Contemporary Management of Osteonecrosis

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Historical Risk Factors for Osteonecrosis (ONJ)

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<th>Radiation Therapy</th>
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<td>Storage diseases</td>
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<td>Corticosteroids</td>
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<td>Advanced age</td>
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<td>Gaucher’s disease</td>
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<td>Human immunodeficiency</td>
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<td>Virus infection</td>
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<td>Chronic inactivity</td>
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<td>Hyperlipidemia and embolic fat</td>
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<td>Osteoporosis</td>
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<td>Neurologic damage</td>
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</tbody>
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Data from Auvilino-Dayas et al.
Mechanisms for Development of ONJ

- **Radiation injury continuum**
  - **Acute**: Direct cellular toxicity, self-limited
  - **Subacute**: Self-limited (radiation pneumonitis)
  - **Delayed**: After latent period (6 months)
    - Endarteritis
    - Tissue hypoxia
    - Secondary fibrosis
  - **3H’s**
    - Hypoxia
    - Hypovascularity
    - Hypocellularity

Biology
Histology

- 0-6 months: hyperemia, inflammation, acute cellular damage, endothelial necrosis, vascular thrombosis
- 6-12 months: Hypovascularity and fibrosis, loss of elastic and muscular coating of vessel wall
  - Fewer osteocytes, marrow fibrosis and sequestrum
  - Loss of spongiosa trabeculation
  - Periosteal fibrosis
  - Paucity of nutrient vessels
  - Paucity of fibroblastic cells
- Rare bacterial infection
- 60-80 Gy results in capillary density of 20-40%

Histology

0-6 months
- Hyperemia
- Inflammation
- Acute cellular damage
- Endothelial necrosis
- Vascular thrombosis
6-12 months:
Hypovascularity and fibrosis, loss of elastic and muscular coating of vessel wall
- Fewer osteocytes, marrow fibrosis and sequestrum
- Loss of spongiosa trabeculation
- Periosteal fibrosis
- Paucity of nutrient vessels
- Paucity of fibroblastic cells

Rare bacterial infection
60-80 Gy results in capillary density of 20-40%
Newer Biological Theory

- Selective suppression of osteoclasts in treated bone is a key element in ORN
  - Osteonecrosis now being seen in some patients treated with only chemotherapy
  - Osteonecrosis has developed in patients treated with biophosphonates

Newer Biological Theory

- Non-radiated bone
- Radiated bone to 36Gy
Osteoradionecrosis

- Definition: Exposed irradiated bone that fails to heal over a period of 3 months
- Incidence 10-15% (may be more with newer combined modality treatment regimens-30%)
- Majority of spontaneous cases present within 2 years of radiation
- Traumatic-induced lesions are bimodal in presentation
  - 1st peak at 3 months post radiation
  - 2nd peak at 2 - 5 years

Osteoradionecrosis - Complications

- Intractable pain
- Drug dependency
- Trismus
- Nutritional deficiencies
- Loss of time from work and family
- Decreased QOL
Mandibular ORN

- Most common site affected in head and neck (95%)
- Compact bone with higher mineral content
- Most common sites are buccal cortices of the premolar and retromolar trigone
- Ramus and condylar portions more resistant
- Blood supply is less reliable (inferior alveolar) with fewer periosteal perforators
- Maxilla less commonly involved due to decreased density of bone and better blood supply

Etiology

- Bone has density 1.6 to 1.8 times greater than soft tissue
- Bone absorbs more photons with higher energy deposition
- Mandible is higher density than other bones in standard H & N radiation fields
Mandibular ORN

Time since radiation
Longer time since radiation causes increased risk of osteoradionecrosis
- 3 years vs. 8 years (p<0.001)

Type of surgery
Mandibulotomy or segmental mandibulectomy resulted in earlier ORN than fibula free flap.

Dose related
- <60 Gy (0%)
- 60-70 Gy (1.8%)
- >70 Gy (9%)

Dose rate delivery
- >0.55 uGy/hour

Mandibular ORN

- Target size related
  - < 33% of mandible to 65 Gy (5%)
  - > 33% of mandible to 60 Gy (5%)

- Type of radiation
  - Brachytherapy
  - Reirradiation
  - Neutron


Mandibular ORN

- 87 patients from 1963-1997
- Most cases of ORN occurred within 36 months of radiation therapy
- ORN was more severe:
  - The higher the dose of irradiation
  - The later it developed after irradiation

Neutron Radiotherapy and ORN

- Greater direct action on tissue
- Large neutron dose per fraction (>150NcGy)
- Worse with concurrent chemotherapy
- 100% on maxilla (4/4) in postoperative setting


Predisposing factors

- 81% iatrogenic: 19% Spontaneous
- Dental extraction
- Surgical trauma (including biopsy)
- Poor oral hygiene
- Poor nasal hygiene (skull base ORN)
- Total dose > 6000 cGy or >1000 cGy/week
- Brachytherapy

Prevention

- Fluoride-5min fluoride gel and bid high content fluoride toothpaste
- Intensive oral irrigation
- Preradiation extraction 21 days before initiation of radiation therapy
- Minimize extractions (especially 1st 12 months)
- Periextraction antibiotics and wound closure if extractions are post-radiation

Osteoradionecrosis

- Initial diagnostic finding
  - Foul Odor 100%
  - Exposed bone 74%
  - Trismus 55%
  - Severe pain 52%
  - Discharging fistula 52%
  - Mucosal defect 39%
  - Cutaneous defect 35%
Workup of Osteoradionecrosis

- Panorex
- Computed tomography scans (Dentascan)
- Magnetic resonance imaging to look at bone marrow and surrounding soft tissue

Osteoradionecrosis - Radiographic Appearance

- Radiolucent mottling with indefinite non-sclerotic borders
- Occasional areas of radiopacity associated with bony sequestrum
- CT scan can complement plain films
Staging system (Marx)

- Stage I: Exposed bone > 6 months
- Stage II: Failure of treatment of stage I
- Stage III: Poor prognostic factors
  - Pathologic fracture
  - Orocutaneous fistula
  - Osteolytic involvement of inferior border

