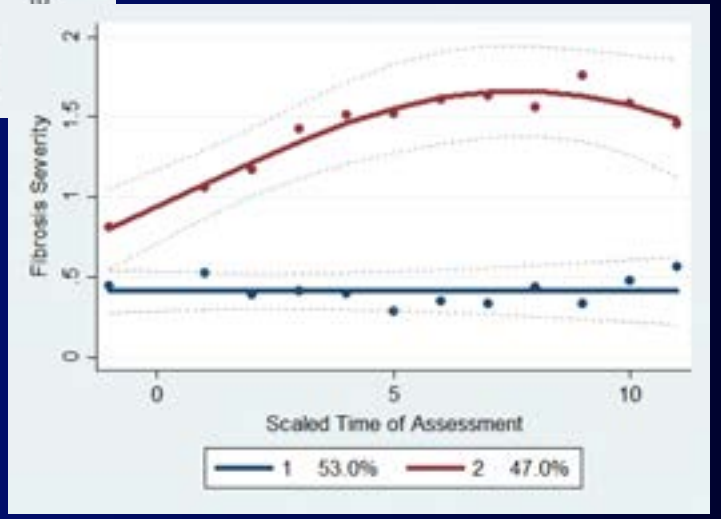
Deng, J. Ridner, S.H., Dietrich, M.S., Wells, N., Wallston, K.A., Sinard, R.J., Cmelak, A.J., & Murphy, B.A. (2012). Prevalence of secondary lymphedema in patients with head and neck cancer. *Journal of Pain and Symptom Management*, *43*(2), 244-252.

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.







Ridner SH, Dietrich MS, Niermann K, Cmelak A, Mannion K, Murphy BA. *A prospective study of lymphedema and fibrosis continuum in patients with head and neck cancer.* Lymphatic Research and Biology.

Biomarker Analysis:

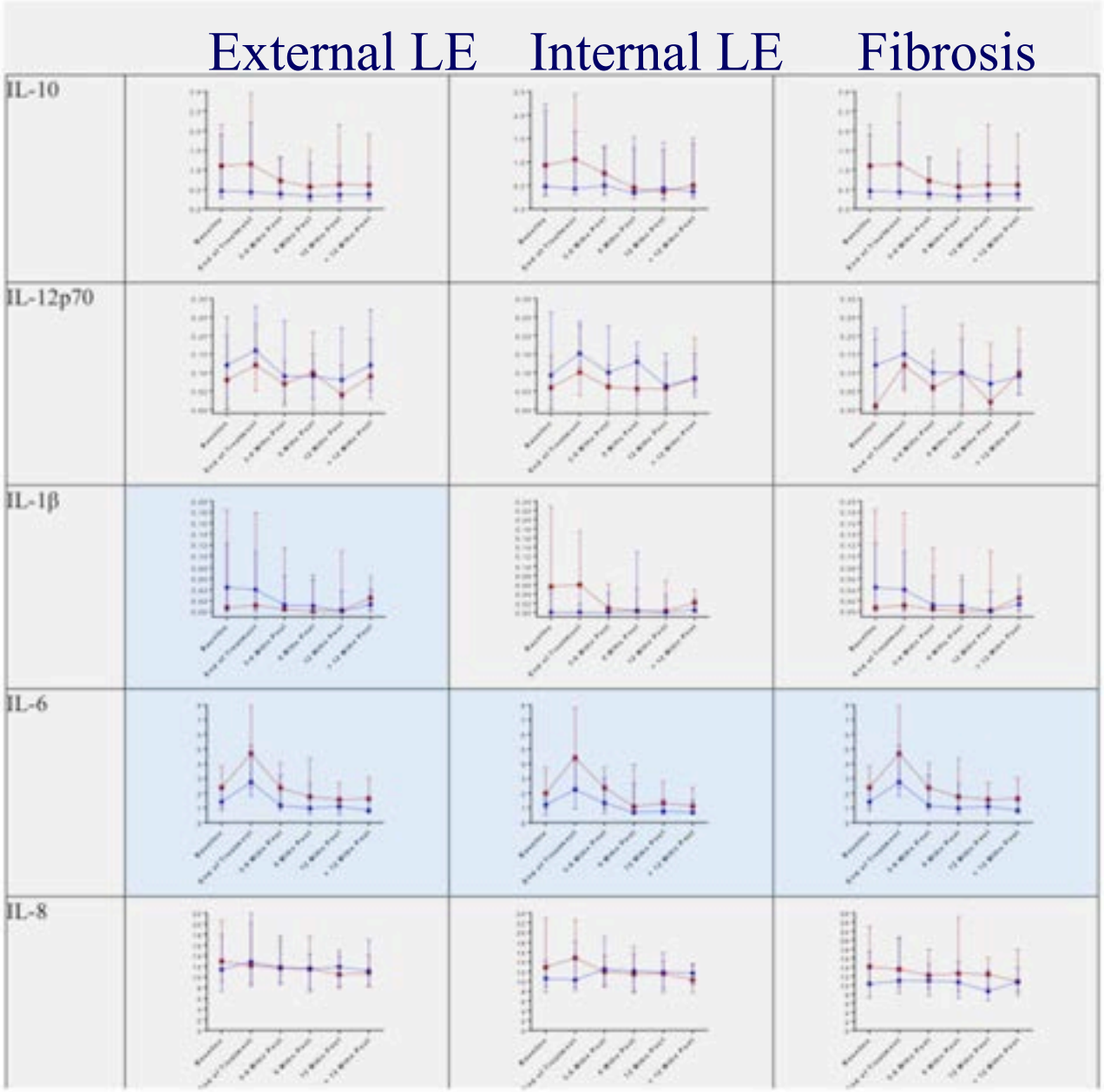
- For each biomarker a two-group solution demonstrated the best fit for the data
- Tested the likely hood that patients in a biomarker group were in a specific lymphedema/fibrosis group
- Biomarker AUC and lymphedema/fibrosis trajectory

