Dental Issues In Cancer Patients Using Bone Modifying Agents

What Every GPO Must Know

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2016 CAGPO Annual Meeting

Four Seasons Hotel, Vancouver, B.C.

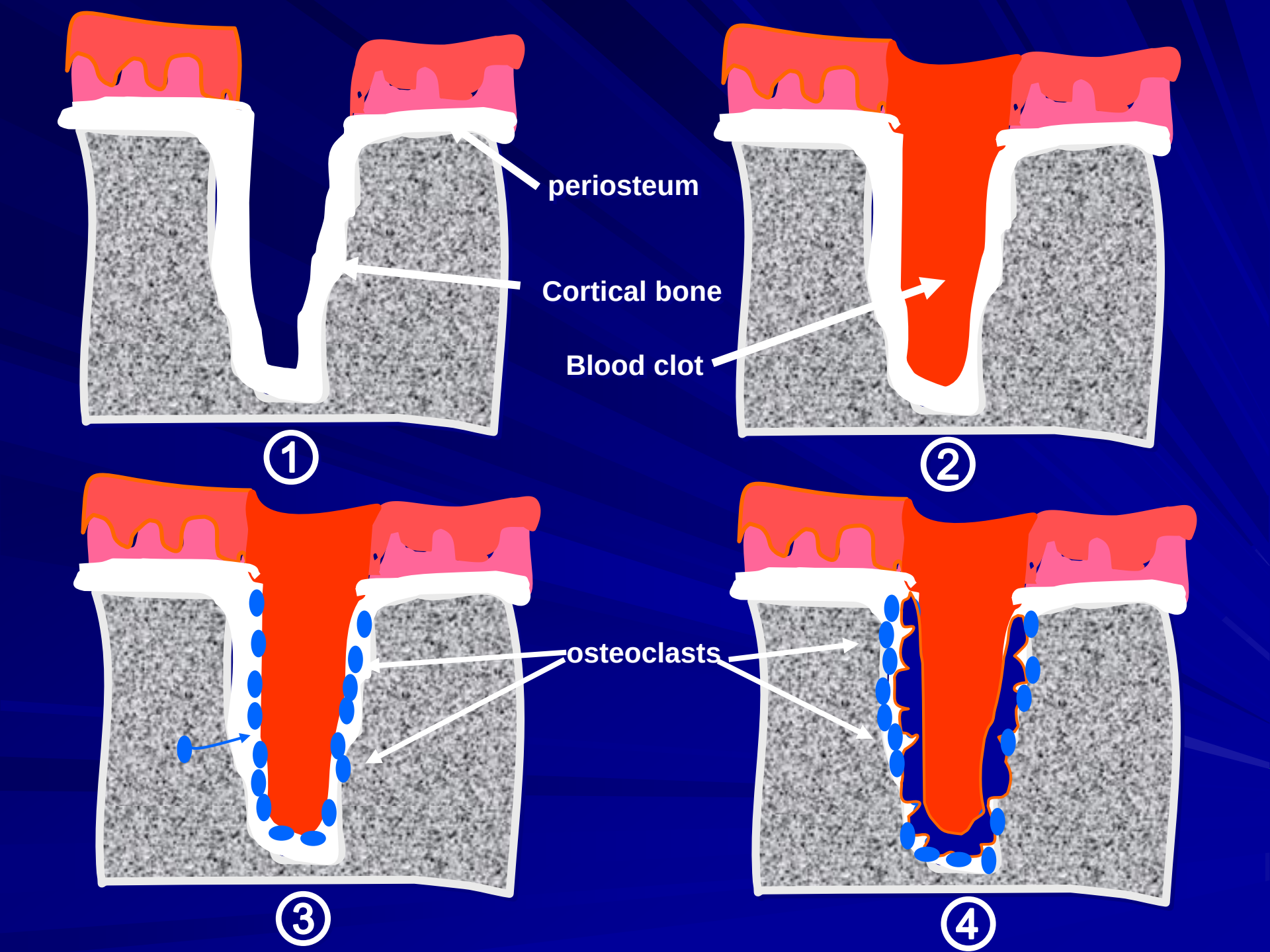
Sunday, October 2nd, 2016

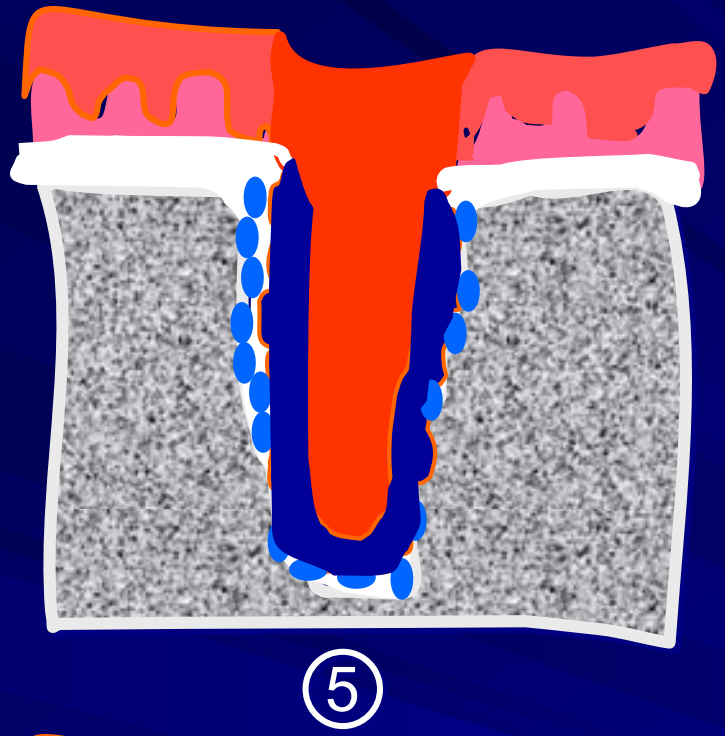
No Conflict of Interests

Jaw Osteonecrosis

- Osteo***RADIO***necrosis

- Osteo***CHEMO***necrosis


periosteum
Cortical bone
Blood clot
①
②
osteoclasts
③
④



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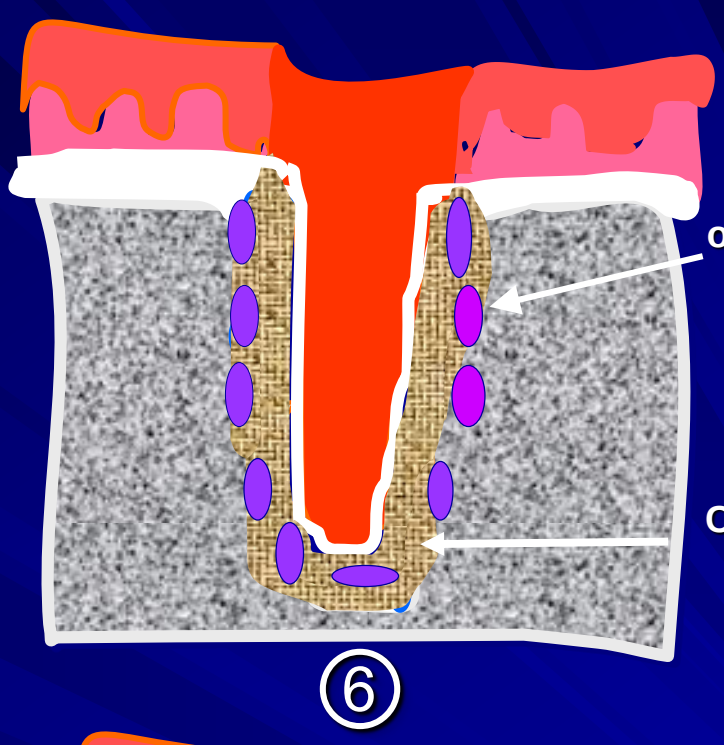

