The Role of Hyperbaric Oxygen Therapy (HBOT) in Preventing Osteoradionecrosis: Interim Results from a Prospective Clinical Trial

ISOO Parallel Session

Saturday, June 30, 2018

Vienna, Austria

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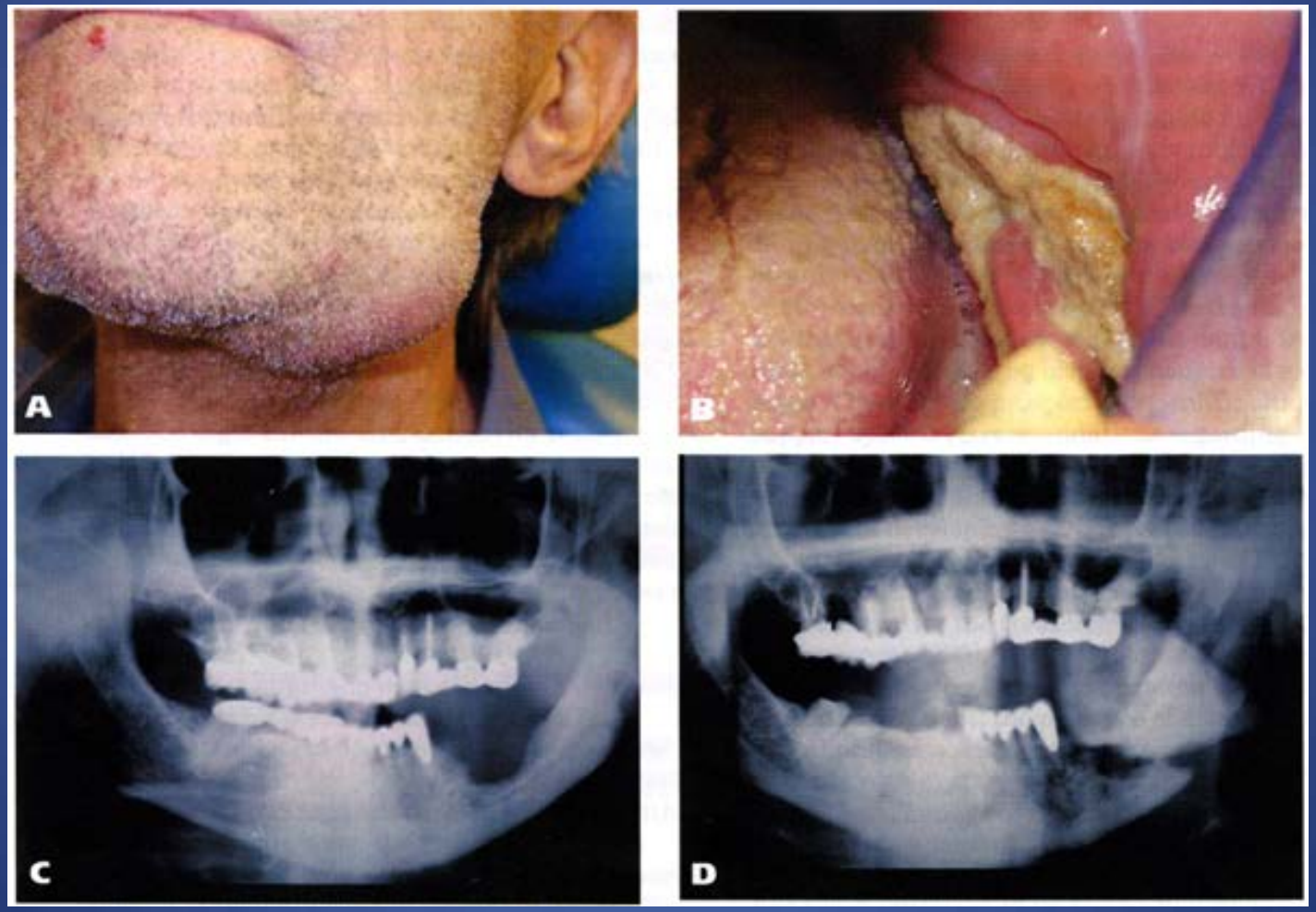
Outline of Presentation

- The Clinical Problem (ORN)
- HBO in Prevention: Does it Work?
- Designing a Study to Find Out
- Interim Results: Emerging Questions

The Clinical Problem (ORN)



Historical Definition of ORN

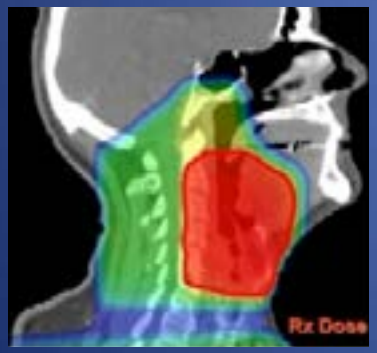
A non-healing mucosal or skin opening with underlying exposed devitalized bone in area of previous high-dose radiotherapy

Prevalence of ORN

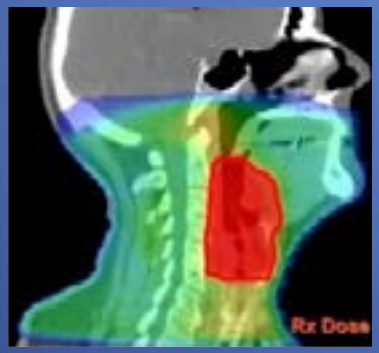
Table 1. Weighted prevalence from 31 studies.[4]

Modality	Prevalence
Conventional RT	7.4%
Intensity Modulated RT	5.2%
Chemo-radiotherapy	6.8%
Brachytherapy	5.3%

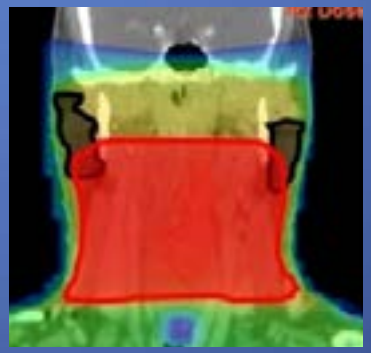
Adapted from Peterson, Hovan et al, 2010