Examples:

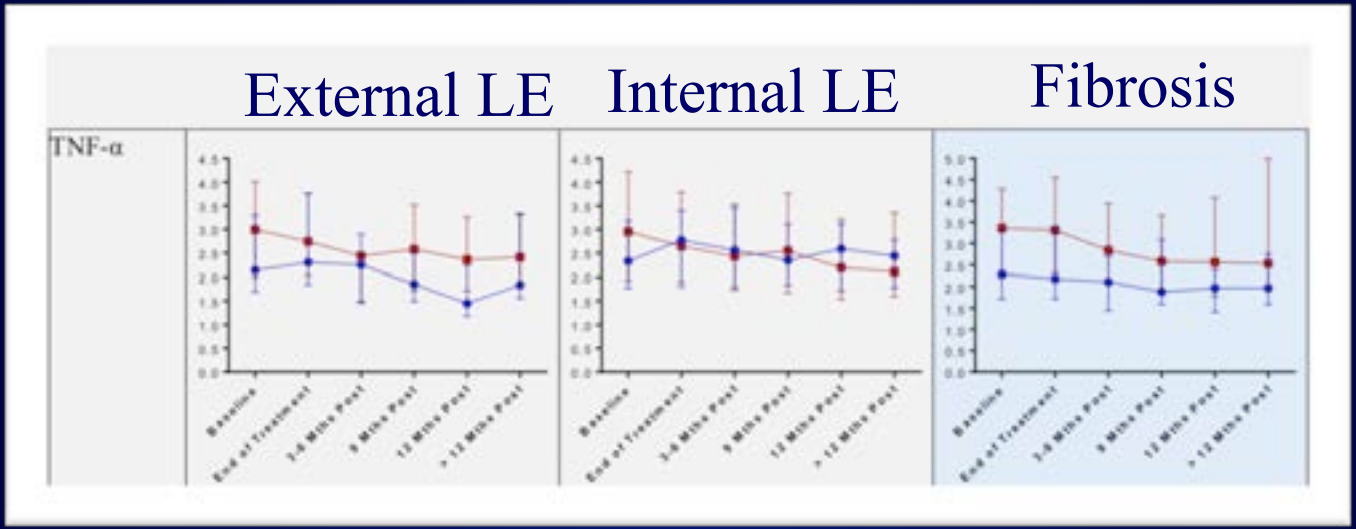
- Il-6:
  - Regulates adipose tissue
  - Plays a role in human lymphedema
  - Active in collagen production
- Il-1β
  - Pro-inflammatory cytokine that is up-regulated by radiation
  - Associated with radiation induced skin fibrosis
- TNF-α
  - Produced as a response to radiation
  - Correlates with pulmonary fibrosis

Biological Correlatives: AUC

	External LE			Internal LE			Fibrosis		
	NM	**MS**	**P-value**	**NM**	**MS**	**P-value**	**NM**	**MS**	**P-value**
	N=19	**N=64**		**N=20**	**N=52**		**N=44**	**N=39**	
	AUC	**AUC**		**AUC**	**AUC**		**AUC**	**AUC**	
IL-10	3.79	8.47	0.052	4.98	8.47	.0697	4.76	9.21	0.020
IL-1β	0.11	0.57	<0.001	0.11	0.54	0.012	0.38	0.60	0.384
IL-6	12.8	24.0	0.001	12.3	23.4	0.002	18.4	28.1	0.097
IL-8	127.4	141.2	0.041	127.8	135.9	0.651	131.8	140.0	0.165
MMP-9	0.90	1.21	0.03	1.01	1.22	0.443	1.01	1.26	0.045
TGF-β2	11162	12138	0.303	14968	11293	0.028	12085	11810	0.715
TNF-α	17.5	25.7	<0.001	21.6	22.5	0.850	19.8	27.4	0.003


External LE
Internal LE
Fibrosis
IL-10
IL-12p70
IL-1β
IL-6
IL-8

TNF-α



- 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.