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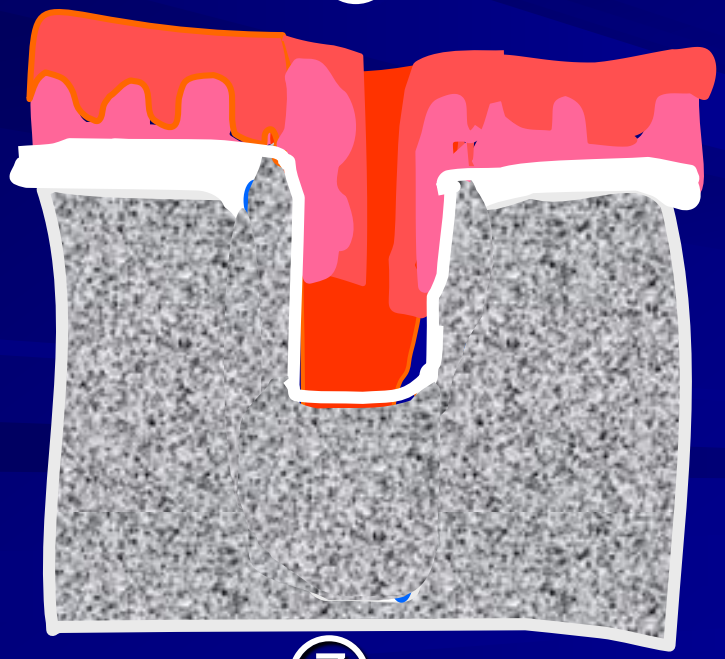

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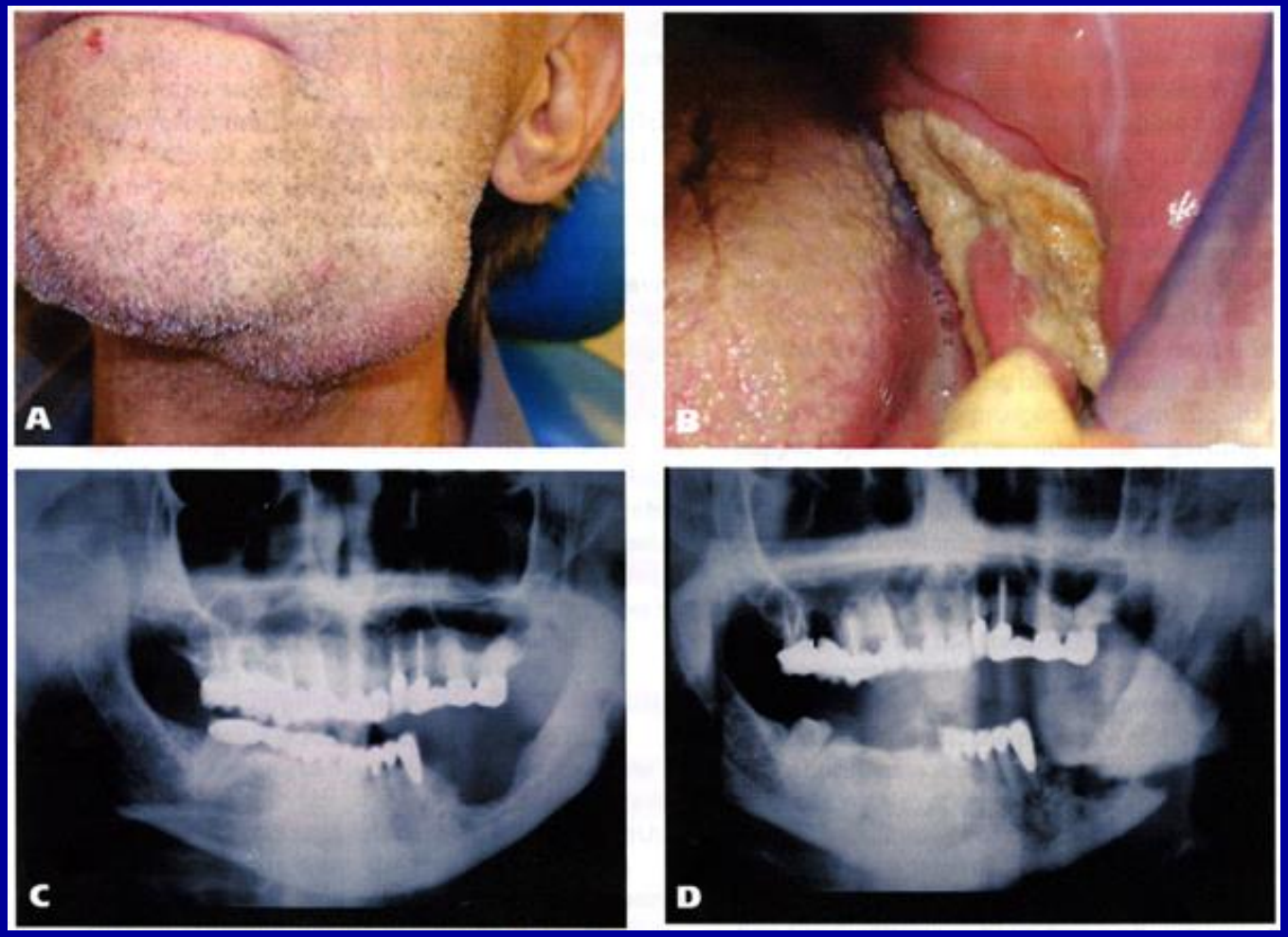
Osteo*radio*necrosis

Non-healing mucosal or skin opening with underlying exposed devitalized bone in area of previous high-dose RT

Potential Sequelae

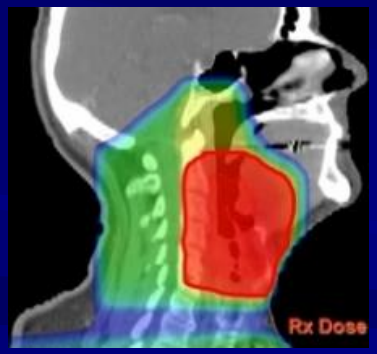


Prevalence of ORN

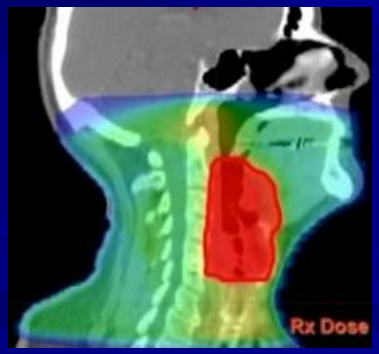
Table 1. Weighted prevalence from 31 studies.[4]

