Mandibular Osteoradionecrosis

Dick Clarke, CHT

Mandibular Osteoradionecrosis

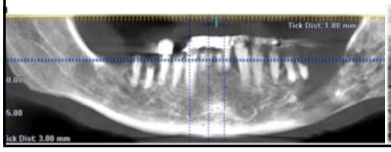
Review & Update

Primary Training in Hyperbaric Medicine
Columbia, South Carolina

"Late radiation tissue injury is a sign of success"

Sanders M, Dische S.
2002 ESTRO Meeting, Prague



Radiation tissue injury; "non-target" tissues

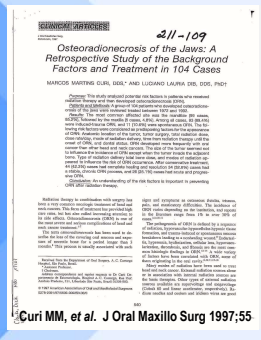
Acute effects: *DNA damage, cell death-rapidly proliferating cells*

self-limiting +/- RT pause

Late effects: *chronic oxidative stress*

dose-dependent > complex wounds/organ loss

"consequential vs. generic"



CLINICAL ARTICLES

211-109

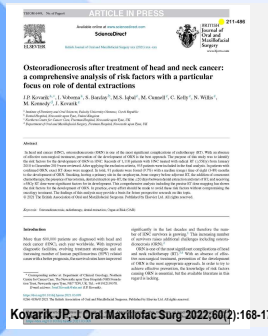
Osteoradionecrosis of the Jaws: A Retrospective Study of the Background Factors and Treatment in 104 Cases

MARCOS MARTINS CURI, DDS,* AND LUCIANO LAURIA DIB, DDS, PhD†

(3 - 7,400 cGy range)	No. Cases
< 5,000 cGy	5
5 - 6,000 cGy	24
6 -7,000 cGy	33
> 7,000 cGy	42

90% traumatically-induced

Curi MM, *et al.* J Oral Maxillo Surg 1997;55



ARTICLE IN PRESS

Osteoradionecrosis after treatment of head and neck cancer: a comprehensive analysis of risk factors with a particular focus on role of dental extractions

Table 2
The impact of the dose of radiotherapy (RT) on frequency of osteoradionecrosis. Data are No. (%).

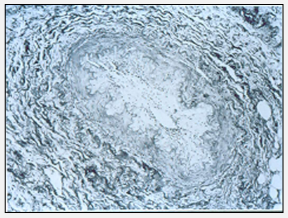
Dose of RT (Gy)	Patients (percentage)
<40	8 (8.8)
40.1 – 45.0	5 (5.5)
45.1 - 50.0	4 (4.4)
50.1 – 55.0	5 (5.5)
55.1 – 60.0	15 (16.5)
>60	54 (59.3)

Kovarik JP, J Oral Maxillofac Surg 2022;60(2):168-173

211-007
CLINICAL ARTICLES

Osteoradionecrosis:
A New Concept of Its Pathophysiology

ROBERT E. MARX, DDS*



Marx RE, J Oral Maxillofac Surg 1983;41:283-288

CLINICAL ARTICLES
211-008

A New Concept in the Treatment of Osteoradionecrosis

ROBERT E. MARX, DDS*

Marx RE, J Oral Maxillofac Surg 1983;41:351-357

Marx ORN Protocol

Stage I. HBO as primary therapy

Stage II. Indication for surgery post-HBO
~ *sequestrectomy*

Stage III. Mandible resection/fixation

Stage III-R. Mandible reconstruction

Classification Methods and Staging Systems for Osteoradionecrosis of the Mandible