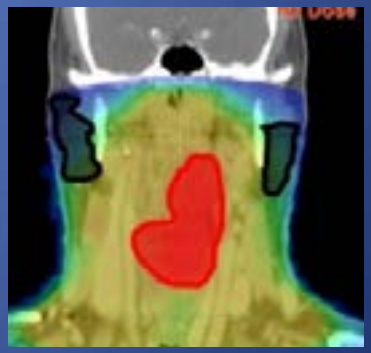
Conventional



IMRT



Conventional



IMRT

4) Peterson, Hovan et al, Support Care Cancer, 2010

Risk Factors for ORN

- Exposure > 6000 cGy [5, 9, 10, 13]
- Posterior mandible exposed [11]
- Poor dentition and oral hygiene [12]
- Poor nutrition [14]
- Smoking [6]
- Ill-fitting prosthesis causing chronic trauma [11]
- **Post-RT extraction** [13]

5) Reuthers et al, Int J Oral Maxillofac Surg, 2003.
6) Freiberger et al, Int J Radiat Oncol Biol Phys, 2009.
9) Katsura et al, Oral Surg Oral Med Oral Pathol, 2008.
10) Thorn et al, J Oral Maxillofac Surg, 2000.
11) Kluth et al, J Prosth Dent, 1988.
12) Murray et al, Oral Surg Oral Med Oral Path, 1980.
13) Schwartz & Kagan, Am J Clin Onc, 2002.
14) Teng et al, Current Opinion, Otolaryng Head Neck Surg, 2005.

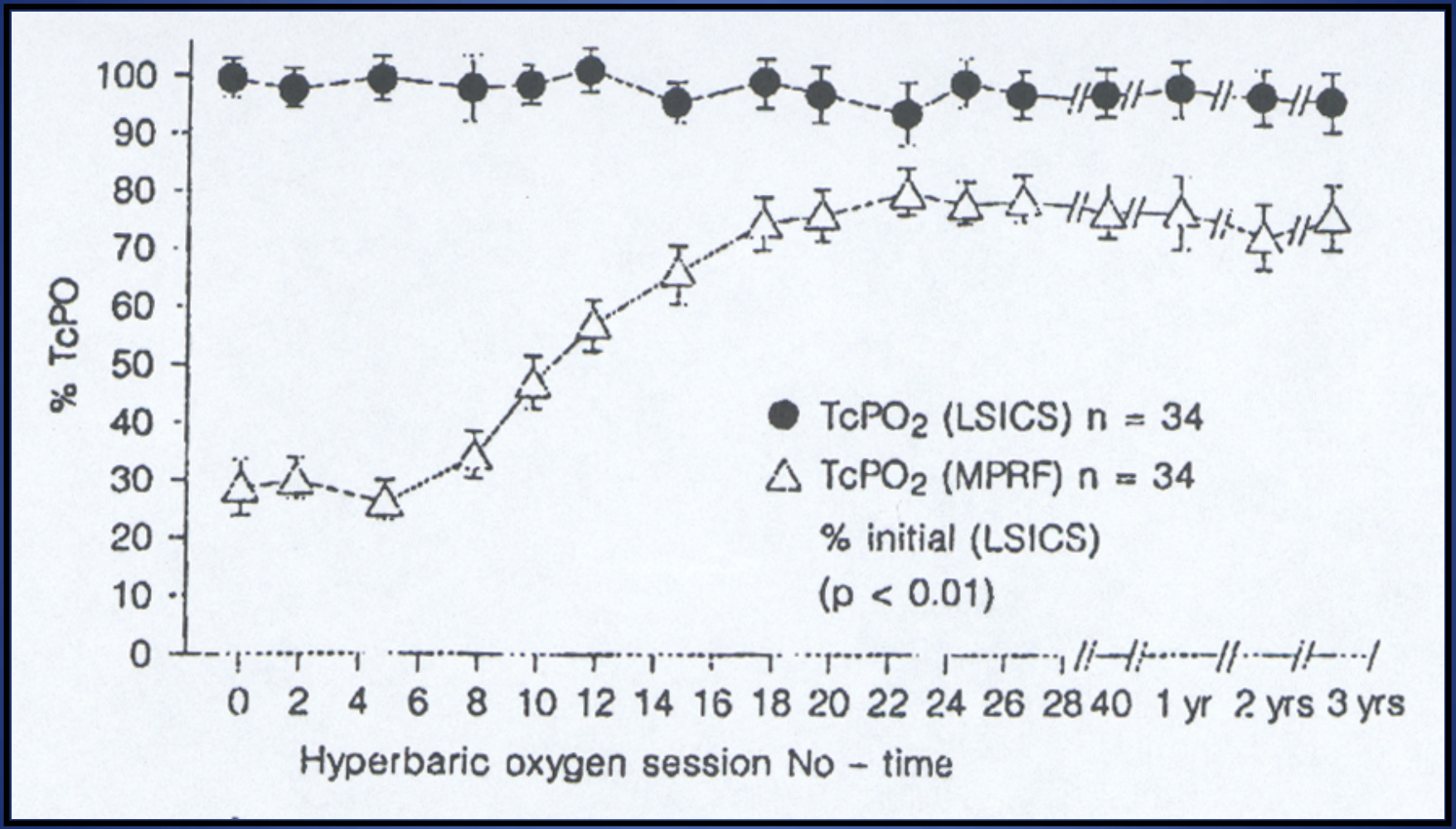
The Purported Solution - HBO
What is HBO?