Modality	Prevalence
Conventional RT	7.4%
Intensity Modulated RT	5.2%
Chemoradiotherapy	6.8%
Brachytherapy	5.3%

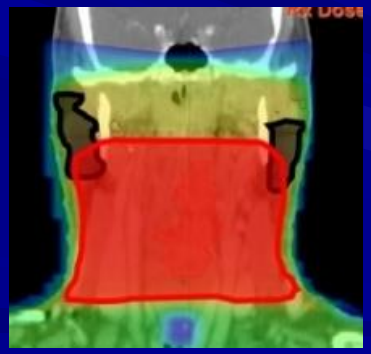
Adapted from Peterson, Hovan et al, 2010



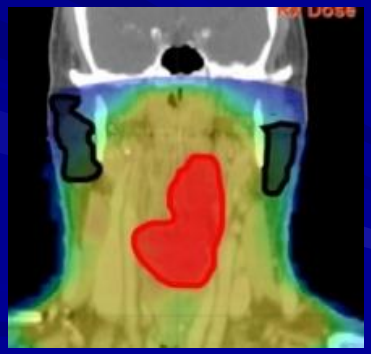
Conventional



IMRT



Conventional



IMRT

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

Pathophysiology of ORN

- Previously considered an osteomyelitis in irradiated bone as a result of a triad of RT, trauma and infection

- Marx (1983) redefined ORN as " a metabolic and tissue homeostatic deficiency created by RT-induced cellular injury"; ischemic necrosis of bone; non-infectious

- Established HBO-guided surgical debridement as treatment of choice for established ORN when conservative management has failed

ORN Conservative Management

"Saucerization" of exposed bone

+

Low-dose Doxycycline (100 mg/day)

+

O.12% Chlorhexidene oral rinse

- If non-responsive/enlarging, consider HBO-guided surgical excision of necrotic bone