Over the past week have you had the following symptoms in *your head and neck:*

Symptom	Yes/No	Severity	Bother
1. Feeling uncomfortable in your head or neck	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
2. Heaviness	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
3. Tightness	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
4. Firmness or hardness of your skin	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
5. Stiffness	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe

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

Deng, J., Murphy, B.A., Dietrich, M.S., Sinard, R.J., Mannion, K., & Ridner, S.H. (2015). Differences of symptoms in head and neck cancer patients with and without lymphedema. *Supportive Care in Cancer*. [Epub ahead of print]

Symptom Prevalence Differences ($p < 0.05$)

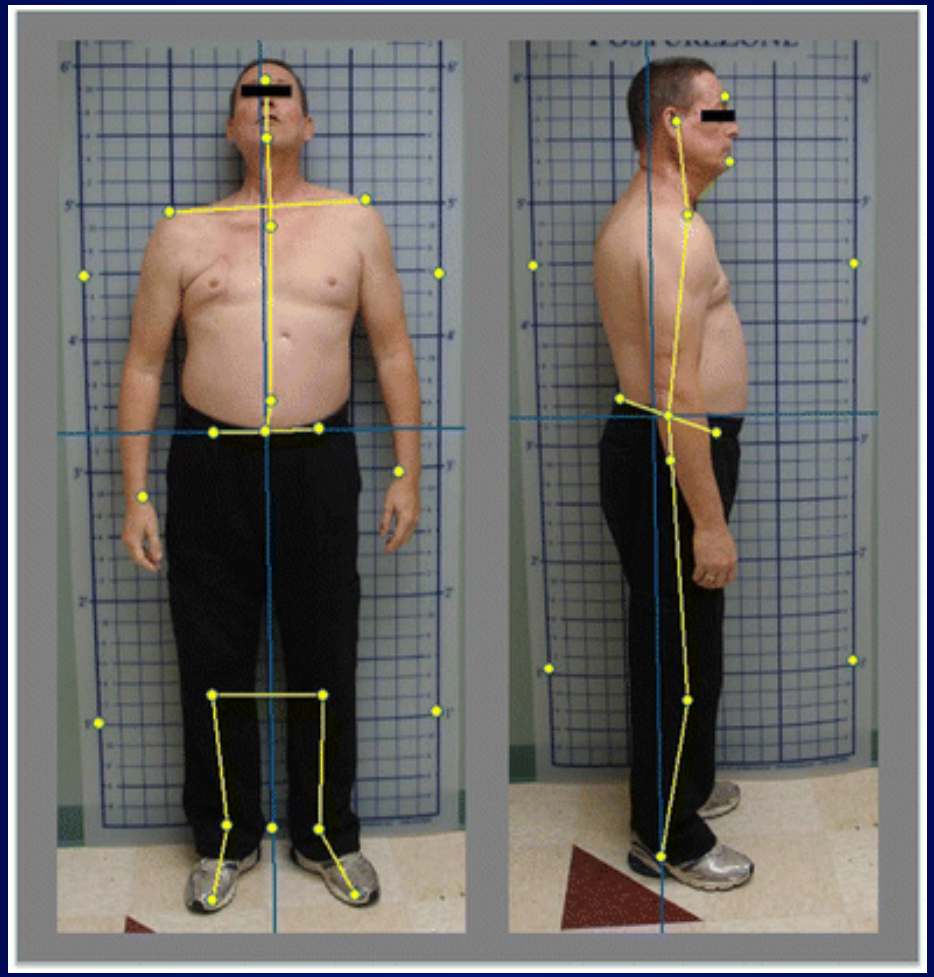
Frequency of Symptoms	LE (%) (N=23)	No LE (%) (N=23)	*p-value*
Altered Sensation			
Numbness of the face/neck skin	34.8	8.7	0.032
Heaviness of the face/neck skin	21.7	0.0	0.018
Warmth of the face/neck skin	17.4	0.0	0.036
Pain without head/neck movement	17.4	0.0	0.036
Neck – Shoulder Musculoskeletal/Skin Symptoms			
Swelling in face	17.4	0.0	0.036
Swelling in neck	21.7	0.0	0.018
Head and Neck-Specific Functioning			
Problems swallowing mashed food	39.1	9.1	0.019
Trouble breathing	26.1	0.0	0.009
Blurred vision	21.7	0.0	0.018
Systemic Symptom			
Feel worse when flying in air plane	25.0	0.0	0.017

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%

Ghiam, M.K., Mannion, K., Dietrich, M.S. et al. Support Care Cancer (2017) 25: 2085. https://doi.org/10.1007/s00520-017-3603-1