- Patient breathes oxygen at a pressure ~ 2.5X greater than normobaric pressure (1ATA) for a predetermined period of time

- Typical "dosing" is 2.4 ATA X 90 minutes

- Drug = Oxygen

- Dosing Apparatus = Hyperbaric Chamber


100
90
80
70
60
50
40
30
20
10
0
% TcPO
TcPO2 (LSICS) n = 34
TcPO2 (MPRF) n = 34
% initial (LSICS)
(p < 0.01)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 40 1 yr 2 yrs 3 yrs
Hyperbaric oxygen session No – time

ORN Treatment Protocol Details

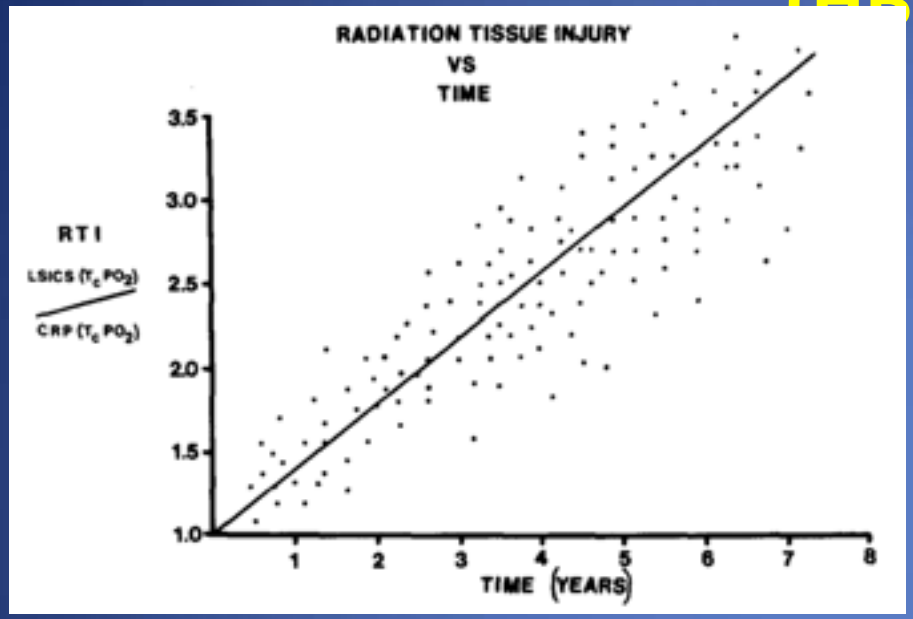
- ***Prophylaxis*** when surgery is performed in radiated tissue without frank RN (eg. dental extractions, implant placement, etc.)

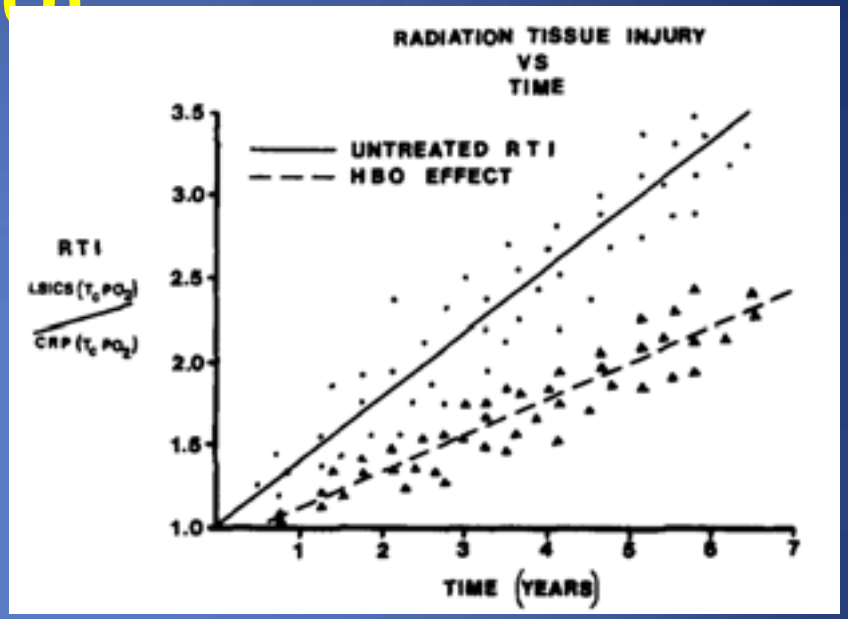
20/10

- ***Established ORN*** (Marx or Miami protocol)

30/10

Rationale for Hyperbaric Oxygen Therapy (HBO)





- HBO increase blood-tissue oxygen gradient
- Fibroblast proliferation, angiogenesis, collagen formation[1, 7]
- Bactericidal & bacteriostatic[7]

1) Marx, J Oral Maxillofac Surg, 1983.

7) Marx & Johnson, Oral Surg Oral Med Oral Path, 1987.

Vancouver HBU Statistics
Treated 2016-2017 (23 months)

Delayed Radiation Injury	69
Problem Wounds	47
CO Poisoning	36
Decompression Sickness	25
Chronic Refractory Osteomyelitis	13
Sensori-Neural Hearing Loss	9
Gas Embolus	9
Necrotizing Soft Tissue Infections	7
Clostridial Myonecrosis	5
Compromised Flaps / Grafts	2
Severe Blood Loss Anemia	1

Peterson et al

Support Care Cancer (2010) 18: 1089-1098

Recommendations for Future Research

1. Are there specific valid predictors of ORN risk?

2. Is there a subset of patients at risk for ORN for whom HBO is/is not effective?

3. **What is the role of "adjuvant preventive therapy" (including HBO)?**

The Controversy: HBO for post-RT extractions?

For

CLINICAL CONTROVERSIES IN ORAL AND MAXILLOFACIAL SURGERY: PART ONE

J Oral Maxillofac Surg
50:268-274, 1992

Management of Dental Extractions in Irradiated Jaws: A Protocol With Hyperbaric Oxygen Therapy

PAUL M. LAMBERT, DDS,* NANCY INTRIERE, DMD,† AND RALPH EICHSTAEDT, DDS‡

Dental management of patients who are about to receive, or who have completed a course of therapeutic radiation involving the jaws, remains a perplexing problem. The center of debate is whether to extract teeth before radiation therapy or to manage them more conservatively and preserve the dentition to the greatest extent possible. The principal concern in this debate is how to minimize the risk of developing the most destructive complication associated with head and neck radiation, osteoradionecrosis (ORN).

