Short and long term sequelae of radiation therapy to the oral cavity

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Radiation Therapy
General Statements

- Radiation alone or with other treatment modalities is used in a significant number of patients with advanced stage oral cancer
- A therapeutic dose of 5000-7000 cGy is externally delivered to the lesion
- Increments of 200 cGy/day is delivered until the accumulated dose is achieved
Classification

Oral Complications of radiotherapy

- Acute
  - Mucositis
  - Skin Reactions
  - Infection
    - Acute
    - Chronic

- Late
  - Xerostomia
  - Radiation caries
  - Trismus
  - Radiation induced malignancies
  - Osteoradionecrosis

Acute Mucositis
WHO Oral Mucositis Scale

Severe Oral Mucositis

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Soreness +/- erythema</td>
<td>Erythema, ulcers</td>
<td>Ulcers, extensive erythema</td>
<td>Mucositis to the extent that alimentation is not possible</td>
</tr>
<tr>
<td></td>
<td>No ulceration</td>
<td>Patients can swallow solid diet</td>
<td>Patients cannot swallow solid diet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mucositis

Clinical Characteristics

Grade I White discoloration
Mucositis

Clinical Characteristics

Grade II Erythema

Grade III Pseudomembranous surface
Mucositis

Clinical Characteristics

Grade IV Ulcerations

Lessons Learned from Oral Mucositis

» Extend to the entire GI tract

Keefe D et al, Curr Opin Clin Nutr Metab Care, 2007
The Alimentary Canal

» The GI tract is all one tube from mouth to anus—formed from primitive endoderm

The Alimentary Canal

» Toxicities resulting from chemotherapy or radiotherapy don’t occur in isolation

» There are common mechanisms & systemic effects

» The GI system can provide a whole new paradigm for research & new intervention strategies
Mucositis

- **Symptoms**
  - Intense pain
  - Food and fluid intake decreases
  - Speech and swallowing difficult
  - May require ceasing therapy

- **Management**
  - Mucosal coating agents
  - Cleansing devices
  - Chlorhexidine
  - Recombinant keratinocyte growth factor
  - GMCSF (Combined Therapy)
  - Thalidomide?
  - Low-level laser therapy?
Radiation Mucositis
Pain Management

Mild Pain
Non-opioids; +/- adjuvants

Mild-Moderate Pain
Weak opioid; +/- non-opioid / adjuvants

Moderate – Severe Pain
Strong opioid; +/- non-opioid / adjuvants

- Rapid progress is being made in the understanding of this complex problem
  » Mucositis is more than the mouth ulcer
  » The mechanism is complex but increasingly understood
  » International collaboration is speeding things up
Acute Skin reactions
Mechanism of radiation-induced late soft tissue injury

- Osteocyte
- Vessels
- Inflammatory infiltrates
- Soft tissue
- Fibroblast
- Cytokines: TNF, TGF, PDGF, IL-1
- Collagen, ↑ECF matrix
- Sequestra
- Osteonecrosis
- ↑permeability
- ↓perfusion/oxygenation
- FIBROSIS
Late
Xerostomia

Xerostomia

- **Pathogenesis**
  - Irreversible acinar cell damage

- **Clinical Characteristics**
  - 50% decreased salivation after 1 week of radiation
  - 75% decrease after 6 weeks
  - 95% decrease years after
  - Thick ropey saliva
  - *Candida albicans* infection
  - Dental caries
  - Dysphagia / Odynophagia
Xerostomia

**Symptoms**
- Difficulty in eating, speaking, & swallowing
- Taste disorders
- Denture-related pain / dysfunction

**Pre-treatment Strategies**

*Current*

- **IMRT / Conformal beam design**
  - Selective field design
    - Attempt oral mucosal sparing
- **Radioprotective agents**
  - Amifostine
  - Antioxidants
- **Salivary stimulation**
  - Pilocarpine; cevimeline; gustatory; other agents
Intensity Modulated Radiotherapy (IMRT) for Head & Neck Cancer: A New Standard of Care

Improved target coverage: better local control
Sparing of OAR: decrease in complications