Staging System-Schwartz

- Stage I- Small area of limited exposed cortical bone
- Stage II-Exposed cortical and underlying medullary bone necrotic (minor procedures+/- HBO)
  - IIA-minimal soft tissue ulceration
  - IIB-soft tissue necrosis including orocutaneous fistula
- Stage III-Full thickness necrosis +/- pathologic fracture (all require surgery)
  - IIIA- minimal soft tissue ulceration
  - IIIB-soft tissue necrosis including orocutaneous fistula

Hyperbaric Oxygen

- Steep oxygen gradient exceeding 20mm Hg initiates angiogenesis
- At hyperbaric conditions, the amount of dissolved oxygen in plasma dramatically increases.
- Oxygen tensions in arteries >2000 mmHg, and tissues >400 mmHg: Compare with Oxygen tensions in center of radiated field (5-10 mm Hg, and at periphery (50-60 mmHg)
- Increase tissue oxygen pressures (50-86% after 30 dives)
- Increase vascular density

Hyperbaric Oxygen

- Hyperoxygenation followed by return to hypoxia
  - Lactate buildup
  - Macrophages migrate and secrete angiogenesis factors
  - Fibroblast proliferation
  - Capillary budding
  - Collagen formation in bone and soft tissue
Lag Phase

- First 6-8 dives
- Period of intense collagen synthesis
- Hypoxic area begins to undergo neovascularization
- No significant increase in $O_2$ tension
**Rapid Phase**
- From dive 8 to 22
- Period of intense angiogenesis
- Reversal of hypoxemia progresses to epi-center
- Significant increase in O₂ tension

**Plateau Phase**
- After 20 to 22 dives
- Reversal of hypoxemia progresses to center
- O₂ gradient eliminated
- No significant increase in O₂ tension with further dives
**HBO Mechanisms and Consequences**

**Elevation of PO2**

Increased O2 diffusion → Increased tissue ROS and RNS

- Augmented pathogen killing in necrotizing infections and hypoxic wounds
- Accelerated inert gas elimination
- Augmented O2 delivery by non-hemoglobin dependent mechanisms
- Oxygenation of marginally perfused tissues

1. Edema reduction
2. Inflammation reduction
3. Stem cell mobilization, angiogenesis, mitochondrial biogenesis and cell proliferation
4. Antioxidant elaboration and preconditioning
Hyperbaric Oxygen

Adverse Effects

- Middle ear barotrauma
- Sinus obstruction
- Ocular effects
- Claustrophobia
- Oxygen toxicity
Contraindications

- Untreated pneumothorax
- History of optic neuritis
- Fulminant viral infection
- Congenital spherocytosis
- Active malignancy
- Obstructive lung disease
- Congenital pulmonary blebs

Hyperbaric Oxygen

- Bacteriostatic and bactericidal by improving phagocytotic capability of leukocytes
- Prophylactically decreases tissue fibrosis
- Improve adjacent tissues ability to heal to flaps
  - 11% vs. 48% wound dehiscence
  - 6% vs. 24% wound infection
  - 11% vs. 55% delayed wound infection
Hyperbaric Oxygen Prophylaxis

- Wound complications
  - Head and neck surgery (87.5% vs. 60% historic control)

Feldmeier Prophylactic hyperbaric oxygen for patients undergoing salvage for recurrent head and neck cancers following full course irradiation
Undersea Hyper Med 1998;25(suppl) 10

Hyperbaric Oxygen-Dental Extraction

- Prospective trial
  - Dental extraction (post radiation therapy)
    - Prophylactic PCN (29.9%) most Stage III
    - HBO 20 dives preextraction and 10 dives postextraction (5.4%) All Stage II

Marx et al. Prevention of osteoradionecrosis: A randomized prospective clinical trial of hyperbaric oxygen versus penicillin
J Am Dent Assoc 1985;11:49-54
Chavez et al. Adjunctive hyperbaric oxygen in irradiated patients requiring dental extractions: outcomes and complications.
Hyperbaric Oxygen-Dental Extraction

- 187 radiated patients (6000-7000 cGy) required dental extractions
  - 7 patients received pre-extraction HBO
- Only 4 patients developed ORN
  - All from molar extractions
- Recommend atraumatic extraction technique and careful patient selection


Dental Rehabilitation

- Osseointegrated implants
  - 20 preoperative dives; 10 postoperative dives
  - Success rates
    - 81%-92% osseointegration vs. 94% in nonirradiated
    - 100% prevention of osteoradionecrosis
Challenges of HBO - Cost

- Each 2 hour treatment
  - $880 for HBO and facility fee
  - $557 for physician supervision
    - Total- $1437
- $110- weekly patient physical exam
- For 30-40 treatments, even at medicare rates, it ain’t cheap!

Challenges of HBO

- 15-26 % of patients don’t complete treatment due to funds, noncompliance, inconvenience, and claustrophobia
- Geographic limitations
- Mandibular osteoradionecrosis
  - With HBO $42,000
  - Without HBO $140,000

McKenzie et al. Hyperbaric oxygen and postradiation ORN of the mandible. Eur J Cancer 1993;29B:201-7
Carcinogenesis of Hyperbaric Oxygen

- No increase in rate of recurrence
- 10% chance of finding a recurrence or new primary in setting of osteoradionecrosis (majority require multiple sequestrectomies for diagnosis)
- In rodent model, HBO appeared to suppress tumor growth


Marx Protocol for Management of Osteoradionecrosis

1. Pathologic Fracture
   - Stage III-R
   - 20 dives
   - Reconstruction w/ bone graft
   - 10 more dives

2. Orocutaneous Fistula
   - Stage III
   - Minimum of 30 prior dives
   - resection w/ MMF/Ex. Fix.
   - Treat to total of 60 dives
   - Wait 10 weeks

3. Radiographic resorption of inferior border
   - Stage II
   - Transoral alveolar sequestrectomy
   - primary closure
   - No Improvement: Advance to Stage III
   - Improvement: treat to total of 60 dives
Osteoradionecrosis - Treatment

- Pre-Stage I
  - Local debridement
  - Saline irrigation (+ peroxide)
  - Antibiotics
  - Pentoxyphilline 400 mg. TID and Vitamin E 400 IU QD

Hyperbaric Oxygen Treatment

- Stage I (Marx) protocol
  - 30 HBO dives at 2.4 atm abs for 90 oxygen minutes
  - If successful improvement then additional 10 dives
Osteoradionecrosis - Treatment