Tumoricidal levels of irradiation damage all tissues exposed. The accepted cause of ORN is progressive obliterative endarteritis and fibrosis resulting in hypovascular, hypocellular, and hypoxic tissues that can necrose spontaneously or in response to trauma. The incidence of ORN after radiation is reported to be widely different in several studies, ranging between 2% and 85%.[1-5] The causal relationship between dental extractions and ORN has been discussed by several authors.[6-10] Beumer et al[11] reported that the most common factors associated with ORN were postradiation extractions (26.5%), spontaneous bone exposure associated directly with the dentition secondary to dental disease (22.8%), and preradiation extractions (20.4%).

In an effort to prevent ORN, Marx et al[12] proposed prophylaxis with hyperbaric oxygen (HBO) before postradiation dental extractions. In a multicenter trial, 74 patients were randomized to receive one of two treatments. One group received penicillin preoperatively and for 10 days after surgery. The second group received no antibiotics, but received HBO (20 sessions of 90 minutes each, breathing 100% humidified oxygen at 2.4 atmospheres absolute pressure before surgery and 10 sessions after surgery). Extractions were performed in the same manner in both groups using elevator mobilization and forceps delivery with minimal alveoloplasty and no attempt to achieve primary mucosal closure. The end point of the follow-up period was a "yes or no" clinical diagnosis of ORN defined as the presence of exposed bone in a study socket after 6 months. There were 137 socket wounds in 37 patients in the antibiotic group and 156 sockets in 37 patients in the HBO group. In the antibiotic group, 31 sockets (22.6%) in 11 patients (29.9%) were positive for ORN, whereas only four sockets (2.6%) in two patients (5.4%) were positive for ORN in the HBO group.

Some clinicians believe that the high cost and limited availability of HBO precludes recommending its universal application for ORN prophylaxis.[13,14] Maxymiw et al[15] performed 449 extractions in 72 radiated (25 to 84 Gy) patients. All extractions were performed without HBO, and no ORN developed during the follow-up period (median, 4.8 years).

In view of these findings, an important question remains with an unclear answer. Should unrestorable teeth be extracted before radiation therapy, after therapy with HBO prophylaxis, or after radiation therapy without HBO prophylaxis? This article presents data from our own experience with adjunctive HBO for dental extractions and reviews the pathophysiology of

* Oral & Maxillofacial Surgeon and Chief, Dental Service, Veterans Affairs Medical Center, Dayton OH; Associate Clinical Professor, Wright State University School of Medicine; Assistant Clinical Professor, Ohio State University College of Dentistry.
† Assistant Chief, Dental Service, Veterans Affairs Medical Center, New York, NY; Formerly, Staff Oral & Maxillofacial Surgeon,

Against

CLINICAL CONTROVERSIES IN ORAL AND MAXILLOFACIAL SURGERY: PART TWO

J Oral Maxillofac Surg
50:1270-281, 1992

Management of Dental Extractions in Irradiated Jaws: A Protocol Without Hyperbaric Oxygen Therapy

LEWIS CLAYMAN, DMD, MD*

The absolute incidence and prevalence of osteoradionecrosis (ORN) of the jaws after radiation therapy (RT) for treatment of oral and oropharyngeal cancer are unknown. Since 1922, when Coutard[1] reported the Fondation Curie's experience with ORN, one finds that it has been observed to occur in both dentulous and edentulous patients, either spontaneously or after wounding. In particular, ORN has been noted to occur after dental extractions performed shortly before or at any time after RT. Reviewing studies from the literature, most of which are retrospective, one finds an overall incidence of ORN of 11.8% before 1968 (Table 1) and 5.4% after that date (Table 2), by which time almost all radiation oncology units had embraced megavoltage or supervoltage therapy. These data were based only on the presence of ORN without subcategorization into dentulous, edentulous, spontaneous, or extraction related. Unfortunately, this risk, although highest during the first 4 to 12 months after RT, has been found to persist for the remainder of the patient's life.[1-10]

The older concept of ORN developing consequent to a triad of RT above a critical dose, local trauma, and infection was articulated in 1938 by Watson and Scarborough[10] with support by others.[11,12] In the 1980s this concept was challenged by Marx,[10,13] who suggested an alternate hypothesis that ORN resulted from radiation-induced deficient cellular turnover and collagen synthesis in an hypoxic, hypovascular, and hypocellular environment in which tissue breakdown exceeded the repair capabilities of the wounded tissue.[10]

Because the presence of carious and periodontally compromised teeth in the irradiated mandible has long been associated with ORN, controversy has existed regarding whether such teeth should be removed before or after RT, whether they should ever be removed, and, if they should be removed, when, by what technique, and by whom. Thirty years ago it was recognized that the maintenance of a healthy dentition was essential for the prevention of ORN. This required the willing participation of a dentist to assess and monitor the dentition and to remove teeth as necessary.[16,17] All teeth that were grossly carious, periodontally hopeless, or had a poor prognosis for retention beyond 12 months[9] were removed before RT,[10] with extractions after RT being avoided as much as possible.[9] Fully embedded teeth were not removed.[10,18] At the time of extraction, alveoloplasty with primary closure, the use of preoperative and postoperative antibiotics, and a 10-day wait before starting RT were recommended. Although the use of systemic antibiotics was well supported in the literature of this time,[7,17,19-21] a more recent article by Marciani and Ownbey[22] reported excellent results both for pre-RT and post-RT extractions without using antibiotics. After the adoption of an organized plan to manage the dentition, and the use of high-energy radiation therapy in the years after 1968, the rate of ORN for extractions performed before RT fell to 4.4% (Table 3).

Most studies have reported a higher rate of ORN after dental extractions after RT than before it. However, in carefully evaluated patients who received aggressive preventive dental care and whose extractions were performed by experienced oral and maxillofacial surgeons, the five most recent studies have reported a prevalence of ORN of only 1.1% in 424 patients who had teeth removed after RT.[21-23]

Controversy: HBO for post-RT extractions?

For

- Marx trial (1985)
  - 74 patients for exo
    - 37 abx + HBO

Protocol	ORN Incidence
Abx + HBO	5.4%
Abx	29.9%

This remains the only randomized trial to-date to study this effect

Against

Systematic reviews:

1) Peterson, Hovan et al, 2010.
   - 1990-2008 (excludes Marx)

"Use of prophylactic HBO therapy for prevention of ORN in post-RT extractions."