HBO in the Management of ORN

- ***Prophylaxis*** when surgery is performed in previously-radiated tissue

eg. dental extractions, dental implants

20/10

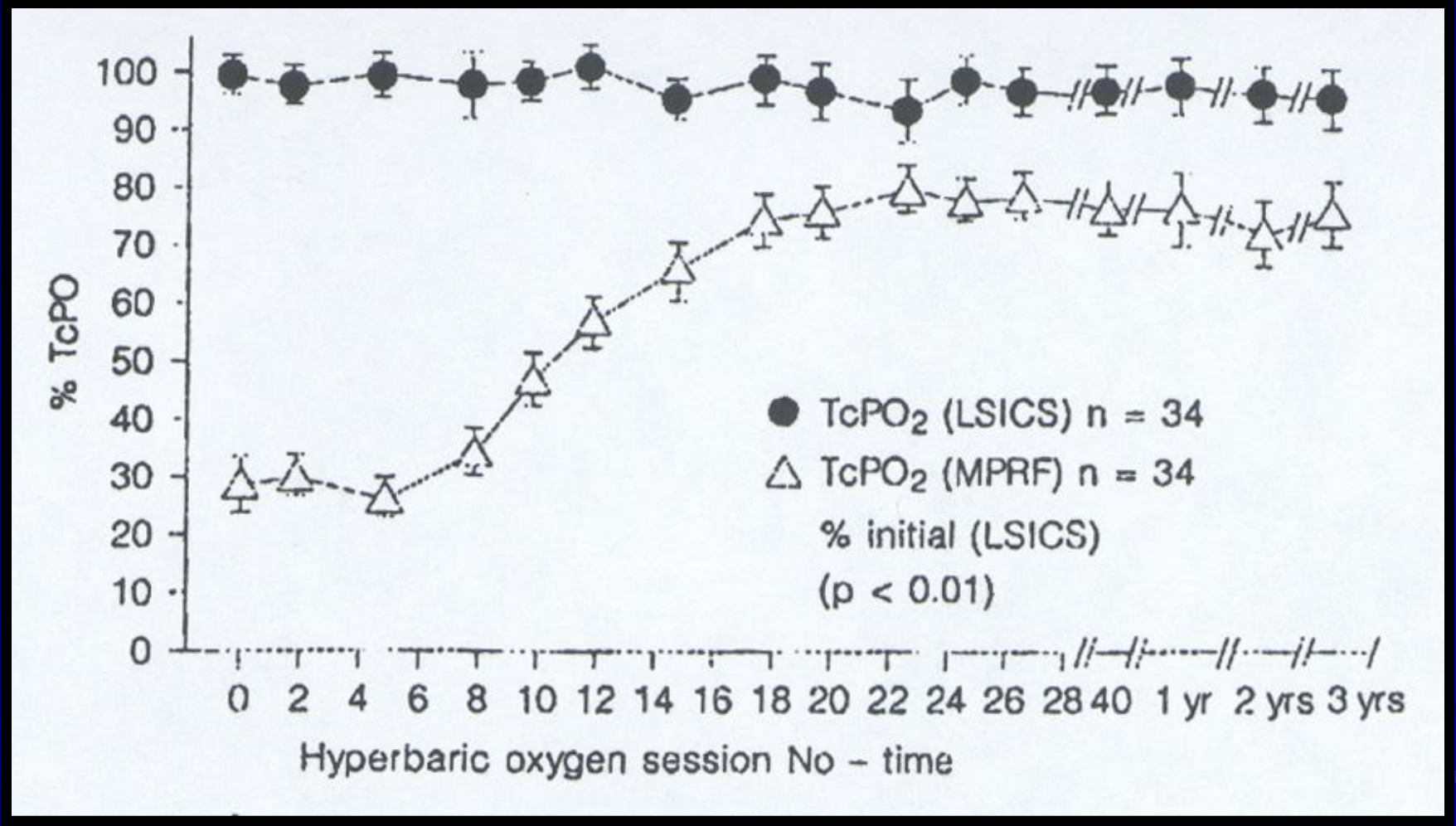
- ***Established ORN***

30/10

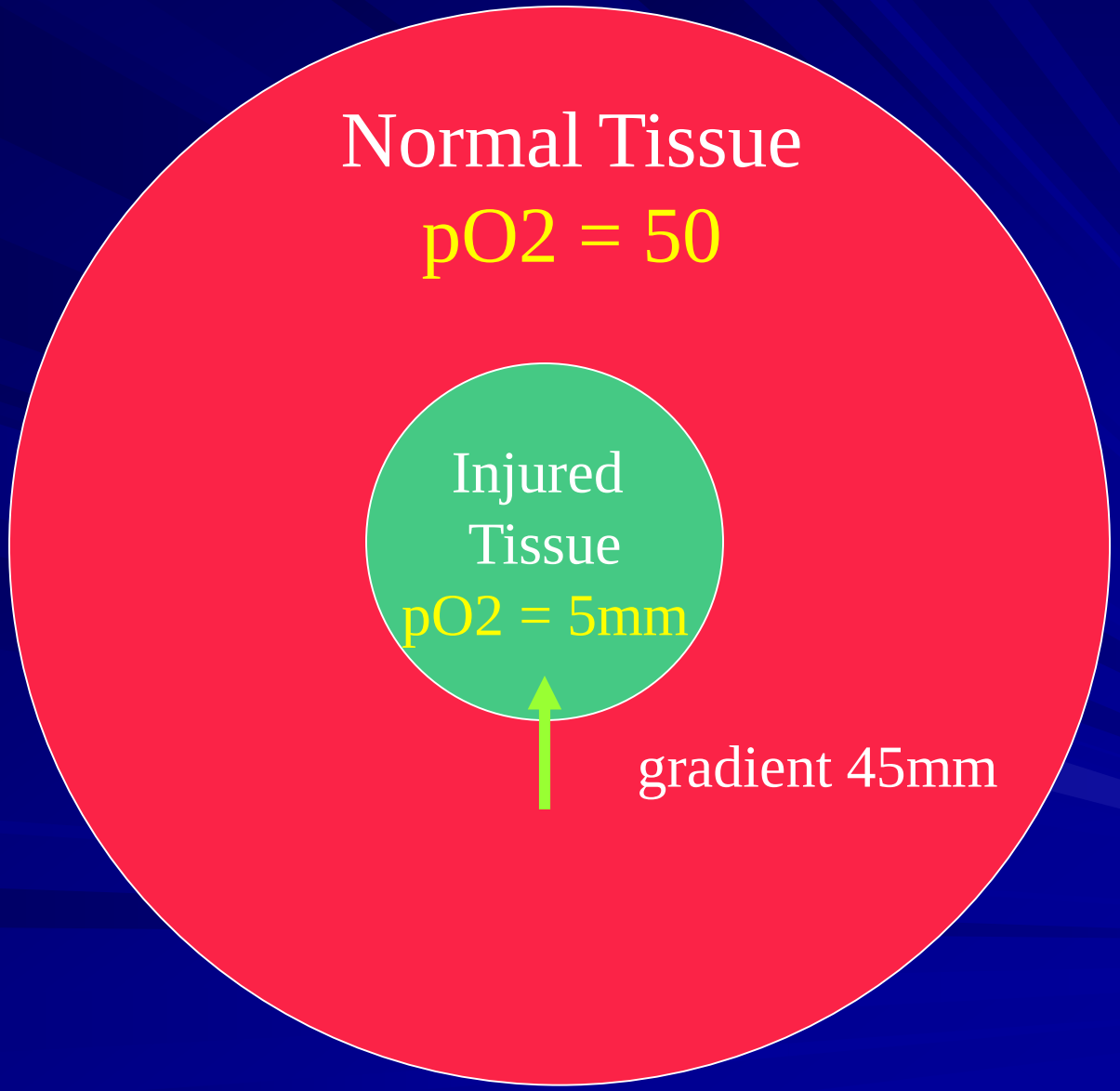
What is HBO?

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

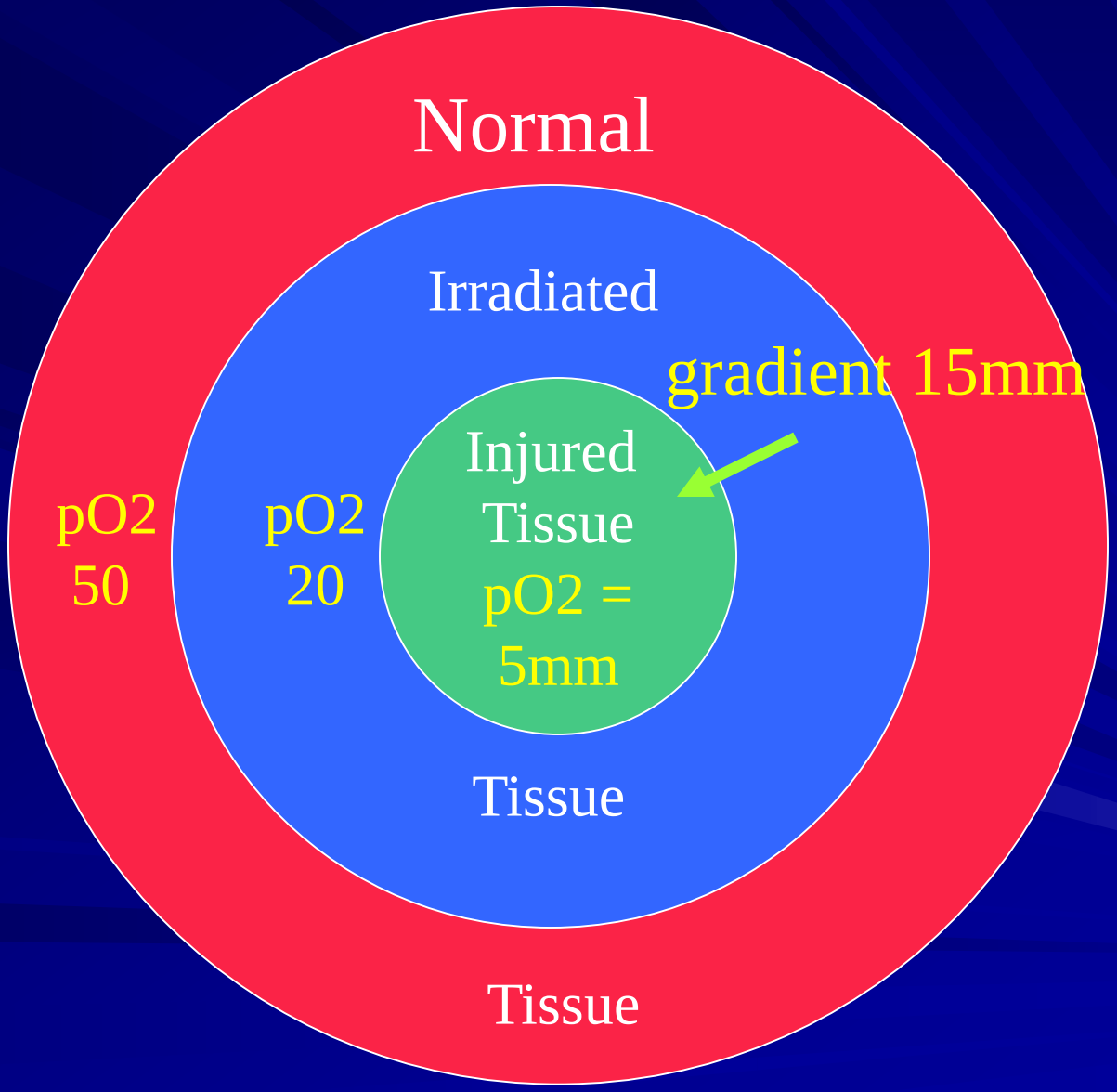
- Typical “dosing” is 2.4 ATA X 90 minutes; each treatment takes approximately 130 minutes