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

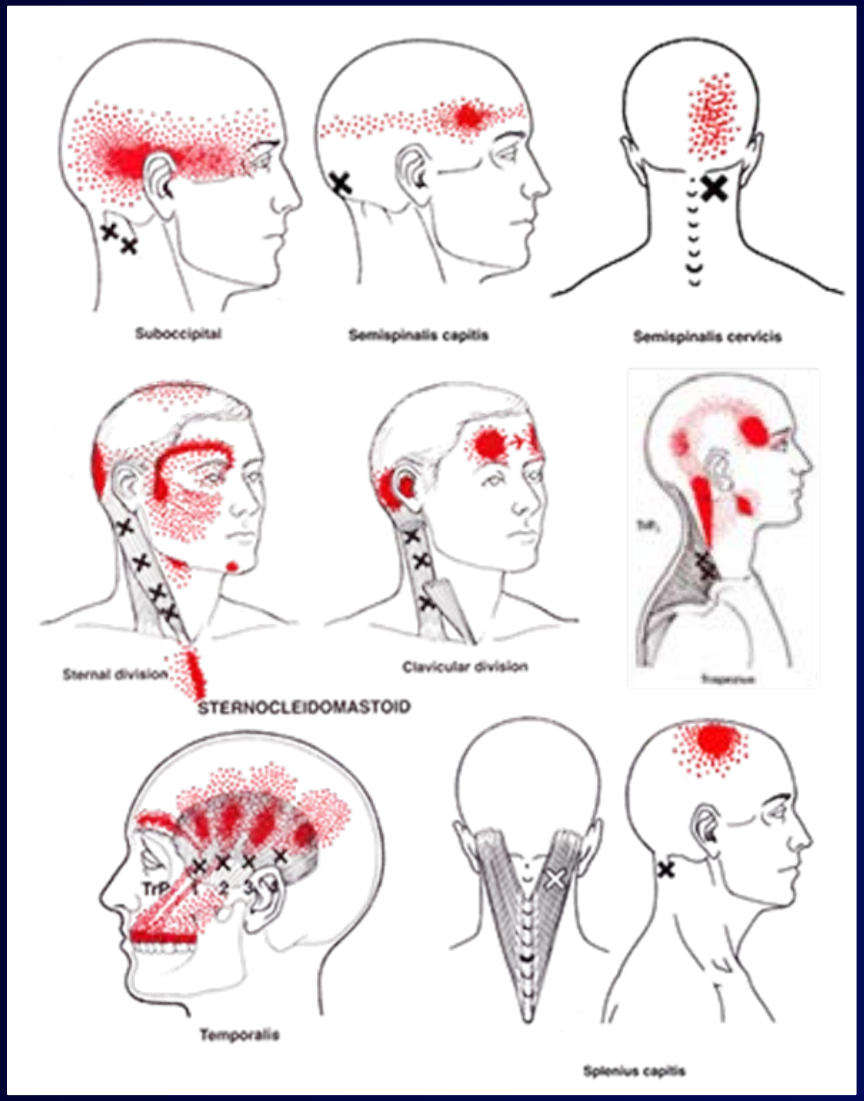
Stubblefield M et al; Arch Phys Med Rehabil. 2008 Mar;89(3):417-21. doi: 10.1016/j.apmr.2007.11.022.

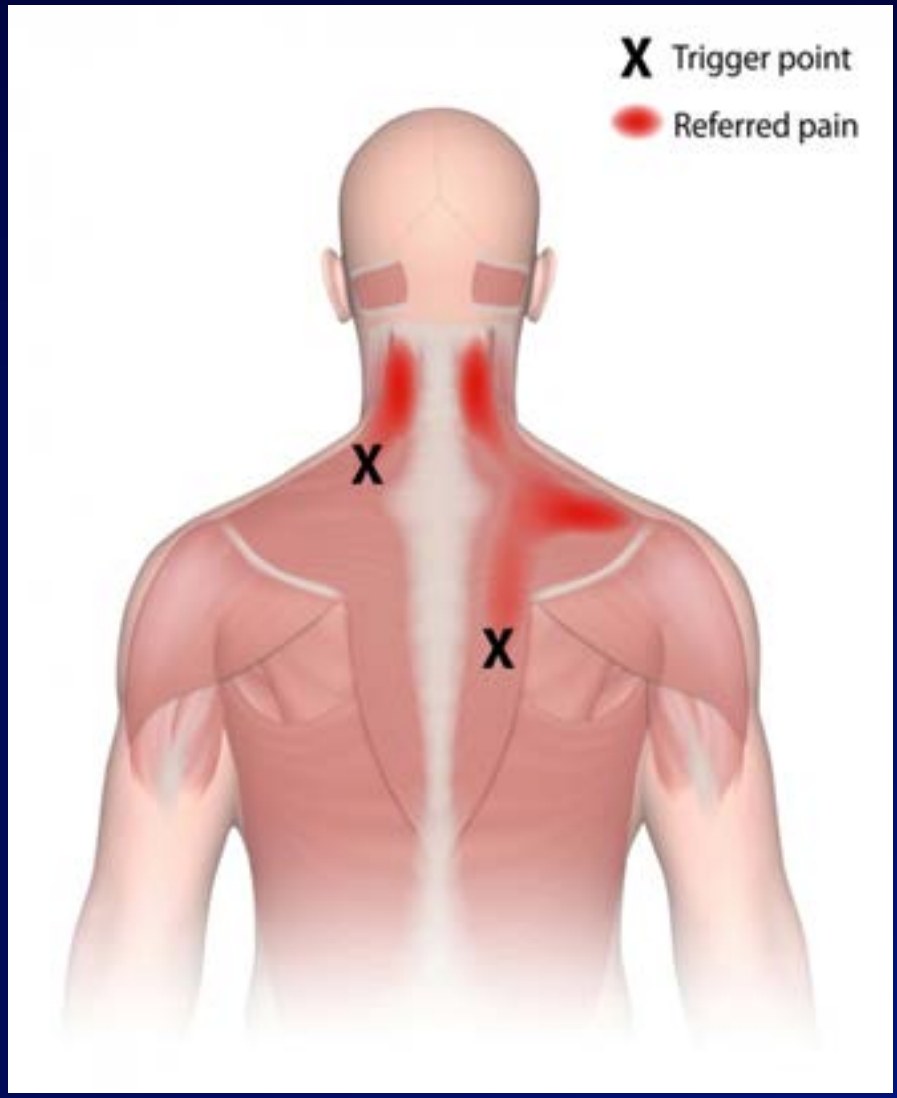
Myofascial Pain In Post Treatment Head and Neck Cancer Patients:

- 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

Cardoso LR et al Head Neck. 2015 Dec;37(12):1733-7. doi: 10.1002/hed.23825. Epub 2014 Sep 25.