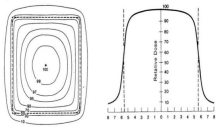
Investigators		Grading Systems	
Marx RE.	**A new concept in the treatment of osteoradionecrosis.** *J Oral Maxillofac Surg 1983;41:351-7*	Stage I:	30 dives of HBO used to attain mucosa recovery
		Stage II:	Grade I non-responders who need transoral alveolar sequestrectomy
		Stage III:	Grade II non-responders; a bone resection needed
		Stage III-R:	An additional 30 dives of HBO given to patients who needed a bone graft
Coffin F.	**The incidence and management of osteoradionecrosis of the jaws following head and neck radiotherapy.** *Br J Radiol 1983;56:8517*	Minor:	Small sequesters that may separate spontaneously over several weeks
		Major:	Bone necrosis extending to the entire thickness of the jaw; pathological fracture sometimes present
Morton ME.	**Osteoradionecrosis: a study of the incidence in the North West of England.** *Brit J Oral Maxillofac Surg 1986;24:323-31*	Minor:	Bone exposure with ulceration and a history of spontaneously resolving bony spicules
		Moderate:	Small sequester limited in nature and resolving spontaneously
		Major:	Large area of exposed bone and sequester; bone fracture and fistula
Epstein JB, *et al.*	**Osteoradionecrosis: clinical experience and a proposal for classification.** *J Oral Maxillofac Surg 1987;45:104-10*	Stage I:	Resolved/healed, with or without pathological fracture
		Stage II:	Chronic/persistent non-aggressive, with or without pathological fracture
		Stage III:	Active/progressive, with or without pathological fracture
Urken ML, *et al.*	**Oromandibular reconstruction using microvascular composite free flaps.** *Arch Otolaryngol Head Neck Surg 1991;117(3):733-744*		Based upon anatomic, functional and aesthetic considerations
			ORN as a function of location within mandible; symphysis, body, ramus and condyle.
Glanzmann C, Gratz KW.	**Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors** *Radiother Oncol 1995;36:94-100*	Stage 1:	Bone exposure without signs of infection and persisting for at least 3 months
		Stage 2:	Bone exposure with infection or sequester and without the signs of stage 3-5
		Stage 3:	Bone necrosis treated with mandibular resection with a satisfactory result
		Stage 4:	Bone necrosis treated with mandibular resection with a satisfactory result
		Stage 5:	Death due to ORNI
Clayman L.	**Clinical controversies in oral and maxillofacial surgery: part two. Management of dental extractions in irradiated jaws: a protocol without hyperbaric oxygen therapy.** *J Oral Maxillofac Surg 1997;55:775-81*	Type I:	Presenting with bone lysis under intact gingiva or mucosa
		Type II:	Bone exposure with secondary contamination; an aggressive form
Wong JK, *et al.*	**Conservative management of osteoradionecrosis** *Oral Surg Oral Med Oral Path Oral Radiol Endod 1997;84:16-21*	Stage 1:	Bone exposure resulting from tumor necrosis where tumor death results in a loss of soft tissue coverage
		Stage 2:	Bone exposure as a consequence of tumor recurrence
		Stage 3:	Bone exposure resultant from oral surgical (surgical lavage operations) or other dental interventions including dental treatment
		Stage 4:	Bone exposure de novo without apparent cause aside from radiation exposure
Stone G, Boysen M.	**Mandibular osteoradionecrosis: clinical behavior and diagnostic aspects.** *Clin Otolaryngol Allied Sci 2000;25:378-84*	Stage 0:	Mucosa defect only
		Stage I:	Radiological evidence of necrotic bone with intact mucosa
		Stage II:	Positive radiographic findings with denuded bone intraorally
		Stage III:	Exposure of the necrotic bone; skin fistula and infection
Schwartz HC, Kagan AR.	**Osteoradionecrosis of the mandible: scientific basis for clinical staging.** *Am J Clin Oncol 2002;25:168-72*	Stage I:	Superficial involvement of the mandible only
		Stage II:	Localized involvement of the mandible, with or without soft tissue necrosis
		Stage III:	Diffuse involvement of the mandible, with or without soft tissue necrosis
Notani K, *et al.*	**Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy.** *Head Neck 2003;25:181-6*	Stage I:	ORN confined to alveolar bone
		Stage II:	ORN limited to the alveolar bone and/or above the level of the inferior alveolar canal
		Stage III:	ORN under the lower part of the inferior alveolar canal, with fistula or bone fracture
Tsai CJ, *et al.*	**Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer.** *Int J Radiat Oncol Biol Phys 2013;85:415-20*	Stage I:	Minimal bone exposure with conservative management only
		Stage II:	Minor debridement required
		Stage III:	HBO needed
		Stage IV:	Major surgery needed