- Stage II
  - After 30 doses HBO, transoral alveolar sequestrectomy to bleeding bone is performed
  - Mucoperiosteum is closed primarily in a layered fashion
  - Proceed with 10 additional HBO treatments
  - If non-responder, move to Stage III
Osteoradionecrosis - Treatment

- Stage III
  - 30 HBO treatments if not already done
  - radical resection of bone to bleeding bone and soft tissue
  - Reconstructive options controversial

6 Criteria for Successful HBO

- Restoration of jaw continuity
- Restoration of alveolar bone height
- Restoration of osseous bulk
- Restoration of arch form
- Maintenance of bone
- Restoration of facial contours

HBO Failures

- Individual radiation effects are variable
- Improvement in oxygen tensions with HBO still do not reach normal
- HBO cannot resurrect dead bone

Conservative Treatment

- 85-90% exposed mandible may heal with conservative treatment
- Bone exposures limited to zone of attached gingiva-especially responsive
- Debride bone and overlying nonviable soft tissue
  - Removal of sequestra allows resorption of residual devascularized bone and ingrowth of neovascularization
- Avoid new incisions (rotational flaps)

Conservative Treatment Failure

- Predictors
  - Pain
  - Large volume of exposed bone
  - Pathologic fractures
  - Radiographic evidence of significant bone destruction
- These are also Stage III presentations

Marx Results

- Stage I 14%
- Stage II 18%
- Stage III 68%
Osteoradionecrosis - Treatment

- Stage III presentations
  - Pathologic fracture
  - Orocutaneous fistula
  - Radiographic changes to the inferior border of the mandible
  - Non responders to Stage II treatment

Osteoradionecrosis – Stage III Treatment

- Generous debridement of devascularized bone and soft tissues
- Coverage with vascularized tissues
- Perioperative HBO therapy?
Pectoralis Major Flap

- 54 year old male 1 year s/p right composite resection, fibula free flap reconstruction and 6850 cGy radiation therapy
- He developed exposed plate after minor trauma which has not healed after 2 months of local therapy
Pectoralis Major Flap

- 59 year old female s/p right neck dissection and 7400cGY radiation therapy for unknown primary carcinoma
  - Severe persistent lymphedema
  - Inability to maintain neck posture with inferior mandible necrosis
Pedicled Flaps

- Pectoralis major
  - Based on the thoraco-acromial vessels
  - Muscle only or a myocutaneous flap
  - Technically easy harvest
  - Can reach to most areas of the oral cavity
  - Bulky in some patients
  - Not a good choice for medially situated defects
Osteoradionecrosis - Vascularized Tissue Options

- Tissue and pedicle outside the radiated field
- Microvascular free flaps offer abundant source of soft tissue and bone unencumbered by pedicle length
- Allows extirpative surgeon not to “skimp” on resection
- Two team approach can be utilized
Osteoradionecrosis - Free Flap Selection

- Size and location of bony and soft tissue defects
- Local condition of recipient bed
- General condition of patient
- Prognosis

Osteoradionecrosis - Free Flap Selection

- Large bony defect
  - Fibula first; scapula, iliac crest, or radius if fibula not available
- Intact debrided mandible lacking soft tissue coverage
  - Radial forearm free flap primarily
- Patient with poor health, poor prognosis and/or posterior mandibular defect
  - Soft tissue free flap or pectoralis major flap
Radial Forearm Free Flap

- Has become the new “workhorse” flap in head and neck reconstruction
- Thin and pliable
- Ability to become sensate
- Long and large vascular pedicle
- Easy to harvest
- Minimal donor site morbidity

Osteoradionecrosis

- 68 year old female 9 years s/p 6950 cGY radiation therapy for mucoepidermoid carcinoma of the floor of mouth
- She has had an area of exposed bone despite previous debridement and 40 dives of peri-operative HBO
- Panorex shows no fracture
Osteoradionecrosis

- A draining orocutaneous fistula has been present for 1 month despite antibiotic therapy and local wound care
- No local vascularised tissues available for closure
Osteoradionecrosis

- 62 year old male 3 years s/p 6700cGY radiation therapy for tonsil carcinoma
- Exposed bone and pain for 6 months
- He presented with malocclusion and pathologic fracture

9 year follow-up
Free Flap Options

- Fibula
  - Up to 25cm bone available
  - Adequate for implants
  - Soft tissue moderately mobile
  - Potential to become sensate
  - Two team approach
  - Minimal morbidity
Osteoradionecrosis

- 57 year old female with pathologic fracture from osteoradionecrosis 7 years status post neutron beam radiation therapy for submandibular gland adenocarcinoma
Osteoradionecrosis

- 62 year old male with osteoradionecrosis in right retromolar trigone region
- He is 3 years status post 6750 cGY radiation therapy for tongue carcinoma

Panorex reveals pathologic fracture
Operative findings confirm the radiographic image
Osteoradionecrosis

- Patient initially does well and undergoes implant placement.
- 18 months after surgery, he develops a fracture of the left body which is fixated elsewhere with a reconstruction plate.

Osteoradionecrosis

- He subsequently develops an orocutaneous fistula which does not respond to conventional therapy.
Osteoradionecrosis - Free Tissue Transfer

- 6 patients with advanced ORN
- All failed conservative treatment and HBO therapy
- All underwent aggressive resection and reconstruction with fibula free flaps
- No significant complications

Osteoradionecrosis - Free Tissue Transfer

- 12 patients with advanced ORN
- 4 patients had prior HBO therapy
- All underwent mandibular segmental resection and fibula free flap repair
- No flap failures
  

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Osteoradionecrosis - Free Tissue Transfer

- One orocutaneous fistula
- One 25% loss of the fibula skin paddle
- Pain relieved in 90% of patients
- Trismus improved in 71% of patients
- Swallowing restored in 83% of patients within 2-4 weeks

Osteoradionecrosis - Systematic Management

- Prospective study of 33 patients
- Combined sequestrectomy with HBO therapy
- 7 patients (21%) with recurrent cancer
- Control rate of the 26 patients with ORN was 77% (20/26)
  Hao, SP, et al. Laryngoscope, 1999