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

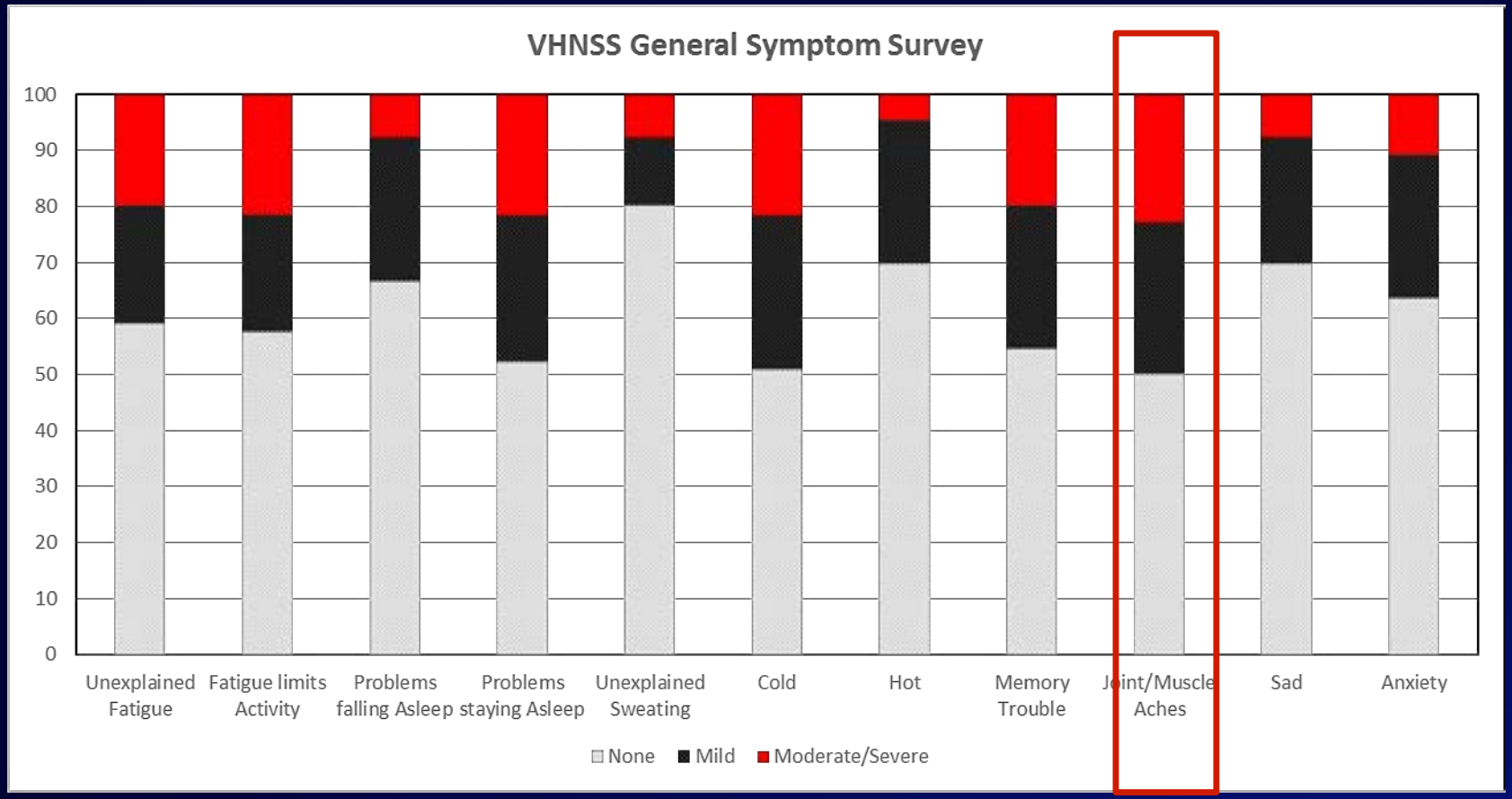
Criteria for the Diagnosis of Fibromyalgia: Modified 2010 American College of Rheumatology Criteria

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.			
Neck	Right knee	Left hand	Right arm
Left upper back	Left jaw	Right ankle	Left hip
Right wrist	Left lower back	Front of chest	Right foot
Left thigh	Right hand	Left shoulder	Right upper back
Right jaw	Left knee	Right hip	Left arm
Right lower back	Mid-upper back	Left ankle	Right thigh
Left wrist	Right shoulder	Mid-lower back	Left foot

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)	
Pain	0 1 2 3 4 5 6 7 8 9 10
Energy	0 1 2 3 4 5 6 7 8 9 10
Stiffness	0 1 2 3 4 5 6 7 8 9 10
Sleep	0 1 2 3 4 5 6 7 8 9 10
Depression	0 1 2 3 4 5 6 7 8 9 10
Memory problems	0 1 2 3 4 5 6 7 8 9 10
Anxiety	0 1 2 3 4 5 6 7 8 9 10
Tenderness to touch	0 1 2 3 4 5 6 7 8 9 10
Balance problems	0 1 2 3 4 5 6 7 8 9 10
Sensitivity	0 1 2 3 4 5 6 7 8 9 10