% TcPO
100
90
80
70
60
50
40
30
20
10
0
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

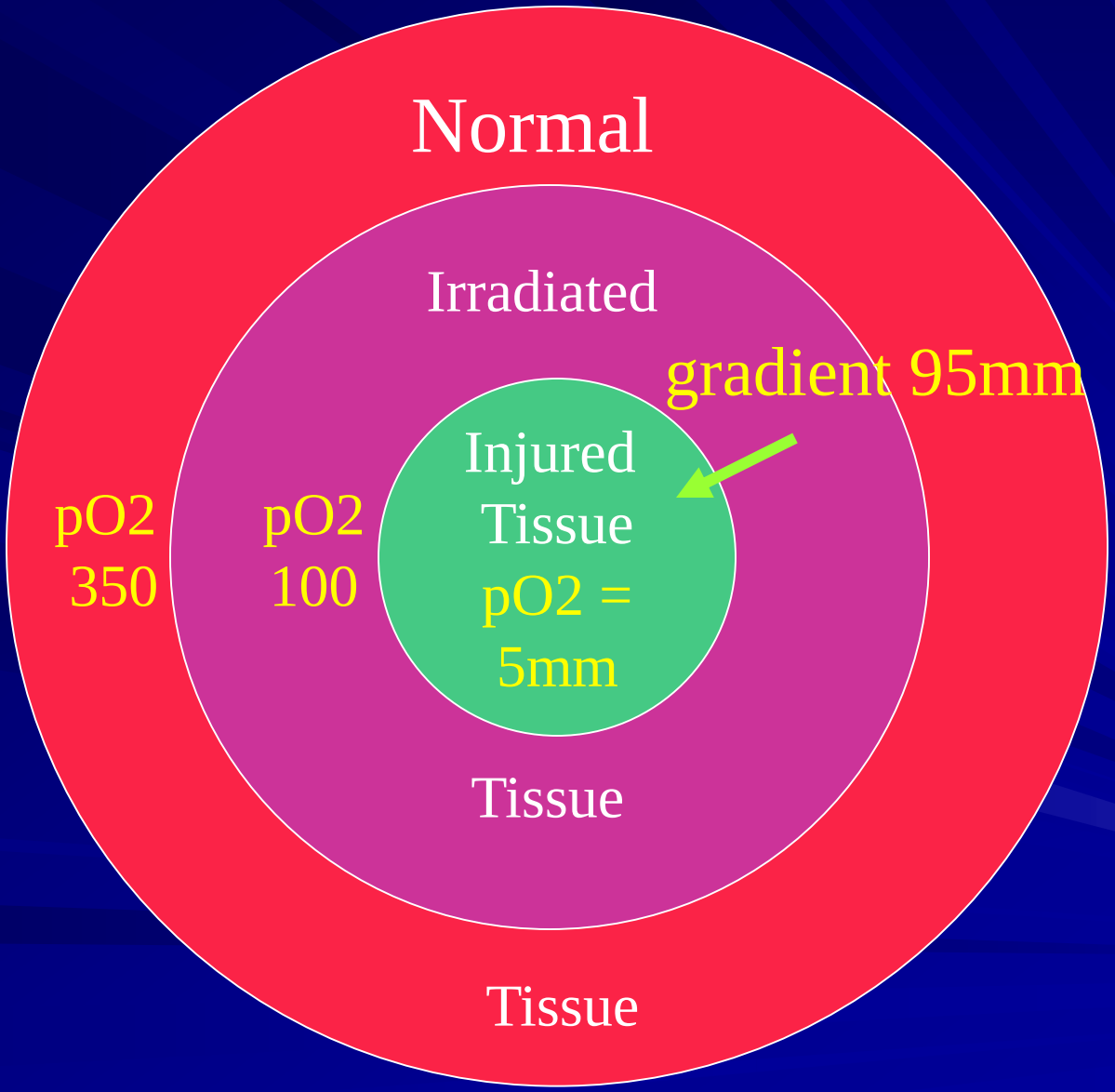
Normal Traumatized Tissue



Irradiated Traumatized Tissue



Irradiated Traumatized Tissue + HBO



Tissue Effects of HBO

- Hyper-oxygenation
- Replenishment of Intracellular ATP
- New Tissue Production

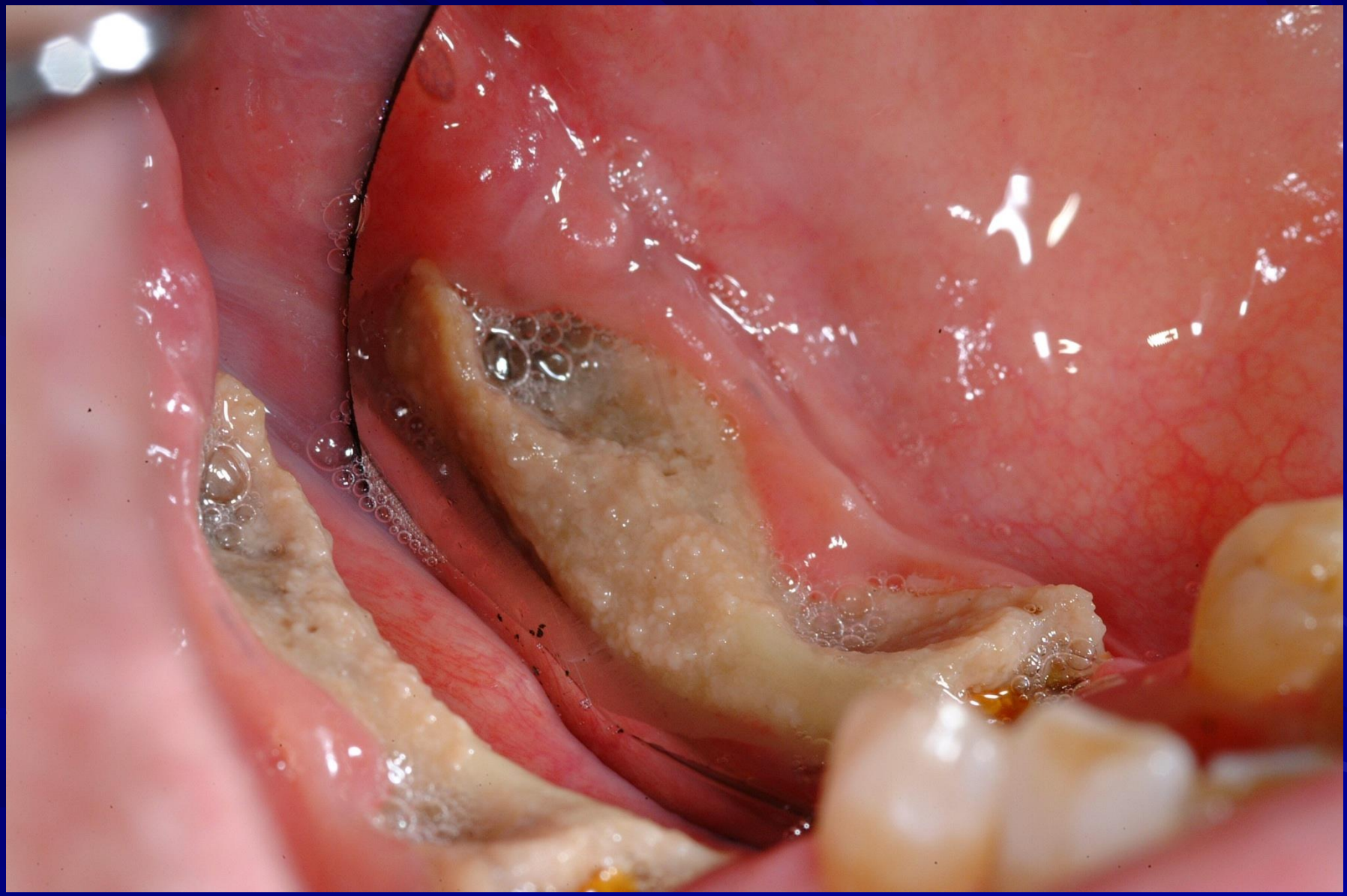
(angiogenesis, neo-vascularization, bone production)