Osteoradionecrosis - Systematic Management

- Limited sequestrectomy followed by HBO
- More radical approach if disease progresses
- If patient presents with Stage III ORN, proceed with radical sequestrectomy and free flap reconstruction
  - HBO not utilized
  Hao, SP, et al. Laryngoscope, 1999
Osteoradionecrosis - Treatment

- Surgery and adjunctive HBO
  - 18 patients
    - HBO plus sequestrectomy - 7
    - HBO plus radical resection - 11
  - 14 patients with complete healing
  - 3 patients with improvement
  - 1 patient with no change
  - Did not employ free tissue transfer

  Curi, MM, et al. IJOMS, 2000

Osteoradionecrosis - Treatment

- 17 Patients
- 1.2% of all head and neck cancer patients treated with radiation therapy
- Dental extraction triggering factor in 60% of cases
- Established treatment algorithm

  Vudiniabala, S, et al. IJOMS, 2000
Osteoradionecrosis - Free Tissue Transfer

- 29 patients
  - 23 patients (79%) treated with prior HBO therapy
  - 24 reconstructed with vascularised bone
  - 5 reconstructed with vascularised soft tissue
  - 4 flaps lost (14%)
  - All, however, had resolution of symptoms


Do We Need HBO?

- In patients with extensive ORN (clinical stage III)
  - 13/20 treated with debridement and clindamycin and postoperative HBO healed
  - 20/21 healed without HBO

Treatment of Advanced Osteoradionecrosis

- 30 patients who presented with Marx Stage III ORN of the mandible
  - Group I had no prior HBO therapy
  - Group II had received prior HBO therapy with debridement(s)
- All underwent debridement/resection with microvascular free flap reconstruction
- Main outcome measure was resolution of ORN as well as peri-operative complications

Gal TJ, and Futran ND. Arch Otolaryngol, 2003

### Demographic Data

<table>
<thead>
<tr>
<th>Marx Stage III</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td>No Previous HBO (N=10)</td>
<td>Failed Prior HBO (N=20)</td>
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<tr>
<td>Male</td>
<td>7 (70%)</td>
<td>8 (40%)</td>
<td>0.12</td>
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<tr>
<td>Mean age</td>
<td>65.8 +/- 14.5</td>
<td>60 +/- 7.7</td>
<td>0.16</td>
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<tr>
<td>Chemo</td>
<td>3 (30%)</td>
<td>3 (15%)</td>
<td>0.33</td>
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<tr>
<td>Cancer Surgery</td>
<td>6 (60%)</td>
<td>16 (80%)</td>
<td>0.24</td>
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<tr>
<td>Bone Resection for CA</td>
<td>1 (10%)</td>
<td>2 (10%)</td>
<td>0.09</td>
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<tr>
<td>Primary XRT</td>
<td>4 (40%)</td>
<td>4 (20%)</td>
<td>0.258</td>
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<tr>
<td>Postop XRT</td>
<td>6 (60%)</td>
<td>16 (80%)</td>
<td>0.243</td>
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<tr>
<td>Perip HBO</td>
<td>3 (30%)</td>
<td>0 (0%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>4 (40%)</td>
<td>3 (15%)</td>
<td>0.13</td>
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</table>
Distribution of Reconstructive Techniques

<table>
<thead>
<tr>
<th>Flap Type</th>
<th>Group 1 (N=10)</th>
<th>Group 2 (N=20)</th>
<th>Adjusted p value</th>
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<tbody>
<tr>
<td>Iliac Crest</td>
<td>2 (20%)</td>
<td>10 (50%)</td>
<td>0.046</td>
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<tr>
<td>Fibula</td>
<td>1 (10%)</td>
<td>8 (40%)</td>
<td>0.024</td>
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<tr>
<td>Forearm</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
<td>0.661</td>
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<tr>
<td>Rectus</td>
<td>1 (10%)</td>
<td>5 (25%)</td>
<td>0.425</td>
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Surgical Complications

<table>
<thead>
<tr>
<th>Flap Type</th>
<th>Group 1 (N=10)</th>
<th>Group 2 (N=20)</th>
<th>Adjusted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound Infection</td>
<td>1 (10%)</td>
<td>8 (40%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Fistula</td>
<td>1 (10%)</td>
<td>3 (15%)</td>
<td>0.661</td>
</tr>
<tr>
<td>Plate Exposure</td>
<td>1 (10%)</td>
<td>5 (25%)</td>
<td>0.425</td>
</tr>
<tr>
<td>Effusion</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td>0.243</td>
</tr>
<tr>
<td>Medical Complications</td>
<td>1 (10%)</td>
<td>2 (10%)</td>
<td>0.646</td>
</tr>
</tbody>
</table>

Treatment of Advanced Osteoradionecrosis

Complications by ORN status
Treatment of Advanced Osteoradionecrosis

- Microvascular reconstruction is effective in the management of Stage III ORN
- Patients who have had prior HBO and debridements had increased incidence of complications compared to the non-HBO group
- Pre-operative HBO therapy is not necessary to achieve a satisfactory outcome

Gal, TJ, and Futran, ND. Arch Otolaryngol, 2003

Osteoradionecrosis - Free Tissue Transfer

- 33 patients
  - 25 patients (76%) treated with prior HBO therapy
  - All reconstructed with vascularised bone
  - 24% wound complications
  - 15% late complications
  - 91% of patients had resolution of symptoms

Laryngeal Necrosis

- Estimated between 1-7% (may be increasing with more frequent use of combined modality treatment)
- Predisposing factors
  - Post treatment biopsy
  - Larger treatment fractions
  - Neutron radiotherapy
  - Inadequate compensation for laryngeal thickness in lateral opposed portals
  - Deeply ulcerative tumors
  - Continued smoking

Laryngeal Necrosis

- Pathophysiology
  - Fibrosis, endarteritis, tissue ischemia, hypoxia
- More acute than osteoradionecrosis
  - 5 months vs. 6-18
- Workup
  - Clinical examination and symptoms
  - ?PET
  - (MRI and CT very limited utility)
    - CT may show sloughing of arytenoid, fragmentation and collapse of the thyroid, +/− gas bubbles around cartilage