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



Neuropathic Pain

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

Question	Number of Patients	≥ 1	≥ 4
Burning in lining of throat or mouth	69	46.4	23.2
Sensitive to hot, spicy or acid food	67	80.6	58.2
Sensitive to dryness	69	85.5	60.9
Changes in food intake	67	61.2	43.3
Prevents teeth brushing	63	17.5	11.1

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**

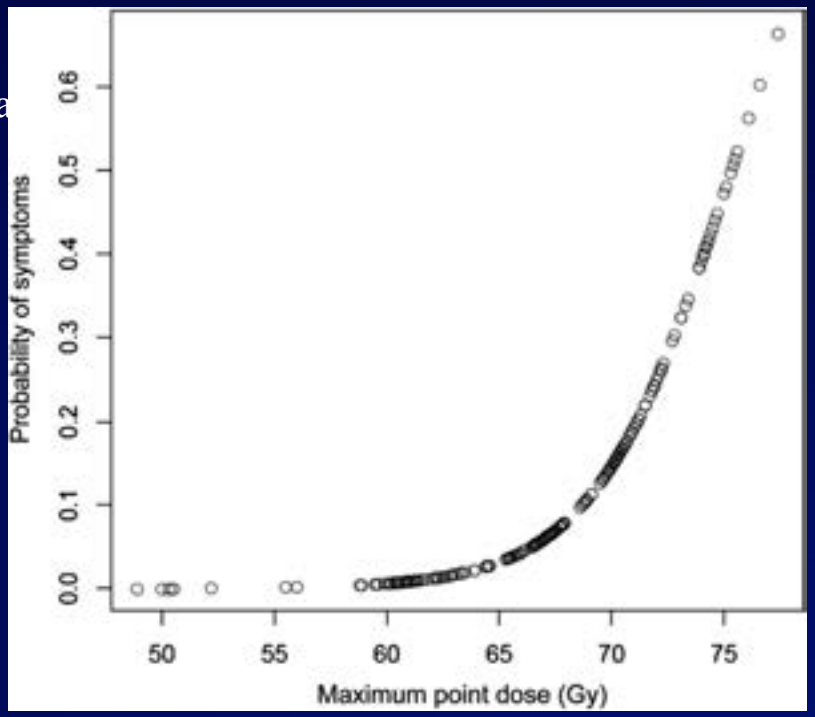
Logan HL, Pain, 2008

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

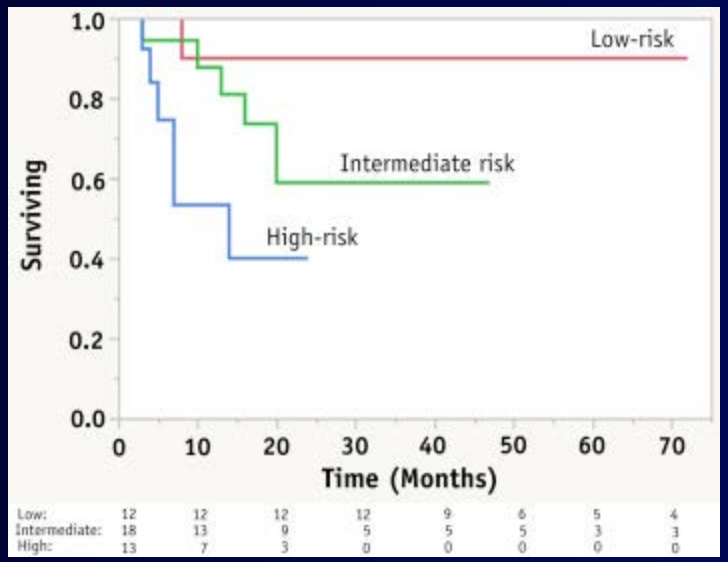
- Population:
  - 330 pts treated with RT for HNC
    - 155 (47%) primary RT; 175 (53% Adjuva RT)
  - Median time from completion 56 months
- Results:
  - 12% reported neuropathic symptoms:
    - Ipsilateral pain 50%
    - Numbness/tingling 40%
    - Muscle atrophy 25%
- Predictors:
  - Neck dissection ($p<0.01$)
  - Radiation dose ($p<0.001$)

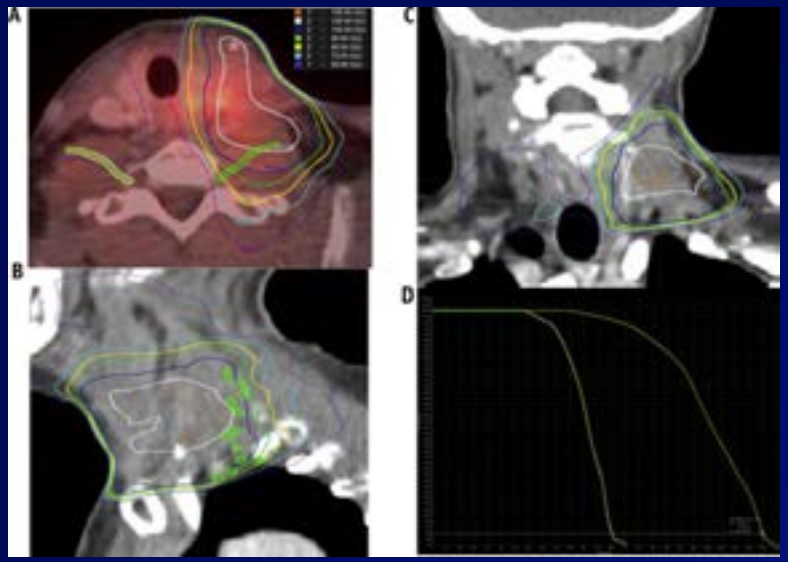


Chen AM et al, Int J Radiat Oncol Biol Phys. 2012 Sep 1;84(1):165-9. doi: 10.1016/j.ijrobp.2011.11.019. Epub 2012 Mar 22.