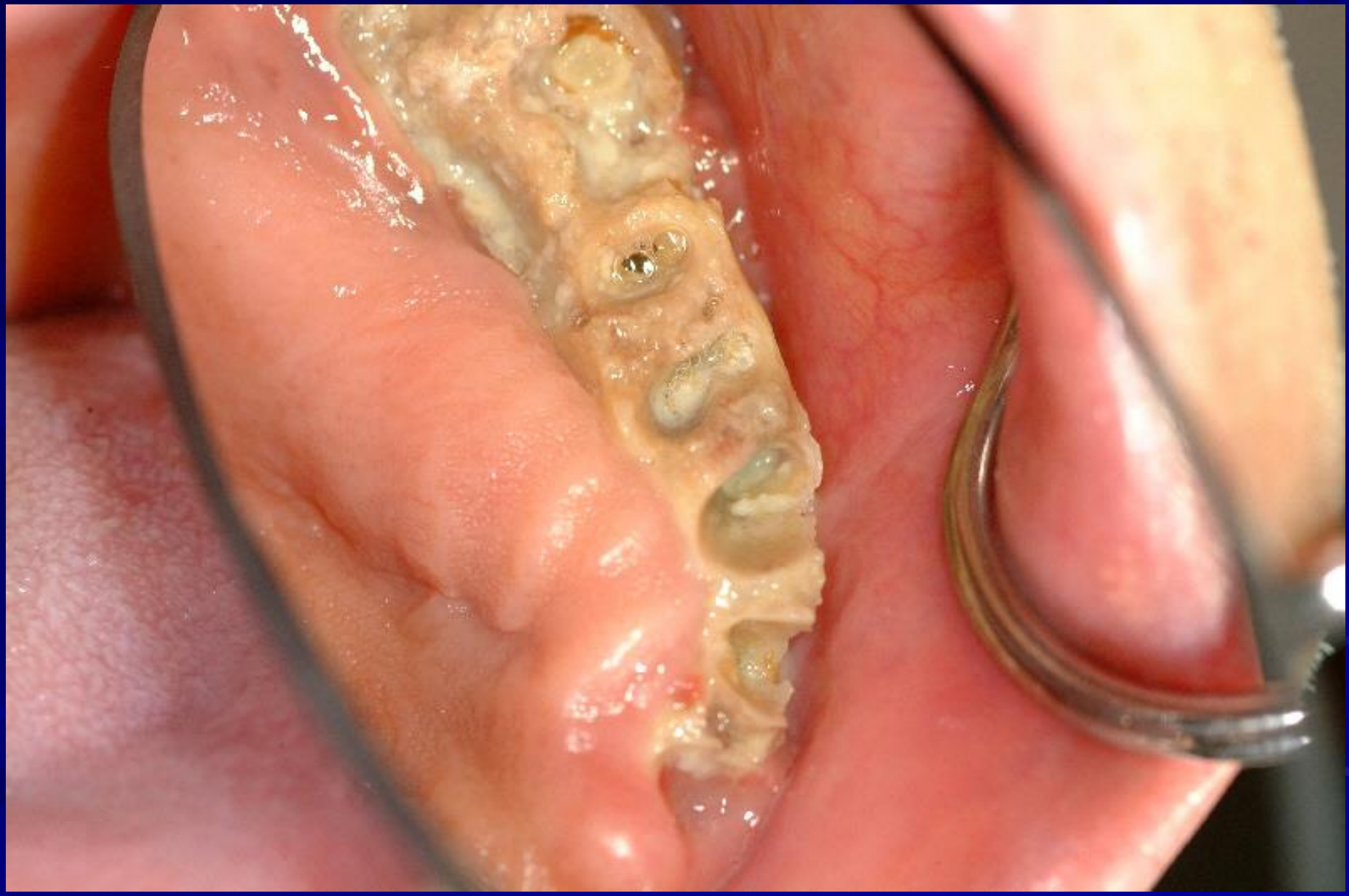
Osteoradionecrosis Summary

- ***Prevention*** is the key
- Life-long risk factor for H&N RT patient
- HBO/surgery approach useful but not 100% successful
- HBO not completely benign treatment
- Huge impact on patient (time, side-effects, etc)

Osteo*chemo*necrosis

AKA “BRONJ”, “Jaw Necrosis Secondary to Anti-Resorptive/Bone Modifying Medications” etc. etc…..