## Chandler’s Laryngeal Necrosis Staging System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Signs</th>
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<tbody>
<tr>
<td>I</td>
<td>Slight hoarseness; slight mucosal dryness</td>
<td>Slight edema; telangectasia</td>
</tr>
<tr>
<td>II</td>
<td>Moderate hoarseness; moderate mucosal dryness</td>
<td>Slight impairment of cord motility; moderate edema and erythema</td>
</tr>
<tr>
<td>III</td>
<td>Severe hoarseness with dyspnea; moderate odynophagia and dysphagia</td>
<td>Severe impairment of cord motility or fixation of one cord; marked edema; skin changes</td>
</tr>
<tr>
<td>IV</td>
<td>Respiratory distress; severe pain; severe odynophagia; weight loss; dehydration</td>
<td>Fistula; fetor oris; fixation of skin; laryngeal obstruction and edema occluding airway; fever</td>
</tr>
</tbody>
</table>


## Laryngeal Necrosis

- **Treatment**
  - Humidification
  - Antibiotics
  - Steroids
  - Analgesics
  - Biopsy
  - Hyperbaric oxygen
  - Salvage surgery
Laryngeal Necrosis

- **Treatment**
  - **Grade I-II**
    - Conservative management
      (Humidification/Antibiotics/Steroids/Analgesics)
  - **Grade III-IV**
    - Hyperbaric and/or surgery
    - 29/35 treated kept larynx


Skull Base Osteoradionecrosis - Nasopharynx

- **Actual percentage of radiated patients developing ORN difficult to ascertain**
  - More common in re-irradiated patients and those with poor nasal hygiene
- **Risk of internal carotid hemorrhage**
- **Endoscopic sequestrectomy successful in a series of 6 patients**
Skull Base Osteoradionecrosis - Temporal Bone

- Also rare, but can occur after parotid and ear canal irradiation
- Sequestrectomy and flap coverage are necessary
- Role of HBO therapy is unclear but likely similar to mandible

Skull Base ORN

- 79 year old male 3 years s/p lateral temporal bone resection and 6900cGY radiation therapy for ear SCCA
- He has had progressive soft tissue and bone breakdown for 6 months
  - Dura exposed
Rectus Abdominus

- Multitude of flap designs are available
  - Abundant amount of soft tissue
  - Excellent bulk
  - Long vascular pedicle
  - Minimal donor site morbidity
- Muscle will atrophy, but the subcutaneous tissue maintains its bulk
Bisphosphonate Osteonecrosis of the Jaw (BRONJ)

- Avascular necrosis of the mandible and/or maxilla associated with bisphosphonate use
- No consensus definition, but considered for exposed maxillofacial bone with no evidence of healing after 6 weeks
- Mechanism may be increased tendency to form intravascular thrombi and hypofibrinolysis
The New Problem

2001-2002: Striking increase in the number of cancer patients (breast cancer and multiple myeloma) presenting with exposed alveolar bone (osteonecrosis) or referred for management of “refractory osteomyelitis”
New Pathologic Entity...Osteonecrosis of the Jaws

- Painful areas of the jaws which occurred after simple dental procedures such as extractions
- Spontaneous areas of breakdown of soft tissues and bone
- Common link....BISPHOSPHONATES

Official name.....BRON / BRONJ

- B.....bisphosphonate
- R.....related
- O.....osteo
- N.....necrosis of the
- J.....jaws
Criteria for BRONJ diagnosis

- Exposed bone in the maxillofacial region that has persisted for more than 8 weeks
- Current or previous treatment with a bisphosphonate
- No history of radiation therapy to the jaws
Osteonecrosis warning
Cancer drugs preclude some dental procedures

BY BARK BERTHESS

Newsmakers, NY—Cancer patients treated with bone-metabolism drugs may be at increased risk for developing "osteonecrosis of the jaw"—and they should see conditions dental professionals, after a pharmacologically

Novartis Pharmaceuticals Corp is seeking a limit in its sales across the country, meanwhile, showing that the oral drug has been shown to cause cancer patients to develop oral osteonecrosis, or "osteonecrosis of the jaw," linked to factors such as antibiotics and steroids. The company said its drug, known as "NovoLog," has been used in the treatment of osteonecrosis of the jaw, a condition that affects cancer patients and others with bone-metabolism disorders.

Novartis recommends that cancer patients avoid dental procedures related to osteonecrosis of the jaw. For more information, contact Novartis Oncology at 800-666-6682 or visit www.novartis.com.

Dr. Holbrook, a member of the American Society of Clinical Oncology, said that osteonecrosis of the jaw is a complex problem that can affect all cancer patients and that the drug should be used cautiously in patients with osteonecrosis of the jaw. He noted that cancer patients should avoid dental procedures, as well as patients with bone-metabolism disorders.

Doctors and surgeons, endocrinologists, dermatologists, and other health care professionals must be aware of the risks of osteonecrosis of the jaw and should consider the use of osteonecrosis of the jaw drugs with caution.

Patients should be educated about the risks of osteonecrosis of the jaw and the potential for drug interactions. The drug should be used cautiously in patients with osteonecrosis of the jaw, especially those with bone-metabolism disorders.

For more information, contact Novartis Oncology at 800-666-6682 or visit www.novartis.com.

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For more information, contact Novartis Oncology at 800-666-6682 or visit www.novartis.com.
Alert on cancer patients issued
Research links bisphosphonate drugs, osteonecrosis of the jaw

“Geristore is so versatile!”
“I am still learning all of Geristore’s uses and it continues to amaze me!”

Scientific Literature Progress
Dental Management of Patients receiving Oral Bisphophonate Therapy-Expert Panel Recommendations

Report of the Council on Scientific Affairs
American Dental Association  July 2008

www.ada.org/prof/resources/topics/osteonecrosis.asp
Bisphosphonate Treatment Linked to Reports of Spontaneous Osteonecrosis of the Jaw

On September 24, 2004, the Food and Drug Administration (FDA) issued a warning about a rare but serious potential side effect of bisphosphonate treatment for osteoporosis, which is the treatment of bone disease in cancer patients. A dental implant patient who has received bisphosphonate therapy may be at risk for osteonecrosis of the jaw (ONJ) if certain criteria are met.

In the U.S., the Food and Drug Administration (FDA) has received reports of patients who developed ONJ while on bisphosphonates. The majority of the reported cases are cancer patients undergoing chemotherapy.