"Level of evidence III, recommendation grade C:
no guideline possible."

4) Peterson, Hovan et al, Support Care Cancer, 2010

Controversy: HBO for post-RT extractions?

For

- Marx trial (1985)
  - 74 patients for exo
    - 37 abx + HBO
    - 37 abx (no HBO)

Protocol	ORN Incidence
Abx + HBO	5.4%
Abx	29.9%

This remains the only randomized trial to-date to study this effect

Against

Systematic reviews:

1) Peterson, Hovan et al, 2010.

2) Nabil & Samman, 2011.
(19 studies)

Protocol	ORN Incidence
Abx + HBO	4%
Abx	6%

"Based on ***weak evidence***, prophylactic HBO is effective in reducing ORN development after post-RT extractions."

15) Nabil & Samman, Int J Oral Maxillofac Surg, 2011.

Controversy: HBO for post-RT extractions?

For

- Marx trial (1985)
  - 74 patients for exo
    - 37 abx + HBO

Protocol	ORN Incidence
Abx + HBO	5.4%
Abx	29.9%

This remains the only randomized trial to-date to study this effect

Against

Systematic reviews:

1) Peterson, Hovan et al, 2010.

2) Nabil & Samman, 2011.

3) Chuang, 2011. (14 studies)

Protocol	ORN Incidence	Median
Abx + HBO	0-11%	4.1%
Abx	0-29.9%	7.1%

No statistically significant difference.

16) Chuang, J Evid Based Dent Pract, 2011.

Is There Any Evidence to Support The Use of Prophylactic HBO Post-XRT?

Study Question:

Does Hyperbaric Oxygen Therapy (HBOT) reduce osteoradionecrosis (ORN) rates and improve Quality of Life (Q of L) in patients requiring oral surgical procedures following a course of high-dose head and neck radiation?

Objectives of Study:

1. *To determine whether there is a lower rate and severity of ORN in head and neck radiotherapy patients who receive prophylactic HBOT prior to dental extractions.*

2. *To determine whether there is a difference in Quality of Life measures in subjects who received/did not receive HBOT*

REB-Approved Study

- *Prospectively enroll all H&N pts who received high-dose RT with or without concurrent chemotherapy who now require dental extractions to determine the prevalence of ORN when treated with or without prophylactic HBO.*

- *The HBO-treated patients will be from the BCCA who are routinely referred to the VGH HBU for prophylactic HBO*

- *The non-HBO control patients will be from the Northeast Cancer Centre in Sudbury Ontario who are not referred for prophylactic HBO*

Study Design

- Baseline assessments prior to oral surgery; each tooth assessed re (a) difficulty of extraction (b) effective dose
- All patients given same pre-op and post-op medications; surgical technique standardized between centres
- Patients seen in first week post-extractions; then at 2 w, 1 m, 6m, 1 y and 2 y follow-ups
- At each visit, assessed re +/- ORN; if present, ORN staged and managed
- EORTC QLQ-30 and EORTC-43 (H&N) questionnaire applied at each visit

ORN Assessment Scales

Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0

Grade 1: Asymptomatic; Radiographic findings only

Grade 2: Symptomatic and Interfering with Function; Minimal Bone Removal Indicated

Grade 3: Symptomatic and Interfering with Daily Life Activities; Operative or HBO

Grade 4: Disabling

ORN Stage: Lyons et al. 2014

Stage 1: <2.5 cm; Asymptomatic

Stage 2: >2.5 cm; Asymptomatic

Stage 3: <2.5 cm; Symptomatic

Stage 4: > 2.5 cm; Pathologic Fracture

Results to Date

Vancouver

- 23 patients enrolled; 22 evaluable for QofL
- 17 male; 6 female
- Age range 45-80 (62.2)

Sudbury

- 45 patients enrolled to date; 30 evaluable for ORN; 27 evaluable for QofL
- 21 male; 9 female
- Age range 43-83 (61.1)

Results to Date

Vancouver

- 52 teeth extracted
(36 mandible; 16 maxilla)

- 1 case of ORN (Lyons); Stage 3; resolved with antibiotics and local debridement

- 2 cases of ORN (CTCAE); One Stage 1*; One Stage 2**

*=radiographic change only
**=fistula to bone; no bone exposure

Sudbury

- 55 teeth extracted
(34 mandible; 21 maxilla)

- 1 case of ORN (Lyons); Stage 3; resolved with debridement and Pentoclo protocol

- 3 cases of ORN (CTCAE); 1 cases Stage 1*; 2 cases Stage 2**

*= radiographic change only
**=fistula to bone; no bone exposure

Quality of Life Data

- At each study visit, patients completed EORTC QLQ-C30 (general) and EORTC QLQ-H&N 43 (specific) and asked about any health and/or medication changes

Questions 29 and 30 (EORTC QLQ-30)

1-7 Lickert Scale (1=very poor; 7=excellent)

29.How would you rate your overall health this week?

30. How would you rate your overall quality of life this week?

Quality of Life Data

Vancouver

Question 29:	Baseline = 5.1	6 Months = 5.9
Question 30:	Baseline = 5.1	6 months = 6.0

Sudbury

Question 29:	Baseline = 5.0	6 months = 4.9
Question 30:	Baseline = 4.9	6 months = 4.8

Quality of Life Data

Vancouver

- 3/23 reported visual changes (one with cataracts)
  - 4/23 reported decreases in hearing acuity

(one patient requiring tubes after 1st HBO dive)

Sudbury

- 1/30 reported decreased hearing acuity; no visual changes

Osteoradionecrosis

A Review of Pathophysiology, Prevention and Pharmacologic Management Using Pentoxifylline, Alpha-Tocopherol and Clodronate (Pentoclo)

Rivero, Shamji and Kolokythas, OOOO Volume 124, No. 5, November 2017

- Review of proposed mechanisms of ORN, various staging classification systems, traditional vs medical management

- Conclusions that there is a lack of scientific evidence to explain the pathogenesis of ORN; therefore, a lack of efficacious conservative management strategies