Bisphosphonates

Bisphosphonates

Intravenous Bisphosphonates

- Aredia™ *(pamidronate)*
- Zometa™ *(zoledronic acid)*

Oral Bisphosphonates

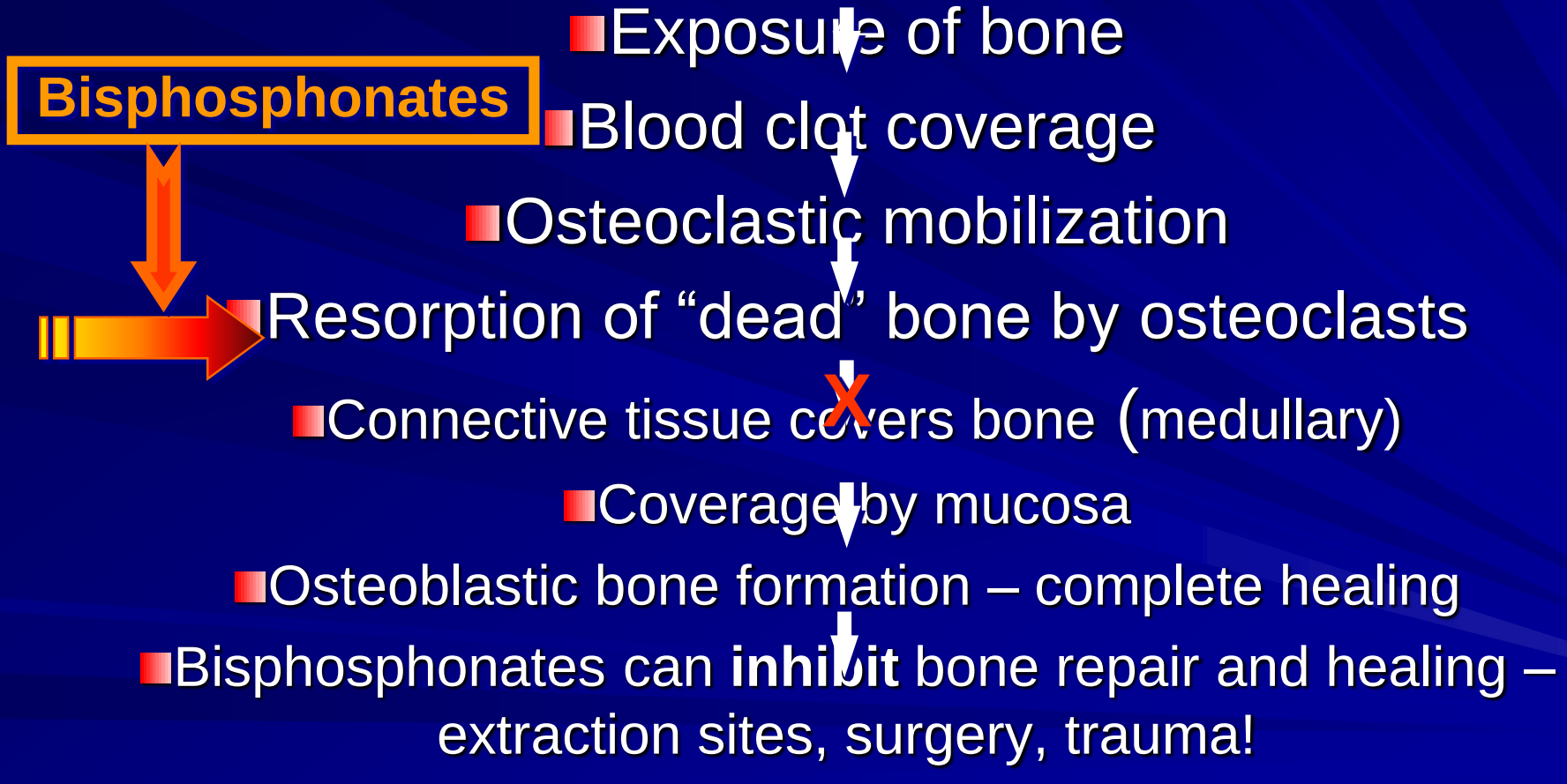
- Fosamax™ *(alendronate)*
- Actonel™ *(risedronate)*
- Didronel™ *(etidronate)*
- Skelid™ *(tiludronate)*

Relative Resorptive Potency of Bisphosphonates

Bisphosphonate	Relative Potency
First Generation Agents	
Etidronate	1
Clodronate	10
Tilundronate	10
Second Generation Agents	
Pamidronate	100
Alendronate	1,000
Third Generation	
Ibandronate	10,000
Zoledronate	20,000

Bisphosphonates and Dentistry:

Normal sequence of bone repair healing



Clinical Use of Bisphosphonates

#1 = osteoporosis

Also used extensively in cancer setting:

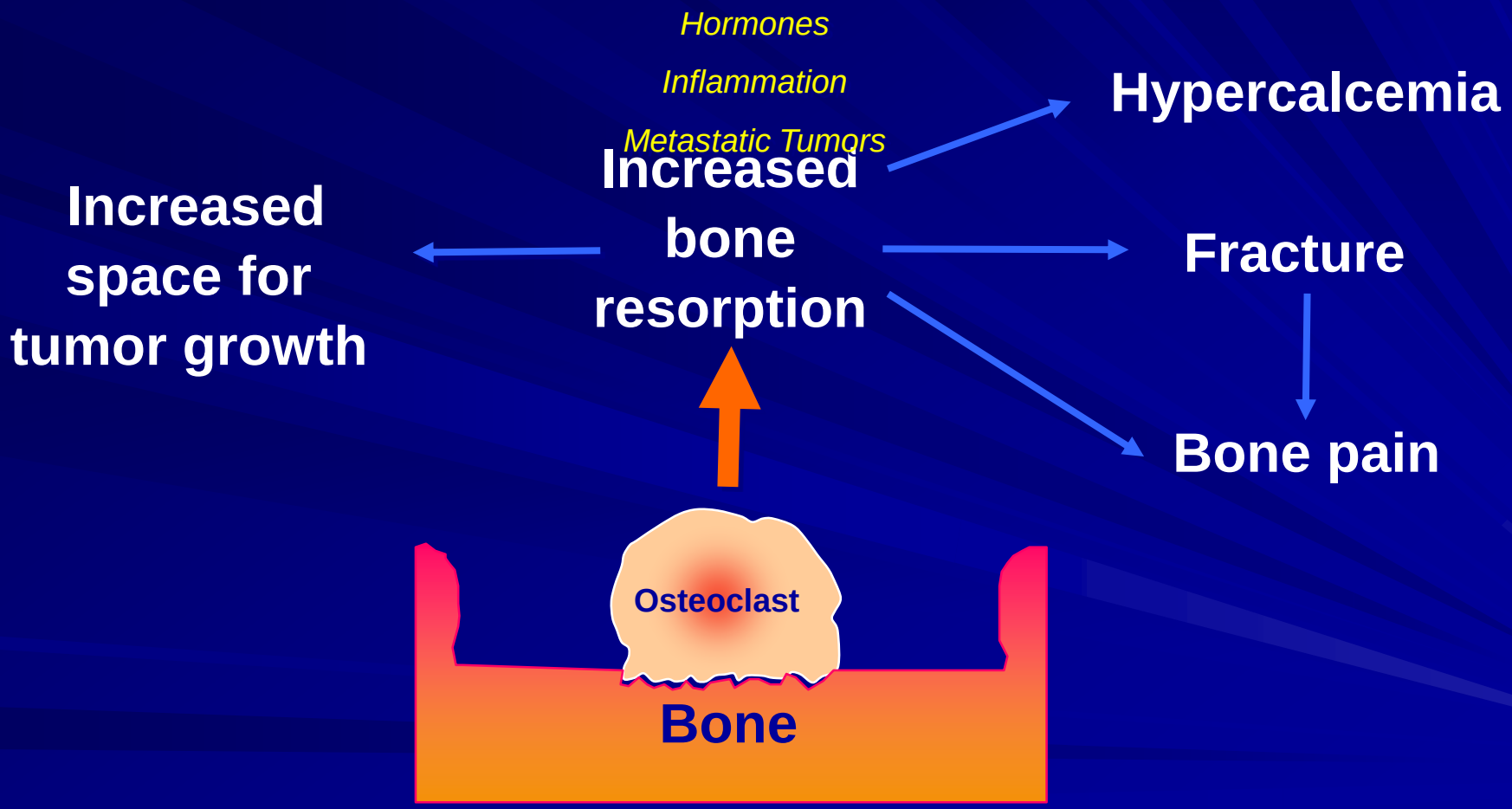
- Preventing metastatic spread to bone (breast, lung, prostate, etc)
- Multiple Myeloma (1st line therapy)
- Preventing hypercalcemia of malignancy

Clinical Benefit of BPs in Cancer **Unquestioned**

- Limits metastatic tumour spread to bone
- Prevents hypercalcemia
- Significant reduction in cancer-related SREs (fractures, RT, surgery to bone, etc)
- Improves quality of life (less bone pain, less analgesic use, greater mobility, etc).