Osteonecrosis of the jaw is a condition that results in bone death and can lead to infection and loss of tooth support. The condition can be painful and can require surgical treatment.

On September 24, 2004, the FDA issued a public health advisory to inform healthcare professionals and consumers about the potential risk of ONJ. The advisory was based on data from the National Cancer Institute's Center for Cancer Research (CCR) and the National Cancer Institute's National Cancer Institute (NCI).

The FDA recommends that healthcare providers discuss the potential risk of ONJ with their patients who are taking bisphosphonates. Providers should also consider the potential risk of ONJ when prescribing bisphosphonates for patients with cancer.

Osteonecrosis of the jaw is a rare but serious condition that can affect the jaw bone. It is most commonly seen in patients undergoing chemotherapy for cancer. The condition can lead to the loss of teeth and the need for surgery.

On September 24, 2004, the FDA issued a public health advisory to inform healthcare professionals and consumers about the potential risk of osteonecrosis of the jaw (ONJ). The advisory was based on data from the National Cancer Institute's Center for Cancer Research (CCR) and the National Cancer Institute's National Cancer Institute (NCI).

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The majority of jaw problems seen with bisphosphonate treatment are associated with the use of intravenous forms of these drugs, which are used primarily for cancer patients.
IV Bisphosphonates

- Pamidronate sodium.....AREDIA
- Zolendronic acid......ZOMETA
- Etidronate......DIDRONEL
- Ibandronate........BONIVA

Oral Bisphosphonates

- Alendronate.....FOSAMAX
- Risendronate.......ACTONEL
- Ibandronate......BONIVA
- Tiludronate.....SKELIDE
- Etidronate.......DIDRONEL
Relative Potency of Nitrogen-Containing Bisphosphonates

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Generic Name</th>
<th>Relative Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosamax</td>
<td>Alendronate</td>
<td>1,000</td>
</tr>
<tr>
<td>Actonel</td>
<td>Risedronate</td>
<td>5,000</td>
</tr>
<tr>
<td>Boniva</td>
<td>Ibandronate</td>
<td>10,000</td>
</tr>
<tr>
<td>Aredia</td>
<td>Pamidronate</td>
<td>100</td>
</tr>
<tr>
<td>Zometa</td>
<td>Zoledronic acid</td>
<td>100,000</td>
</tr>
<tr>
<td>Reclast</td>
<td>Zoledronic acid</td>
<td>100,000</td>
</tr>
</tbody>
</table>

Table 2. Oral and Intravenous Bisphosphonates

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Formulations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actonel</td>
<td>Proctor &amp; Gamble Pharmaceuticals</td>
<td>risedronate</td>
</tr>
<tr>
<td>Boniva</td>
<td>Micromedex</td>
<td>clodronate</td>
</tr>
<tr>
<td></td>
<td>Roche/GlaxoSmithKline Pharmaceuticals</td>
<td>ibandronate (not commercially available in the U.S.)</td>
</tr>
<tr>
<td>Didronel</td>
<td>Proctor &amp; Gamble Pharmaceuticals</td>
<td>etidronate</td>
</tr>
<tr>
<td>Fosamax</td>
<td>Merck &amp; Co.</td>
<td>alendronate</td>
</tr>
<tr>
<td>Fosamax Plus D</td>
<td>Merck &amp; Co.</td>
<td>alendronate</td>
</tr>
<tr>
<td>Skelid</td>
<td>Sanofi-aventis</td>
<td>tiludronate</td>
</tr>
<tr>
<td><strong>Intravenous Formulations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aredia (cancer therapy)</td>
<td>Novartis</td>
<td>pamidronate</td>
</tr>
<tr>
<td>Boniva (cancer therapy)</td>
<td>Schering AG</td>
<td>clodronate</td>
</tr>
<tr>
<td>Boniva IV (intravenous infusion for osteoporosis)</td>
<td>Roche/GlaxoSmithKline Pharmaceuticals</td>
<td>ibandronate</td>
</tr>
<tr>
<td>Reclast (cancer therapy)</td>
<td>Novartis</td>
<td>zoledronic acid</td>
</tr>
<tr>
<td>Zometa (cancer therapy)</td>
<td>Novartis</td>
<td>zoledronic acid</td>
</tr>
</tbody>
</table>
Bisphosphonates

- Initially given intravenous (IV) to combat hypercalcemia seen in multiple myeloma and metastatic disease such as breast cancer
- Used to treat Paget’s disease of bone
- Prevents bone breakdown

How do Bisphosphonates Work?

- PRIMARILY inhibit osteoclast activity
- Also affects osteoblast activity, which secondarily affects osteoclast activity
- The combined action causes physiologic bone remodeling and deposition to be severely affected
How do Bisphosphonates Work?

- Also have antiangiogenic properties and may be tumoricidal, making them important in cancer therapy
- Bind directly to bone mineral and concentrate selectively in bone
- If not used...excreted in urine

Uses of Bisphosphonates

- Effective osteoclast inhibitor used for:
  - Hypercalcemia of malignancy
  - Breast cancer (bone metastases)
  - Multiple myeloma
  - Paget’s disease
  - Osteoporosis
Osteoporosis

- Major public health threat for 44 million Americans, or 55% of people 50 years of age and older
- In USA, 10 million have osteoporosis
- In USA, 34 million have low bone mass, placing them at risk for osteoporosis

BRONJ is more common with IV bisphosphonate use but can also occur with oral bisphosphonate therapy........
***** KEY ITEM *****

- The half life of bisphosphonates is extremely LONG, still uncertain, and measured in YEARS

Incidence of BRONJ

- IV bisphosphonates….0.8 % - 12 %
- Oral bisphosphonates….0.09-0.34 %
- “THERE MAY BE SERIOUS UNDER-REPORTING”

- IV bisphosphonate patients having dentoalveolar surgery are at least 7 times more likely to develop BRON than patients not having dentoalveolar surgery
Osteoporosis

- 1.5 million people suffer bone disease related fractures each year
- 4 out of 10 white women, 50 years and older in USA will experience a hip, spine or wrist fracture during their remaining life
- 13% of white men will experience an osteoporosis fracture

Osteoporosis….complications

- Chronic pain, disability and in some cases….DEATH
- 2/3 never regain their full level of function experienced prior to fracture
- 20% of hip fractures die within 12 months
- Patients surviving hip fracture, 50% require long term assistance with ADL and 25% require full time nursing home care
OSTEOPOROSIS is a major public health issue and is “bad disease”