- Preliminary studies using Pentoclo have been promising but additional research needed to elucidate role of pharmacologic therapy in the management of ORN

Pentoclo – Early Publications

Delanian et al; Journal of Neurological Sciences 275 (2008): 164-66

Journal of the Neurological Sciences

Significant clinical improvement in radiation-induced lumbosacral polyradiculopathy by a treatment combining pentoxifylline, tocopherol, and clodronate (Pentoclo)

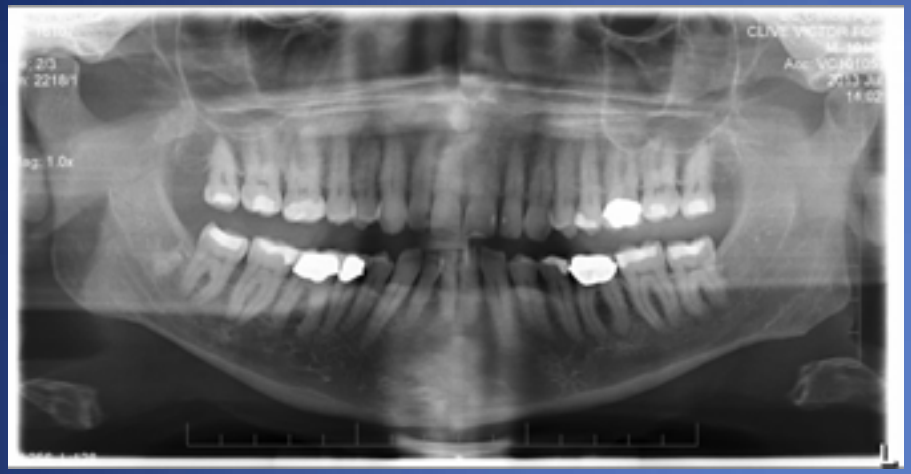
Delanian et al; Int Journal Rad Onc Biol Phys 80(3), 832-39, 2011

CLINICAL INVESTIGATION

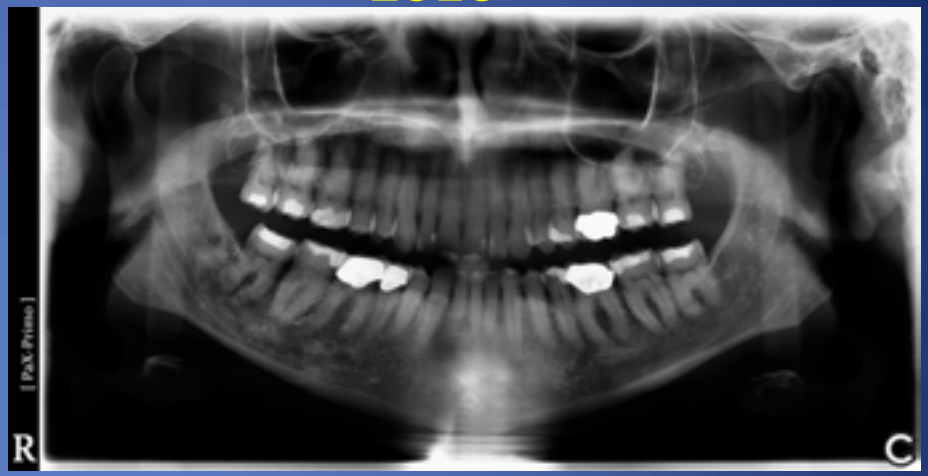
COMPLETE RESTORATION OF REFRACTORY MANDIBULAR OSTEORADIONECROSIS BY PROLONGED TREATMENT WITH A PENTOXIFYLLINE-TOCOPHEROL-CLODRONATE COMBINATION (PENTOCLO): A PHASE II TRIAL