C

Consequences of Increased Bone Resorption



Clinical Consequences of Metastatic Bone Disease†

	% of patients / yr	
Pathologic fractures	10 – 25	SREs
Spinal cord compression/collapse	3 - 5	
Radiation therapy	15 – 20	
Surgery to bone	5 – 10	
Hypercalcemia	2 – 10	
Bone pain	50	
Use of analgesics	40	
Quality-of-life effects		
Survival		

SREs = Skeletal-related events.

† From PLAC arms of randomized clinical trials with Aredia® or Zometa®.

IV Bisphosphonates—Major Impact in Reducing Skeletal Complications for Cancer Pts With Metastatic Bone Disease

	% with SRE			# SREs per yr		
	Placebo	BP	%↓†	Placebo	BP	%↓
Prostate (Saad et al.)	49	Z-38	**22***	1.5	0.7	**47***
Breast (Hortobagyi et al.)	64	A-51	**20***	3.7	2.4	**35***
(Kohno et al.)	50	Z-30	**40***	1.42	0.7	**50***
Myeloma (Berenson et al.)	51	A-38	**26***	2.0	1.0	**50***
Others (Rosen et al.)	46	Z-39	**15**	2.7	1.7	**37***

SRE = Skeletal-related event; Pbo = Placebo; BP = Bisphosphonate; Z = Zometa®; A = Aredia®;
* $P < 0.05$; † Relative decrease

Novartis

Bisphosphonate Osteonecrosis (BRONJ) A Recent History

- 2003 - First literature report (i.v.)
- 2004 – First literature report (oral)
- 2005 - FDA statement
- 2006 – BRONJ monograms (Novartis, Merck)

Why Now?

- Health Canada approval only in 1996
- Time-dependent phenomenon
- Survival rates for many cancers have improved, allowing more time for the phenomenon to occur; more patients having oral procedures done that put them at risk

Why the Jaws?

- Dental surgery common
- Thin mucosa and periosteum
- Masticatory forces lead to microdamage
- Trauma and infection increase the demand for remodeling and repair

Osteonecrosis of the Jaw in Patients Receiving Intravenous Bisphosphonate Therapy *** MD Anderson Cancer Center Retrospective Chart Review

33 cases of ONJ identified in 4000 cancer patients (16 breast, 15 myeloma, 1 prostate, 1 thyroid):

Overall frequency:	33/4000	(0.83%)
Breast cancer:	16/1340	(1.2%)
Multiple myeloma:	15/550	(2.8%)

- 33 mandible
- 27 maxilla
- 4 maxilla and mandible
- 2 hard palate

*** true incidence rates hard to establish at this time

MDACC = MD Anderson Cancer Center; ONJ = osteonecrosis of the jaw

1. Hoff AO, et al. Presented at 27th ASBMR; September 23-27; Nashville, Tenn. Abstract 1218.

Literature Report of ONJ: Ruggiero et al. 2004*

63 cases between Feb 01- Nov 03

- MM (28), BC (20), prostate (3), other (5), no cancer (7)
- Pamidronate (57%), zoledronic acid (31%), oral BP (12%)
- 71% female; mandible (63%) / maxilla (37%)
- Typical presentation: pain, non-healing extraction socket, exposed bone
- Previous dental procedure: **86%**

* **Ruggiero SL, et al. *J Oral Maxillofac Surg; 2004; 62* (5):527 - 534.**

Protocols for Dental Care

1. Prior to Initiation of Bisphosphonate Therapy
2. Once Patient is On Bisphosphonate Therapy
3. Once BRONJ has occurred.

Prior to Initiating Bisphosphonate Therapy

- Complete oral exam, including x-rays
- Eliminate potential sources of infection or trauma; restore salvageable teeth
- Extractions, periodontal surgery 4-6 weeks prior to bisphosphonate therapy

Once Patient is on Bisphosphonate Tx

- Encourage routine preventive and restorative treatment (crowns > large fillings)
- frequent prosthesis checks
- Non-surgical perio/endo therapy
- Implants / orthodontics contraindicated in patients on i.v. BPs; worrisome in patients on oral BPs

Patient considered "at risk" after 3 months iv; 3 years oral

Once BRONJ has occurred…

Unlike ORN, there are currently no known treatments capable of *predictably* healing BP-associated ONJ lesions

Management of BRONJ
What Is Being Used/Tried

Smaller Necrotic Lesions

Gentle removal of sharp bone; protective stent; antibacterial rinses; cross your fingers

Larger Necrotic Lesions

Surgical removal of bone. Issue is establishing necrotic bone margin. Some centres using antibiotic labeling of bone and fluorescent light source to outline margins (BCCA Protocol)

Should BP Therapy Be Discontinued for Dental Extractions?

- Controversial in literature; probably won't help
- Pharmacokinetics after infusion unclear
- Half life in bone = YEARS; therefore, compromised healing response will always be present
- Must also consider risks associated with d/c BPs (metastatic bone spread, SREs, etc)

Denosumab (Xgeva)

- Fully human monocloncal antibody
- Targets RANK ligand on pre-osteoclasts
- Anti-resorptive potency ~ Zoledronic Acid
- Advantages: toxicity profile; half-life ~ 21 days (vs years for iv BPs). Therefore, rationale for drug holiday if dental extraction planned.

Other Considerations

- Most cases of BRONJ/ONJ associated with surgical procedure but spontaneous cases do occur
- Mandible and maxilla ~ equally affected (unlike ORN)
- Emerging # of cases of spontaneous BRONJ in patients on angiogenesis inhibitors, monoclonals, immunotherapetics
- Suggestion that pre-existing periodontal disease increases risk of post-surgical jaw necrosis

Take Home Message

- ORN a life-long risk in H&N RT patients, Risk relative to XRT dose, complexity of oral surgical procedure and other factors (eg smoking). Management options exist.
- BRONJ risk low in patients on oral BPs; considered at some risk after 3 years of oral BP therapy.
- BRONJ considered significant, life-long risk in patients after 3 months of IV BP therapy. Drug holidays controversial. Management options limited.
- Whether ORN or BRONJ/ONJ, **PREVENTION** is key. Pre-treatment dental assessment and ongoing dental care remains the cornerstone to preventing this potentially serious side-effect of cancer therapy