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 < 2years between treatment courses and Dmax >95 Gy

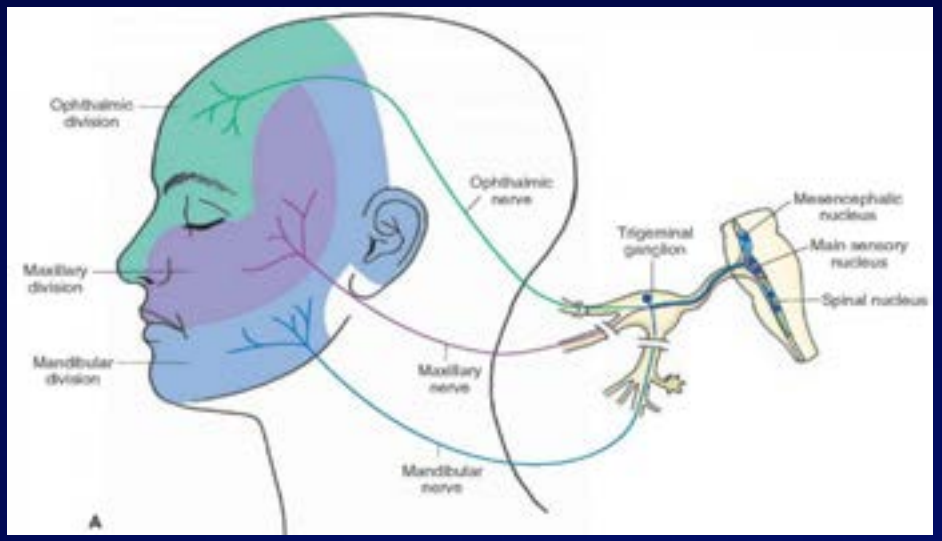




Chen AM, IJROBP, VOl98, Issue 1, 2017, 83-90

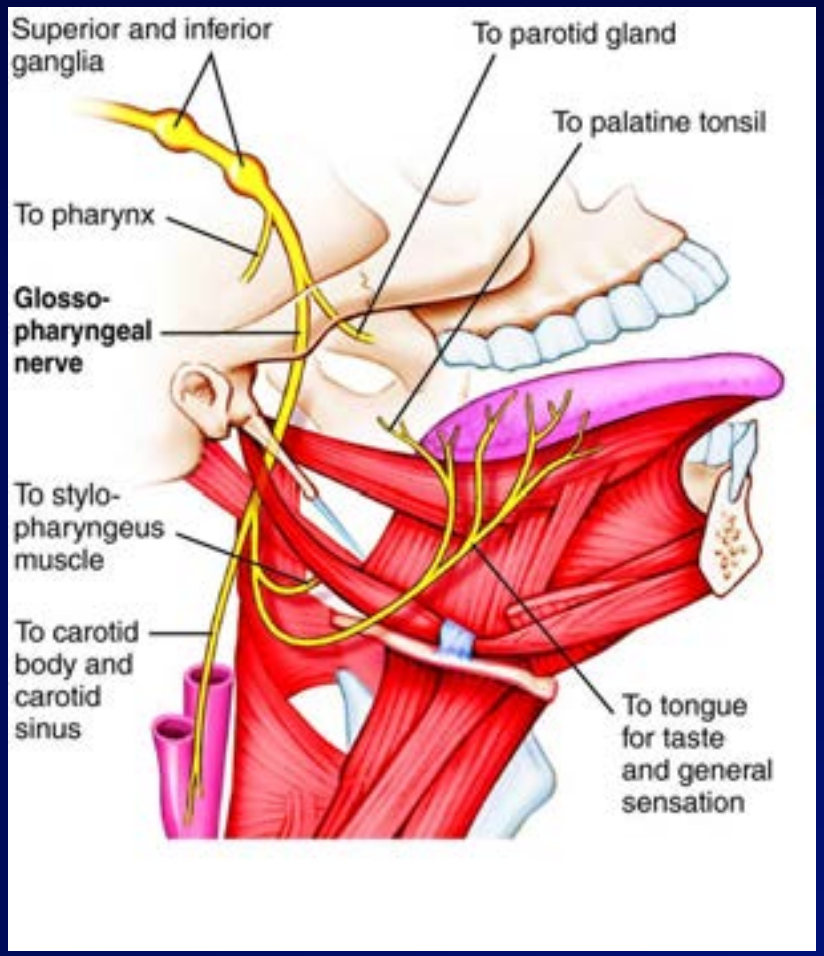
Trigeminal Nerve Involvement:

- 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
  - Opthalmoplegia, 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