Patient CF

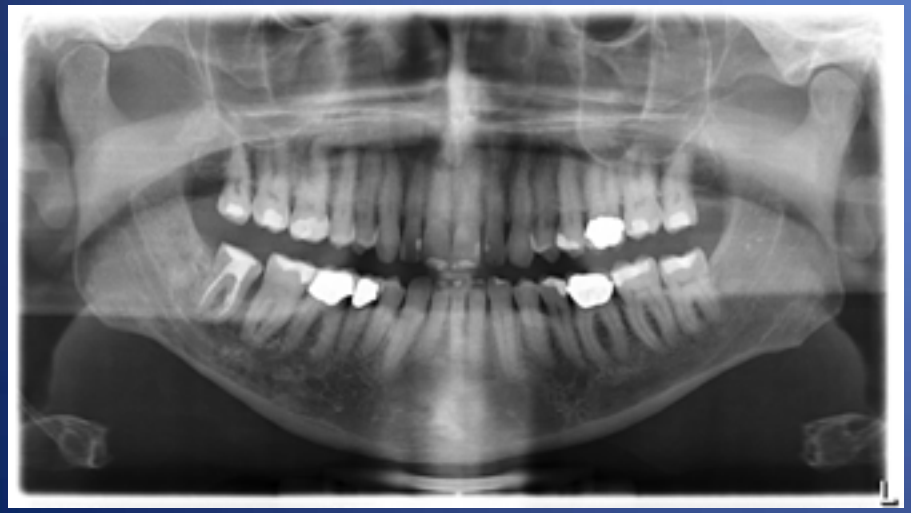
2013



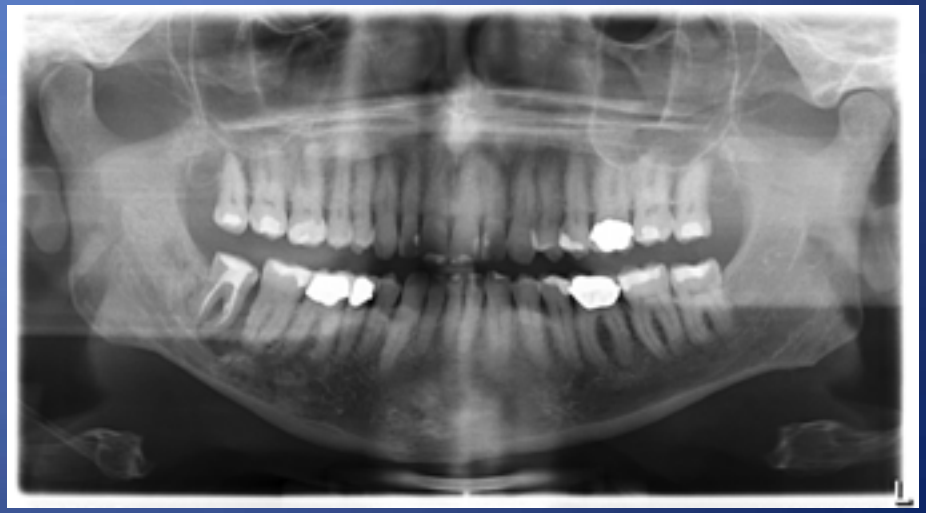
2016



2017

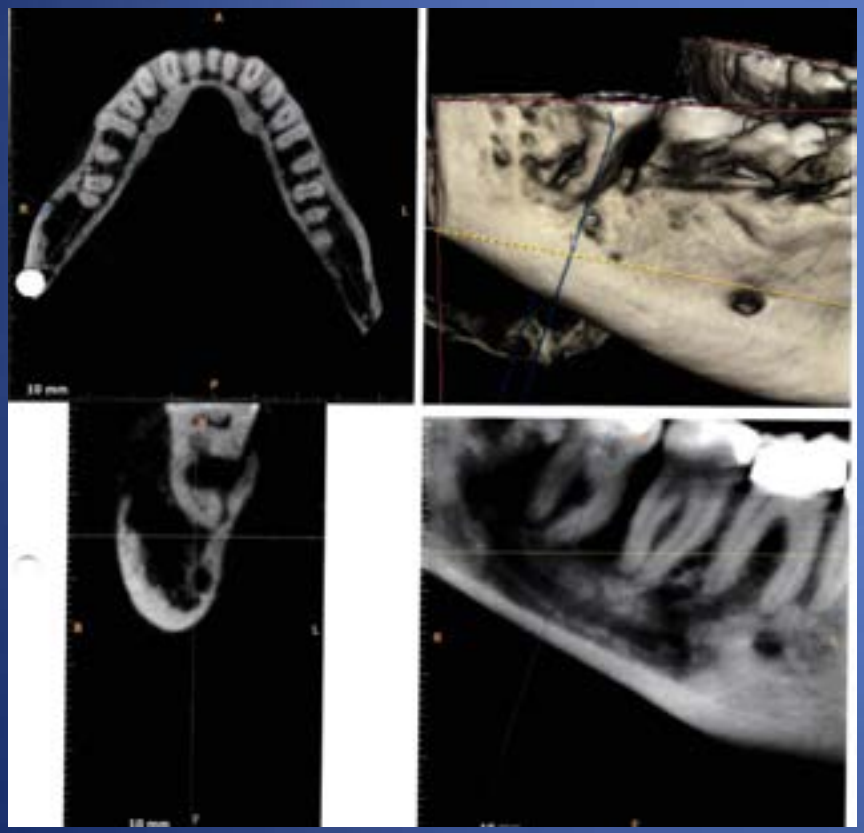


2018



CBCT Results

May 2016



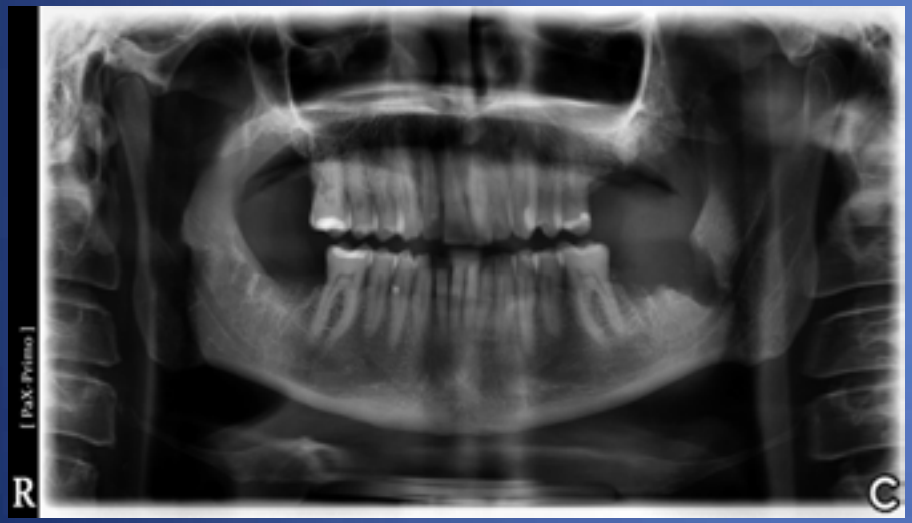
November 2016

Issues – Patient CF

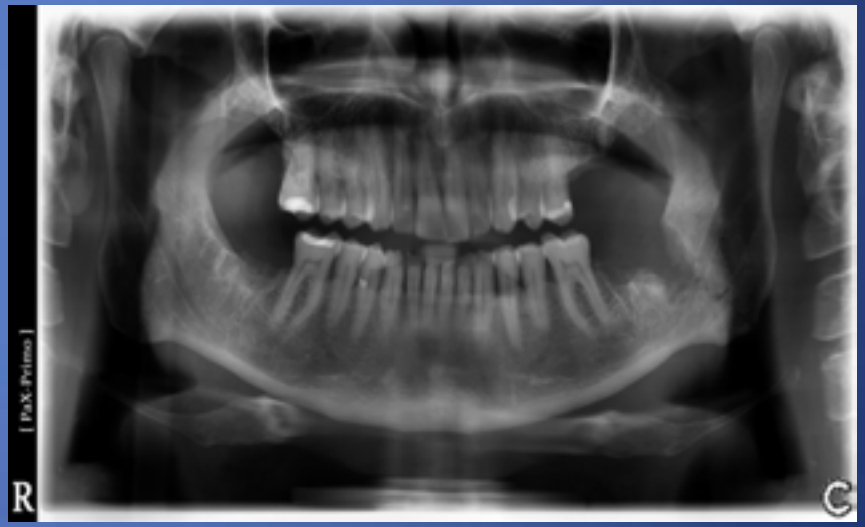
- Worsening bone loss despite conservative management and HB0 (70 dives total)
- Surgeon reluctant to extract 48/47 for fear of jaw fracture; worsening or reinitiating ORN
- Patient essentially asymptomatic since starting Pentoclo protocol despite no objective improvements; doesn't want to be on meds indefinitely
- Should we extract tooth/teeth? Bone biopsy or other diagnostic tests?