Conventional Radiotherapy

Intensity Modulated Radiotherapy
Xerostomia
Dealing With It

- Replacement
- Lubricants
- Gustatory stimulation
- Drug intervention
- Submandibular gland relocation
- Daily living “tricks” or maneuvers

Conclusion

- IMRT for treatment of advanced oral cavity cancer should be considered during treatment planning
- Potential benefits in terms of reduced xerostomia rates and osteoradionecrosis rates
Late Radiation caries

Pathogenesis
» Shift to cariogenic microflora and xerostomic environment

Clinical Characteristics
» Cervical, cusp, & incisal decay
» Coronal fractures
Late

Trismus

Trismus

• more common with high posterior fields of radiation as muscles of mastication are in field (10%)
• retention of coronoid process
• made worse by concomitant chemotherapy
Trismus

● **Pathogenesis**
  » Direct effects of radiation on muscles and/or TMJ

● **Clinical Characteristics**
  » Limited range of motion

● **Management**
  » Prevent with stretching exercises
  » Prophylactic or therapeutic pentoxifylline, \( \alpha \)-tocopherol

Late
Radiation induced malignancies
Late complications following RT

- **No event**
- **Event occurs above threshold dose, severity ↑ with dose**
- **Event can occur at any dose level**
- **Probability, not severity, ↑ with dose**

Increasing RT dose

Late complications following RT

- Xerostomia
- Soft tissue fibrosis
- Osteoradionecrosis
- Radiation associated tumors

Increasing RT dose
Radiation Associated Tumours

Criteria
- Positive history
- Within the radiation field
- Different histology
- Latency ~ 5 years

Infections
Erythematous candidiasis and angular cheilitis from mucositis

Infection Pseudomembranous candidiasis from ulcerative / pseudomembrane mucositis and / or HSV-1
1 of 3 to 1 of 2 H & N cancer patients receiving RT or CRT will develop pseudomembranous candidiasis. The infection should respond to GI tract absorbed antifungal within 3 to 4 days.

**Management of candidiasis**

- Identify and minimize / alleviate particular risk factors
- Salivary gland function protection
- Mucosal protection from xerostomia
- Administration of antifungals
Management of candidiasis

- Topical antifungal agents
  » Polyene compounds
- Systemic antifungal agents
  » Azole group compounds

Late

Osteoradionecrosis
Background

- Devastating complication of radiation therapy that can be more difficult to treat than original tumor
- Clinical definition: Devitalized, irradiated bone that is exposed through overlying mucosa or skin persisting for ≥ 6 months

- Osteoradionecrosis presents as a broad spectrum of disease severity
- It is rare at radiation therapy doses of less 60 Gy
- It is more common when brachytherapy is used
- The mandible must be in the treatment volume area
- Dental extractions, surgery or trauma frequently proceed its onset
- Secondary infection may be present
Pathophysiology of osteoradionecrosis

Direct radiation effects on normal tissue may be lethal or sublethal

Lethal damage is caused by ionization within the desoxyribonucleinic acid (DNA) preventing cell replication and resulting in tissue death

Sublethal damage may cause cell mutation leading to further neoplasia

3 “H” Hypothesis & Osteoradionecrosis

Hypovascularity

Hypoxia

Hypocellularity

Tissue injury (usually)

Tissue breakdown / non-healing wound
The incidence of osteoradionecrosis is reported to be between 5-25% of patients receiving radiotherapy in the head and neck area.

There are several classifications for mandibular osteoradionecrosis and they all stage the disease according to the severity of signs and symptoms in either Stages, Grades or Scores.

**Table 1. Incidence of ORN according to the sexes**

<table>
<thead>
<tr>
<th>Patients with</th>
<th>Patients with</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>radiotherapy</td>
<td>ORN</td>
<td>(%)</td>
</tr>
<tr>
<td>Male patients</td>
<td>645</td>
<td>62</td>
</tr>
<tr>
<td>Female patients</td>
<td>194</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>839</td>
<td>68</td>
</tr>
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</table>

**Table 1. Late radiation bone morbidity according to the RTOG scoring criteria (see text for comments)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Bone morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Asymptomatic, no growth retardation, reduced bone density</td>
</tr>
<tr>
<td>2</td>
<td>Moderate pain or tenderness, growth retardation, irregular bone sclerosis</td>
</tr>
<tr>
<td>3</td>
<td>Severe pain or tenderness, complete arrest of bone growth, dense bone sclerosis</td>
</tr>
<tr>
<td>4</td>
<td>Necrosis, spontaneous fracture</td>
</tr>
</tbody>
</table>