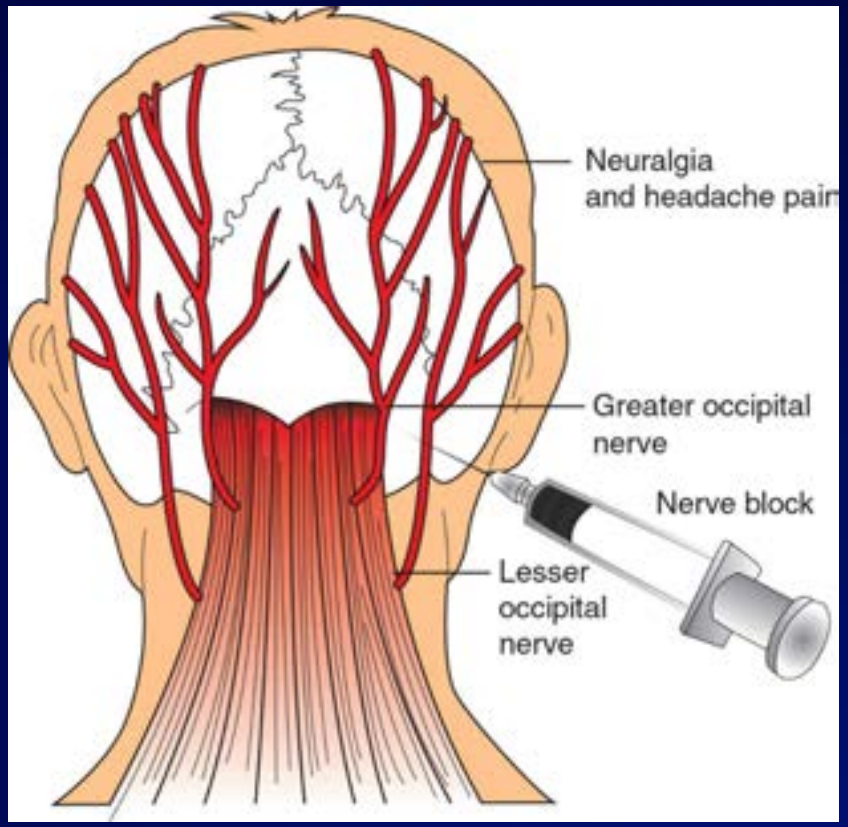
Glossopharyngeal Neuralgia: Cranial Nerve IX

- 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

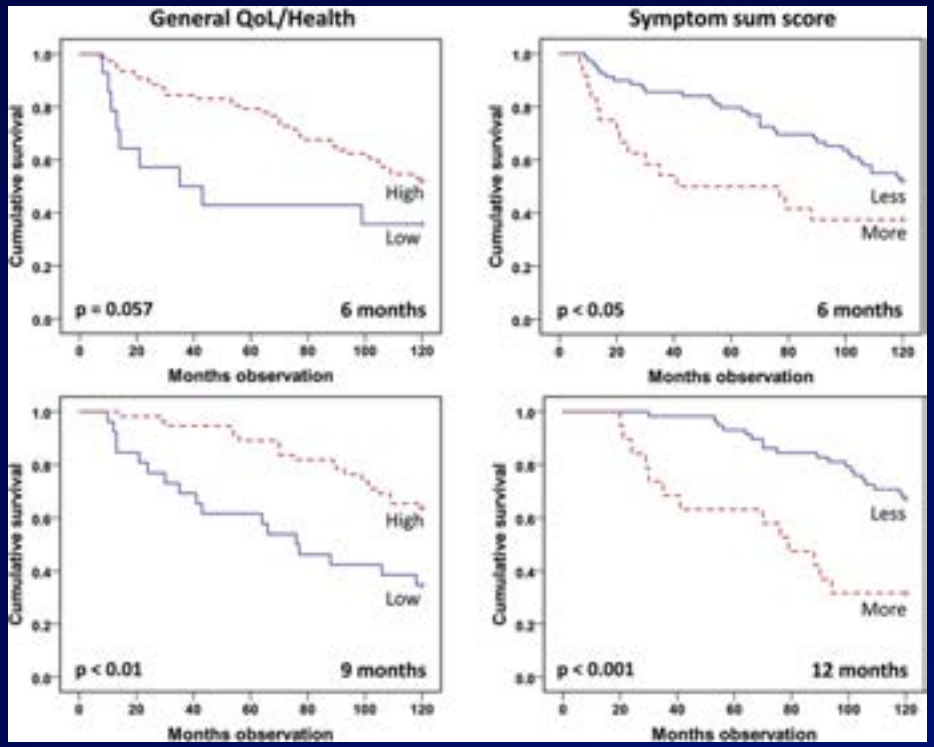
Complex Cancer Pain

- Requires a multi-modal approach to care
  - Anesthesia Pain
  - Functional Neurosurgery
  - Radiology
  - Radiation Oncology
  - Medical Oncology
  - Physical Therapy

	FACT-G Subscale				HN Mod.
VHNSS	**Physical**	**Social**	**Emotional**	**Functional**	
Global	.764	.288	.275	.699	.775
Cluster					
Swallow	.775	.008	.511	.614	.568
Nutrition	.607	.170	.279	.609	.687
M/DM	.579	.500	.114	.545	.662
Pain	**.705**	**.214**	**.277**	**.643**	**.725**
Voice	.719	.098	.332	.512	.564
Dentition	.333	.069	.079	.241	.336
Hearing	.337	.079	.165	.306	.210

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



Hans Jorgen Aarsad, European Archives of Oto-Rhino-Laryngology: 2018 Vol 275, pp207-217

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