ONJ…Dental Comorbidities

- Periodontitis 84%
- Dental caries 28%
- Abscessed teeth 13%
- Root canal therapy 10%
- Presence of mandibular tori 9%
Precipitating Events of ONJ

- Tooth extraction 37%
- Spontaneous 25%
- Advanced periodontitis 28%
- Periodontal surgery 11%
- Dental implants 3%
- Apicoectomy 1%

Patients may be considered to have BRONJ if all of the following 3 characteristics are present:

1. Current or previous treatment with a bisphosphonate
2. Exposed bone in the maxillofacial region that has persisted for more than 8 weeks
3. No history of radiation therapy to the jaws
4 Stages of BRONJ

- Stage 0: Signs and symptoms short of exposed necrotic bone that might indicate a histologic necrosis or a prenecrotic state;
- Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection;
- Stage 2: Exposed/necrotic bone in patients with pain and clinical evidence of infection; and
- Stage 3: Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border.

Clinical Presentation
CT Scans
How do you Manage This?

- Biopsy….rule out malignancy?
- Conservative debridement?
- Aggressive debridement/resection?
- IV antibiotics …. Longterm??
- Hyperbaric oxygen(HBO) treatments…similar to ORN
Conservative Debridement

Post-op
Resection...Dead Bone

Reconstruction
Vascularised Bone Flap
Where are we Today???
Reported Cases of ONJ

<table>
<thead>
<tr>
<th>Study</th>
<th>Data collection</th>
<th>Findings</th>
<th>Estimates of BON in oral bisphosphonates (cases per million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tcholakian T, Cheifetz S, et al.</td>
<td>Survey on oral bisphosphonate use among patients with ONJ</td>
<td>1 case of BON per 1,000,000 patients receiving oral bisphosphonates</td>
<td>1 out of 2,000 (0.0005%)</td>
</tr>
<tr>
<td>Blackwell D, et al.</td>
<td>Randomized controlled trial with one year follow-up of patients receiving bisphosphonates</td>
<td>No spontaneous reports of BON during the study</td>
<td>0</td>
</tr>
<tr>
<td>Donahue S, et al.</td>
<td>Use of oral bisphosphonates and the risk of asymptomatic oral osteonecrosis: A nested case control study</td>
<td>A retrospective review of the database identified 23 possible cases of BON in the treatment group and 2 in the control group</td>
<td>0</td>
</tr>
<tr>
<td>Gansky SA, et al.</td>
<td>U.S. Medicare claims data of 17,417 patients</td>
<td>30 cases per million-per-year cohort, risk ratio 2.5 (95% CI 1.1 - 5.6)</td>
<td>0 out of 2,763</td>
</tr>
</tbody>
</table>

Major Goals of Treatment

- Prioritization and support of continued oncologic treatment in patients receiving IV bisphosphonates
- Preservation of quality of life through:
  - Patient education and reassurance
  - Control of pain
  - Control of secondary infection
  - Prevention of extension of lesion and development of new areas of necrosis
58 patients
- 41 surgically treated with conservative debridement and or local flap coverage

28 patients fully healed at 6 month follow up

11/12 patients with flap closure fully healed
What about HBO?

- The jury is still out
- Some case reports suggest there may be a beneficial role
- Two randomized clinical trials are underway at Duke University and University of Minnesota
Our Knowledge Base is Getting Better

- “Hot topic” among medical and dental specialties
- Research is under way
- “Expert group” guidelines available

Problem with Guidelines

- At this point…nobody really knows for sure
- They will clearly be modified as scientific data becomes available
- They are OPINION…..but the best we have currently
Management Strategies

- Patients about to begin bisphosphonates
- COMMUNICATION between MD and dentist
- Delay treatment until dental health optimized
- Extractions of teeth heal 14-21 days before treatment
- Carefully inspect dental prosthesis
**Management Strategies**

- Patients receiving IV bisphosphonates
  - Maintain good oral hygiene and dental care
  - Avoid osseous surgery
  - RCT preferred over extraction

**Management Strategies**

- Patients on oral bisphosphonates
  - “sound recommendations that are based on strong clinical research designs are lacking”
  - “for individuals taking bisphosphonates LESS than 3 years and have no clinical risk factors…no delay in planned surgery is necessary”
Management Strategies

- Patients with oral bisphosphonates less than 3 years and risk factors
- Patients with oral bisphosphonates greater than 3 years
- CONSIDER “drug holiday” off bisphosphonates 3 months before surgery

Management Strategies

- Patients with BRONJ Stage 1
- Exposed bone …asymptomatic..no infection
- NO SURGERY…treat conservatively
- Peridex rinses
Management Strategies

- Patients with BRONJ Stage 2
- Exposed necrotic bone with pain and infection
- Peridex rinses
- Oral antibiotics …penicillin, quinolones, Flagyl, Cleocon
- Debridement with local tissue closure
- HBO therapy

Management Strategies

- Patients with BRONJ Stage 3
- Exposed/necrotic bone with pain, infection and pathologic fracture or extraoral fistula or osteolysis extending to inferior border
- Surgical debridement/resection followed by vascularised tissue reconstruction
- Antibiotic treatment
Management Strategies

- HBO use still equivocal but some clinical studies suggest benefit
- Regardless of disease stage, mobile segments of bony sequestrum should be removed
Now.....a Dose of Reality.....the lawyers are involved
April 26, 2000
Fred Look
FRED LOOK, DMD
6TH, 114
5141 DOVE HWY
LOUISVILLE, KY 40218

Re: Medical/Legal Alert — Fosamax and Dead Jaw Syndrome

Dear Dr. Look:

Fosamax, the most commonly prescribed bisphosphonate in the United States, is commonly used to build bone density in postmenopausal patients, as well as some cancer patients. Fosamax has now been linked to subluxations of the jaw, which is sometimes referred to as “dead jaw.” A report in the Journal of Oral and Maxillofacial Surgery confirmed the role that Fosamax plays in this very serious condition. This prompted an FDA warning regarding the relationship between bisphosphonates and osteonecrosis, including Fosamax. A copy of this FDA notice is enclosed for your review.