RTOG: Radiation Therapy Oncology Group
Extractions & Osteonecrosis
Traditional Concepts

- Twice the risk of ORN is seen when selected teeth are extracted following radiation therapy
- Pre-radiation extractions associated with a 3.4% risk of ORN
- Risk of ORN persists for years and reduced healing capacity may be considered permanent

The role of hyperbaric oxygen
The use of Hyperbaric Oxygen (HBO)

HBO treatment involves the delivery of 100% oxygen at high pressure in special chambers. The pressure of the oxygen inhaled by the patient is usually 2.4 times more than the atmospheric pressure and can be as high as 3 times more.

Advocates of HBO therapy support the view that HBO represents the only medical treatment for osteoradionecrosis. HBO can revert the delayed radiation changes in tissues by generating steep oxygen gradients between the normal and the irradiated tissues causing oxygen to diffuse into the affected areas.
The use of Hyperbaric Oxygen (HBO)

HBO has been used as an adjunctive conservative measure along with antibiotics and irrigation since the 1960s.

Using Marx’s theory that osteoradionecrosis is a result of hypoxia, hypocellularity and hypovascularity, HBO seems likely to increase oxygen supply in hypoxic tissues, stimulating fibroblast proliferation and angiogenesis.

The role of HBO in the treatment of osteoradionecrosis.

The Marx protocol (1982)

The use of HBO in the treatment of osteoradionecrosis despite its widespread use had been largely theoretical or anecdotal because of the paucity of controlled trials and the lack of unified assessment of symptom improvement.


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The role of HBO in the treatment of osteoradionecrosis.

The study by Annane et al (2004)

The first randomized, placebo-controlled, double-blind study assessing the efficacy and safety of HBO for the treatment of overt mandibular osteoradionecrosis and included 68 patients.
The trial was terminated prematurely because of the failure to demonstrate any beneficial effect of HBO over placebo (19% vs. 33% respectively). They also reported the progression of disease in recovery in the arm of HBO patients and better recovery rates in the arm of the placebo treated patients.

The study by Annane resulted into strong criticism and disbelief by several authors quoting that it violated an ethical principle by exposing the control group to the potentially serious risk of acute decompression illness; a risk not present in the treatment group.

Others stated that a major error in Annane’s study was the fact that the studied group of patients with an osteoradionecrosis was not well defined.

There were though supporters of the Annane study presenting evidence that the beneficial results of HBO treatment are equivocal and the method is time consuming and expensive.

*The debate is still going on.*
Management of early and advanced osteoradionecrosis

Established ORN does not regress spontaneously. It either stabilizes or gradually worsens. One of the adverse factors implemented in the development of ORN is the Radiation Induced Fibrosis (RIF) and necrosis. It has been shown that RIF greatly regressed after antioxidant treatment with the combination of pentoxifylline, tocopherol and clodronate.

MAJOR HEALING OF REFRACTORY MANDIBLE OSTEORADIONECROSIS AFTER TREATMENT COMBINING PENTOXIFYLLINE AND TOCOPHEROL: A PHASE II TRIAL

Sylvie Delanian, MD, PhD, Joel Depondt, MD, PhD, Jean-Louis Lefaix, PhD

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2 Chirurgie Cervico-Faciale, Hôpital Bichat APHP, Paris, France
3 DSV/RR, CEN-FAR, 92265 Fontenay-aux-Roses, France

Accepted 5 July 2004
Published online 7 January 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20121
With this treatment applied to 18 patients with advanced ORN, 16 (89%) recovered after a median 6 months of treatment.

The results of this trial raise many questions primarily about the precise mechanisms of action of the drugs used, which will remain unanswered until further randomized clinical trials will be conducted.