Patient TS

August 2016
Pre-HBO

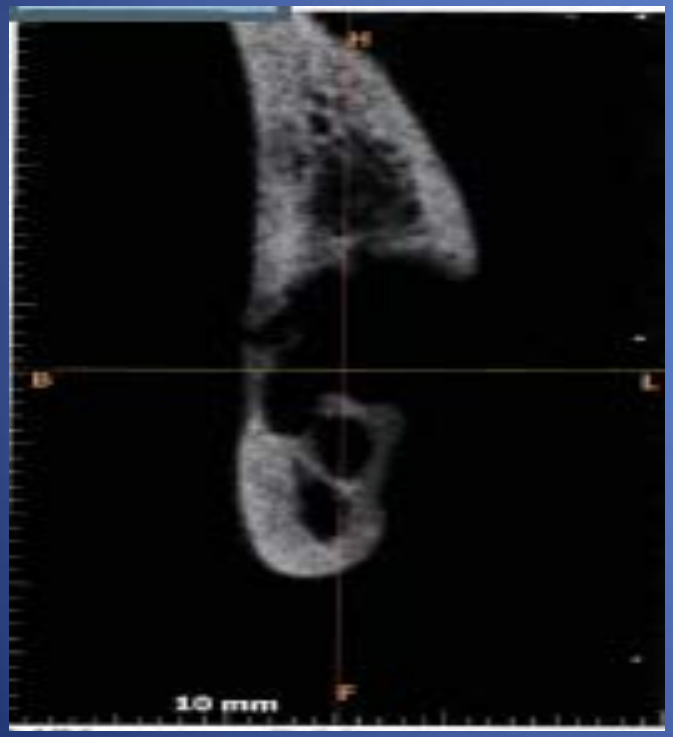


March 2017
Post-30 dives HBO

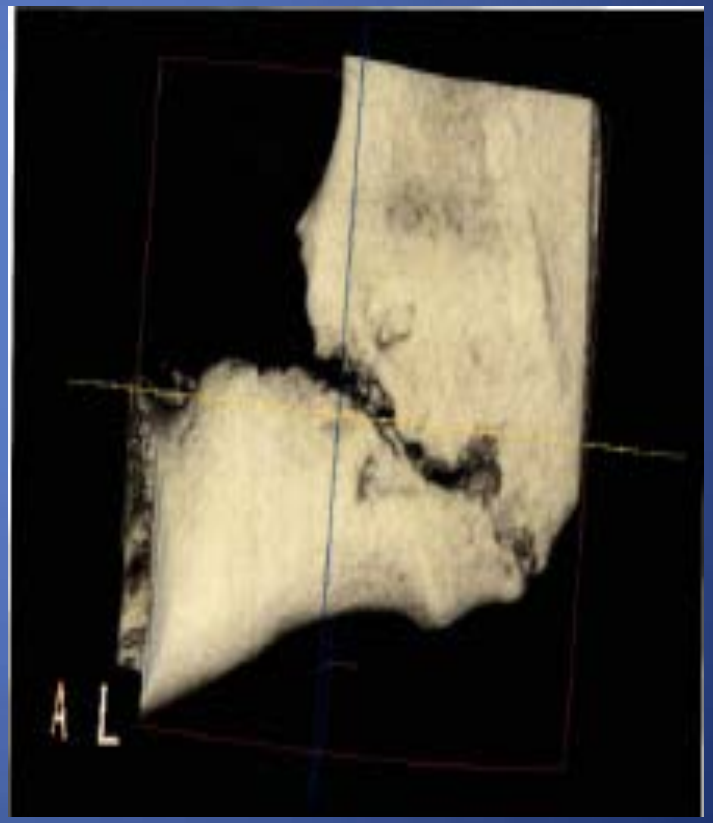


TS – Cone Beam CT

March 29, 2017



March 29, 2017



Issues – Patient TS

- Patient lives and works in Brunei with limited access to specialized care (Singapore for oncologic care)
- Very minor improvement (??)since completing 30 dives of HBO; pathologic fracture evident on March 2017 CBCT
- Patient remains asymptomatic despite radiographic change
- Patient now on Pentoclo. Other management strategies?

Pentoclo Protocol

Medication*	Dose	Frequency
Prednisone	20 mg	Daily
Amoxicillin/ Clavulinic Acid	2 g/ 500 mg	Daily
Ciprofloxacin	1g	Daily
Fluconazole	50 mg	Daily

PENTOCLO

Medication*	Dose	Frequency
Pentoxifylline	400 mg	Twice daily, five days per week
Vitamin E	600 IU	Each morning, five days per week
Vitamin E	400 IU	Each evening, five days per week
Clodronate	1600 mg	Daily, five days per week
Ciprofloxacin	1 g	On remaining two days per week
Prednisone	20 mg	On remaining two days per week

IU- International Units

All medications taken orally.

Conclusions

- Using classic definition, ORN appears to occur at a similar rate (< 5%) regardless of whether prophylactic HBO is used or not
  - QofL scores higher at 6 months in HBO-treated group
- Visual changes more commonly reported in patients treated with HBO
- ***Doing prospective clinical trials in oncology is challenging!!***

Thoughts

- *Medical management to prevent peri-extraction and to treat post-extraction ORN should be considered as an alternative to HBO*
- *Bone biopsies should be considered at time of extraction in post-XRT setting*
- *Definition of ORN should be expanded to include radiographic changes w/o frank bone exposure (ASCO Guideline Development)*

Questions?

Vancouver

Sudbury