Hughell & Coleman is representing individuals who have suffered osteonecrosis following use of Fosamax or other bisphosphonates. We are available to consult with any of your patients who are suffering from osteonecrosis. If you have any such patients please feel free to provide them with a copy of this letter and the FDA notice. I am also enclosing some of my business cards. Our firm has offices in Nashville, Tennessee, and Louisville, Lexington, and Bowling Green, Kentucky. We represent individuals throughout Tennessee and Kentucky.

If you have any questions or comments please contact me directly at (615) 785-2194 ext. 127 or by email at Coleman@HughellColeman.com.

Sincerely yours,

[Signature]

Leif L. Carter
Trial Lawyer
The Future……..

- We are getting more answers……slowly
- Research is ongoing…..
- There are still many questions…..

Conclusions

- BRONJ is a “real problem”
- We have just seen the “tip of the iceberg”
- BRONJ may be managed but may not be cured
- Bisphosphonate patients will cause re-evaluation of dental treatment plans
- Otolaryngology will be required to communicate and interact with internal medicine and dental colleagues
Conclusions

- This is a different disease than ORN
  - Not an isolated focus of bony change
- Preventative measures similar to ORN
- Role of HBO therapy unclear at this time
- Conservative management with minimal debridement, antibiotic therapy, chlorhexidine rinse is the rule
- ? Stop bisphosphonate therapy if possible

“even a small percent complication rate, when applied to a large patient pool……leaves you with a significant number of affected individuals…..”
Conclusions

- Osteonecrosis of the jaws is a spectrum of bone damaging disease
- Osteonecrosis is a preventable disease in many cases
- HBO therapy is a valuable tool in the treatment algorithm for ORN
- Keys to success:
  - Adequate debridement of non-viable bone, cartilage, and soft tissue
  - Reconstruction and coverage with well vascularized tissues
Osteoradionecrosis - Indications

- Small areas of exposed bone may be treated conservatively
- Indications for active treatment
  - Pain
  - Large expanse of exposed bone
  - Orocutaneous fistulae
  - Radiographic evidence of extensive bone damage
  - Pathologic fracture
Osteoradionecrosis - Marx Staging

- I - Bone exposed for greater than 6 months
- II - Wounds which do not resolve when treated as Stage I
- III - Poor prognostic factors
  - Fracture
  - Fistula
  - Full thickness bony changes

Osteoradionecrosis - Treatment

- Stage 1
  - 30 HBO treatments at 2.4 ATA for 90 minutes each
  - Maintain wound irrigation
  - If good response proceed with 10 HBO treatments to achieve full mucosal coverage
  - Non-responders move to Stage II
Osteoradionecrosis - Treatment

- Stage III
  - Option 1
    - External fixation, 10 dives of HBO with reconstruction 10-12 weeks later
  - Option 2 (preferred)
    - Immediate reconstruction with soft tissue and/or bone containing tissue transfer

Osteoradionecrosis - Free Flap Selection

- Large bony defect
  - Fibula first; scapula or iliac crest if fibula not available

- Intact debrided mandible lacking soft tissue coverage
  - Radial forearm free flap primarily

- Patient with poor health, poor prognosis and/or posterior mandibular defect
  - Soft tissue free flap
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Osteoradionecrosis - Prevention

- Include dental care prior to start of radiation therapy
- Pre-radiation dental procedures
  - Fluoride trays
  - Frequent cleaning for plaque and cavity control
  - Patient education
Osteoradionecrosis - Prevention

- If dental extractions or implants are required after radiation therapy:
  - 20 pre-op dives of HBO followed by:
    - Invasive dental therapy
    - Perioperative antibiotic coverage
    - 10 post treatment dives of HBO

30:10 Protocol

- 30 preoperative dives
  - Decrease area of necrotic tissue
  - Allow surrounding area to heal
- Surgery-Debride back to bleeding tissue
- 10 postoperative dives
Hyperbaric oxygen treatment cont.

- Stage II (Marx):
  - If Stage I patients do not have improvement after 30 dives, they are classified as Stage II.
  - 30 dives
  - Local surgical debridement (transoral alveolar sequestrectomy)
  - 10 additional dives

- Stage III (Marx):
  - Stage II patients who do not have improvement after 30 dives and debridement
  - Patients with a fistula, pathologic fracture or radiographic evidence of osteolysis at the inferior border
Hyperbaric Oxygen treatment cont.

- Stage III Protocol
  - 30 dives
  - Sequestrectomy
  - Transoral partial mandibulectomy
  - 10 dives
  - Mandibular reconstruction 10 weeks post completion with cadaveric bone tray
  - 10-20 dives
  - Prosthetic rehabilitation 3 months afterwards

Radical surgical treatment

- Indications
  - Pathological fracture
  - Exposed necrotic bone
  - Persistent fistula
Osteoradionecrosis:

- Rarely reported complication of fixture placement
- 5 out of 17 patients in present series
- Devastating complication requiring sequestrectomy or segmental resection of bone
- Primary Placement of fixtures
- Use of perioperative H.B.O if delayed placement
Mt. Sinai Protocol

- Algorithm developed for implant placement

Alternatively….

Delayed implant placement at 18 to 24 months (without the use of adjunctive HBO) to allow for bone to recover after radiation treatment
Recommendation:

- Primary Placement
- Use of Hyperbaric Oxygen for delayed placement
- Delayed secondary placement (with Caution)

Hyperbaric Oxygen:

- Indicated when RT dose > 6000 R (60 Gy)
- Produces angiogenesis in damaged irradiated tissues
- Increases fibroblast-like mesenchymal cell population in area
- Reverses the hypoxia inherent in radiated tissues
EFFECTS OF HYPERBARIC OXYGEN

- Induction of angiogenesis
  - Related to oxygen gradients
- Induction of fibroplasia
- Increased resting oxygen tension levels
- Increased healing capacity as host bed may support reconstructive efforts, resist infection, and respond to trauma

Hyperbaric Oxygen Protocol:

- 20 pre-operative dives 100% O₂ at 2.4 ATA for 90 minutes each
- Surgical procedure
- 10 post-operative dives at 2.4 ATA for 90 minutes each

Note:
  - Effect of HBO is long lasting. Only post-op dives are necessary when pt. Requires additional surgical procedures