

Chemoradiation: Late Local Effects

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How do we define a late effect of therapy?

- First, need to define the temporal relationship with therapy
- Second, need to define the important outcome parameters
 - The presence or absence of tissue damage?
 - The presence or absence of symptomatology?
 - The presence or absence of functional deficits with resulting handicaps and disabilities
 - Incidence of general health outcomes?
- Third, need to define the underlying mechanism

Trajectory of Late Treatment Effects:

- When do late effects begin?
 - Classical definition: 3 months post completion of therapy
 - Assumption: late effects evolve out of aberrant repair mechanisms
- Does not adequately explain the trajectory
 - Acute toxicities
 - Resolve after therapy has completed
 - Acute toxicities that become late effects
 - Fail to totally resolve after therapy has completed
 - Late Effects
 - Toxicities that become clinically evident after therapy has been completed

The Presence of Tissue Damage?

- Subclinical tissue damage
 - No clinical impact
- Tissue damage resulting in mild symptom burden or function loss
 - No intervention required
- Tissue damage results in clinically significant symptoms burden or function loss
 - Requires intervention or adaptation's by the patient
- Tissue damage resulting in handicap or disability

Inflammatory Disease States:

- Universal underlying biologic responses to disease and tissue damage
- Stereotypical manifestations of acute/chronic disease:
 - Fatigue
 - Weakness and deconditioning
 - Anorexia
 - Cachexia
 - Anemia
 - Neurocognitive changes
 - Mood disorders
- Mediators:
 - Host biologic mechanisms meant to deal with stress and aid in repair
 - Chronic or exuberant host response results in symptom cluster as noted above
 - Furthermore, the host response may actually cause harm

Mucosal Sensitivity:

- Neuropathic pain described as burning, worsened with spiced or acid foods
- Potential Mechanism: Pro-inflammatory cytokine mediated
 - Up-regulation of Na⁺ channels
 - Sensitization of peripheral nociceptors
- 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

Mucous Production:

- Time course:
 - Begins midway through radiation therapy
 - Resolves to some degree after treatment has been completed
- Characteristics:
 - Thick mucus that is difficult to clear
- Complications:
 - Coughing and gagging
 - Difficulty swallowing
- Treatment:
 - Anti-cholinergics
 - Mucolytics
 - Humidification
 - Anti-histamines

Mucous: VHNSS 2.0 Development Data

Question	Number	≥ 1	≥ 4
• Thick mucus/phlegm	67	82.1	47.8
• Choking/gagging results	67	58.2	28.4
• Swallowing difficult	67	61.2	25.4
• Sleep effected	67	49.3	20.9

Taste Alterations:

- Time course:
 - Begins within 2 weeks of starting radiation
 - Initiated at 20 Gy, 90% at 60 Gy
 - Recovery begins 2 to 4 weeks after therapy
 - May take years to recover taste or may not return to normal
 - Salt and bitter return first followed by sweet
- Effects:
 - Decreased oral intake
 - Nausea and vomiting
 - Altered digestion due to lack of taste organ stimulation
 - Decreased QOL
- Treatment:
 - Zinc found to be ineffective in a large randomized trial in HNC patients.

Taste Change: VHNSS 2.0 Development Data

Taste change	Number	≥ 1	≥ 4
• Taste altered	68	80.9	47.1
• Decreased desire to eat	68	61.8	38.2
• Altered food choices	66	68.2	42.4
• Decreased food eaten	66	59.1	33.3

Smell: VHNSS 2.0 Development Data

Question	Number	≥ 1	≥ 4
• Sense of smell changed	69	43.5	30.4
• Altered food choices	67	37.3	19.4

Stricture Formation:

Proximal Esophageal Stricture: Incidence

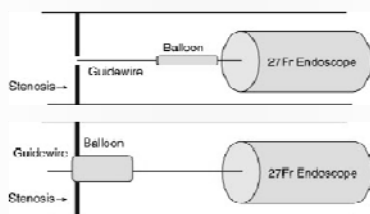
- Radiation therapy – Laurell, Cancer 2003, 97:700
 - 3.4% stricture overall
 - 2.6% stricture for patients with ≥ 60 Gy
 - 0.8% stenosis for patients with ≥ 60 Gy
- Chemoradiation - Lawson, AJ of Oto 2008, 29:13
 - 13% stricture overall
 - 5% stenosis
 - Increased stricture/stenosis in patients ≥ 60 Gy
 - Taxanes – 23%; Cisplatin 9%

Endoscopic Management of UES:

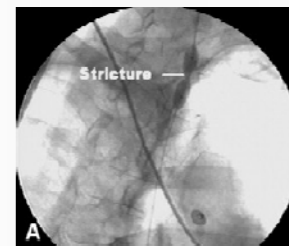
- Design: retrospective
- Patient population:
 - 24 patients treated for HNC with either CCR or surgery
- Outcomes:
 - Technical success: luminal diameter of 42 F or greater
 - Patient self-report of dysphagia relief
- Treatment: Endoscopy with dilatation
- Results:
 - **Technical success: 80%**
 - **Patient reported relief dysphagia: 84%**
 - Need for repeat dilatation: 58%

Sushil, Gastrointestin Endosc 2008, 68:19

Balloon Dilatation of Proximal Stricture



Steele, A J of Otolaryngology 2007, 28:98



Trismus

Structures Required for Normal Occlusion:

- Mandible
- Maxilla
- **Muscles of mastication**
 - Pterygoids, masseters and temporalis
- Dentition and support structures
- Nerve supply
- Vascular supply

Jaw Range of Motion:

- Depression
 - Lateral pterygoids
- Elevation
 - Temporalis, masseter, medial pterygoids
- Protrusion
 - Lateral pterygoids, masseter, temporalis
- Retraction
 - Posterior fibers of temporalis, deep masseter
- Lateral
 - Contralateral pterygoid and bilateral temporalis

Treatment Effect on Mandibular Opening and Mobility

- Radiation and Surgery can result in altered movement of the mandible and cause malocclusion
- Seauellea:
 - Deviation of the mandible
 - Joint sounds
 - Dislocation or locking of the TMJ on movement
 - Pain on movement
 - Restricted movement
 - Difficulty eating, impaired speaking, limitations in dental care/interventions, difficulty with intubation, reduced pulmonary function

Radiation Induces Effects on Mandibular Opening and Mobility

- Correlates with dose to muscles of mastication
 - Goldstein, Oral Surg Oral Med 1999; 88, 365
- Steep dose response curve
- Felt to be secondary to fibrosis
- Starts 2 to 6 months post treatment and is ongoing
- Concurrent chemotherapy may increase incidence
- Unclear whether IMRT can alter the incidence
 - Kent, Supportive Care Cancer 2008; 16, 305

Treatment Effect on Mandibular Opening and Mobility

- Maximal Vertical Dimension - Trismus
 - Distance between opposing incisal edges
 - If edentulous, measure to the alveolar ridge
- Helkimo Masticatory Dysfunction Index
 - Mobility Index
 - TMJ Function p opening and closing
 - Pain During movement
 - Muscle pain on palpation
 - Pain on palpation of the TMJ

Trismus:

- Altered range of motion in jaw:
 - Mild <35 mm
 - Severe <25 mm
- Adverse effects:
 - Nutrition
 - Dental Hygiene
 - Swallowing
 - Phonation

Effect of Trismus on Oral Intake

- 40 mm
 - “chew as well as ever”
- 30 mm
 - Could eat soft foods, but could not chew some foods
- 24 mm
 - Soft solids could not be chewed

Scott, Oral Oncology 2008, 44:430

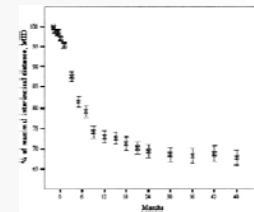
Incidence of Trismus:

- Patient population:
 - 89 post-operative patients
- Trismus:
 - Defined as opening <35mm
- Results:
 - Fully dentate: 31%
 - Partially dentate: 40%
 - Edentulous: 57%

Dijkstra, Oral Oncology

Time Course for Trismus

- 17 patients studied long term
- No change in maximum Interincisal Distance during RT
- Rapid decrease in MID months 1-9
- Slowing but continued worsening of trismus thereafter



Wang, Laryngoscope, 2005, 115: 1458

Treatment:

- Physical Therapy:
 - Improves trismus, however, not as effective in cancer related
 - Dijkstra, Oral Oncology 2007, 43:389
- Botulinum Toxin Injection:
 - No consistent improvement
 - Hartl, Otolaryngology – H and N Surg 2008, 138: 459
- Pentoxifylline:
 - Pilot study of 400 mg po tid x 8 weeks demonstrated modest improvement (mean 4 mm)
 - Chan, Amer J Clin Oncol 2001, 23:366
- Microcurrent Therapy:
 - Pilot study demonstrated modest improvement in trismus
 - Lennox, Int J Rad Oncol Biol Phys 2002, 54:23

Dystonia:

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 oblongata suggest a central process
- Botulinum toxin therapy may effectively palliate this syndrome

Conclusions:

- Head and neck cancer patients experience a high frequency and severity of late treatment effects
- The late treatment effects alter function.
- Some late effects are treatable
- It is important to assess patients on a routine basis for late effects of therapy and to intervene where indicated
- Further research is greatly needed to define late effects and identify effective interventions.