### Selection of treatment in ORN

#### Stage I
- **Superficial Ulceration**
- **Exposed cortical bone**

**Conservative management:**
- **Debridement**
- **Meticulous oral hygiene**
- **Antibiotics**
- HBO
Selection of treatment in ORN

Stage II
Exposed medullary bone
+ soft tissue changes

Conservative management:
HBO cannot revitalize dead bone

Sequestrectomy
in addition to other conservative measures
Selection of treatment in ORN

Stage III
Sinus/Fistula
Pathologic Fracture

Surgical Intervention:

- Extensive soft tissue involvement
- Extensive bony loss
- To include # and fistula
The only successful treatment of advanced (Stage III) mandibular osteoradionecrosis is the surgical resection of diseased tissues and their reconstruction with free tissue transfer.

The question whether HBO should be a precedent treatment or should be administered post-operatively or not at all is unanswered.

Reconstructive options in the treatment of severe (Stage III) mandibular osteoradionecrosis

1. The radial forearm osteocutaneous flap
2. The fibula osteocutaneous flap
3. The use of additional flaps
The Role of the Osteocutaneous Radial Forearm Free Flap in the Treatment of Mandibular Osteoradionecrosis

Oleg N. Militsakh, MD, Derrick I. Wallace, MD, J. David Kriet, MD, FACS, Terance T. Tsue, MD, FACS, Douglas A. Girod, MD, FACS

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Tobacco (pack-years)</th>
<th>ETOH* use</th>
<th>No. of medical problems</th>
<th>Primary diagnosis</th>
<th>Primary site</th>
<th>Oncologic treatment</th>
<th>XRT dose (Gy)</th>
<th>Bone defect</th>
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<td>60</td>
<td>F</td>
<td>40</td>
<td>No</td>
<td>Mild</td>
<td>Melanoma</td>
<td>Cheek skin</td>
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<td>70</td>
<td>RB</td>
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<tr>
<td>2</td>
<td>54</td>
<td>M</td>
<td>40</td>
<td>No</td>
<td>Mild</td>
<td>SCCA</td>
<td>Oral cavity</td>
<td>postoperative XRT</td>
<td>66</td>
<td>B</td>
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<td>3</td>
<td>57</td>
<td>F</td>
<td>60</td>
<td>No</td>
<td>0</td>
<td>SCCA</td>
<td>Oral cavity</td>
<td>Surgery with</td>
<td>67</td>
<td>RB</td>
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<tr>
<td>4</td>
<td>59</td>
<td>M</td>
<td>45</td>
<td>No</td>
<td>2</td>
<td>SCCA</td>
<td>Oropharyngeal</td>
<td>postoperative XRT</td>
<td>67</td>
<td>B</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>M</td>
<td>60</td>
<td>No</td>
<td>2</td>
<td>SCCA</td>
<td>Major salivary gland</td>
<td>Surgery with postoperative XRT</td>
<td>70</td>
<td>BS*</td>
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<tr>
<td>6</td>
<td>71</td>
<td>M</td>
<td>40</td>
<td>Heavy</td>
<td>0</td>
<td>SCCA</td>
<td>Oral cavity</td>
<td>XRT, surgery</td>
<td>74</td>
<td>BS*</td>
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<td>7</td>
<td>62</td>
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<td>40</td>
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<td>1</td>
<td>SCCA</td>
<td>Oropharyngeal</td>
<td>XRT</td>
<td>61</td>
<td>B</td>
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<td>8</td>
<td>46</td>
<td>M</td>
<td>35</td>
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<td>1</td>
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<td>Oropharyngeal</td>
<td>XRT</td>
<td>74</td>
<td>RB</td>
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<tr>
<td>9</td>
<td>66</td>
<td>M</td>
<td>40</td>
<td>No</td>
<td>1</td>
<td>SCCA</td>
<td>Oral cavity</td>
<td>XRT, surgery</td>
<td>61</td>
<td>BS</td>
</tr>
</tbody>
</table>

* R = remus, B = body, S = symphysis; *TOH = alcohol use; XRT = radiation therapy; SCCA = squamous cell carcinoma.

Militsakh ON et al, Otolaryngol-Head and Neck Surg 2005

RESECTION AND IMMEDIATE MICROVASCULAR RECONSTRUCTION IN THE MANAGEMENT OF OSTEORADIONECROSIS OF THE MANDIBLE

Ashok R. Shaha, MD, Peter G. Cordeiro, MD, David A. Hidalgo, MD, Ronald H. Spiro, MD, Elliott W. Strong, MD, Ian Zlotolow, DMD, Joseph Huryn, DDS, Jatin P. Shah, MD

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Site of primary</th>
<th>Histology</th>
<th>Time from initial therapy (mo)</th>
<th>Mandible reaction</th>
<th>Follow-up period (mo)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>F</td>
<td>Roor of mouth</td>
<td>SQ CA</td>
<td>6 angle to angle</td>
<td>60</td>
<td>60</td>
<td>Rejected partial removal of hardware, osteomigrated implants: excellent osseointegration</td>
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<tr>
<td>2</td>
<td>52</td>
<td>F</td>
<td>Lateral tongue</td>
<td>SQ CA</td>
<td>6 angle to angle</td>
<td>27</td>
<td>60</td>
<td>Excellent results, considered for osteomigrated implants: healed, good osseointegration</td>
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<tr>
<td>3</td>
<td>56</td>
<td>M</td>
<td>Base of tongue</td>
<td>SQ CA</td>
<td>6 angle to angle</td>
<td>204</td>
<td>24</td>
<td>Healed, good osseointegration</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>Base of tongue</td>
<td>Adenoid cystic</td>
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<td>46</td>
<td>21</td>
<td>Healed, good osseointegration</td>
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<tr>
<td>5</td>
<td>57</td>
<td>M</td>
<td>Lateral tongue</td>
<td>SQ CA</td>
<td>6 angle to angle</td>
<td>24</td>
<td>20</td>
<td>Healed, good osseointegration</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>M</td>
<td>Roor of mouth</td>
<td>SQ CA</td>
<td>6 angle to angle</td>
<td>24</td>
<td>20</td>
<td>Healed, good osseointegration</td>
</tr>
</tbody>
</table>

SQ CA = squamous carcinoma.

Shaha A et al, Head Neck 1997
Patients

- 47 patients between 1991 and 2006
  MSKCC=41; GACI=7
- Age 34-81 (median 59) years
- 32 Males 15 Females
- Symptoms & Signs
  - Pain 75%
  - Non-healing ulcer 66%
  - Draining Fistula/sinus 29%

Type of Reconstruction

- Fibula 75%
- OC-FRFF 19%
- Other 6%

n=16
Osteoradionecrosis of the mandible is a dreaded and devastating complication of radiation therapy for malignant tumors of the head and neck area. Various tumor, patient and treatment factors influence its development but the exact pathophysiology is still under investigation.

It is especially important to prevent the development of osteoradionecrosis of the mandible by eliminating the so far known risk factors.

When osteoradionecrosis reaches an advanced stage, the treatment of choice is resection of the necrosed tissues and immediate reconstruction with free tissue transfer.

Other radiation sequelae

Carotid injury (stenosis)

Friedlander AH, Freymiller EG. J A, Dent Assoc 2003
Other radiation sequelae

Carotid injury (stenosis)

» Mechanism: Generation of inflammatory cytokines / growth factors stimulate atherogenesis
» Increased stroke risk
  – The incidence of significant carotid stenosis following head and neck irradiation range from 30% to 50%. Patients with carotid stenosis are at increased risk for stroke.
» Factors such as hypertension, diabetes, smoking and obesity increase the risk.

Carotid stenosis is a major sequela of head and neck irradiation that has not received the attention it deserves.

Evaluation:

» Imaging
  – Ultrasonography, CT, MRA

Other radiation sequelae
Carotid injury (stenosis)

- **Management:**
  - Endarterectomy; stenting
  - Anticoagulation


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**Summary**

- Radiotherapy is an important Rx modality in oral cancers
- Modern RT planning and treatment techniques improve treatment outcome
- Advances in Rx may actually increase late complications
- Site specific approach allows organ-sparing with high conformality RT (e.g. parotid-sparing)
- Modest benefits associated with medical treatment of established complications
- Aggressive Rx of certain complications is indicated
- Importance of prevention of late complications through identification, correction and avoidance of risk factors
Second World Congress of the International Academy of Oral Oncology (IAOO)
July 8 – 11, 2009
Sheraton Centre, Toronto

Invitation to Toronto!