Karagozoglu KH, *et al.*	**Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy.** *Med Oral Patol Oral Cir Bucal 2014;19:e433-7*	Stage 0:	Bone exposure more than 1 month; no distinct changes on imaging
		Stage I:	Bone exposure with no distinct changes on imaging, with or without symptoms
		Stage II:	Bone exposure with distinct changes on imaging, with no involvement of the lower mandible border
		Stage III:	Necrotic bone involving the lower border of the mandible
Lyons A, *et al.*	**Osteoradionecrosis – a review of current concepts in defining the extent of the disease and a new classification proposal.** *Br J Oral Maxillofac Surg 2014;52:392-5*	Stage 1:	<2.5 cm length of bone affected; asymptomatic
		Stage 2:	>2.5 cm length of bone affected; involving fracture or the inferior dental nerve
		Stage 3:	>2.5 cm length of bone affected; symptomatic, with no other features
		Stage 4:	>2.5 cm length of bone affected; bone fracture and involving inferior dental nerve or fistula
Bone/soft tissue		**Classification**	
He Y, *et al.*	**Retrospective analysis of osteoradionecrosis of the mandible: proposing a novel clinical classification and staging system.** *Int J Oral Maxillofac Surg 2015;44:1547-1557*	BO:	No distinct changes or just osteolytic images on radiography, but patients suffering from typical ORNM-related symptoms (bone exposure or pain)
		B1:	Maximal diameter of the lesion on radiography <2.0 cm
		B2:	Maximal diameter of the lesion on radiography ≥ 2.0 cm
		B3:	Pathological fracture
Soft tissue defect (S)		S0:	Mucosal and skin integrity
		S1:	Intraoral mucosal defect or external skin fistula
		S2:	Intraoral mucosal and external skin defect; through-and-through defect
		Stage 0:	Conservative therapy
		Stage I:	Sequestrectomy and primary closure
		Stage II:	Marginal resection without reconstruction, or segmental resection combined with osteocutaneous flap reconstruction; an additional soft tissue flap should be used in patients with an orocutaneous fistula
		Stage III:	Segmental resection combined with osteocutaneous flap reconstruction; an additional soft tissue flap should be used in patients with an orocutaneous fistula

Radiation damaged tissue as a unique wound

BEAM PROFILE

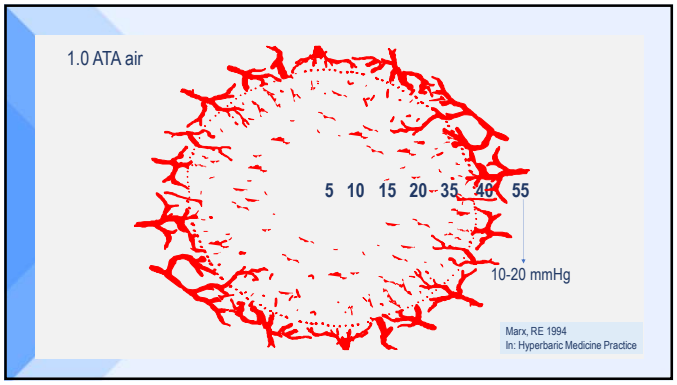
The dose variation across the field at a specified depth.

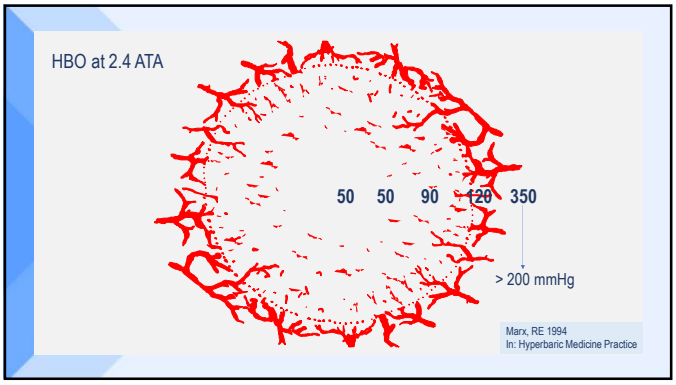


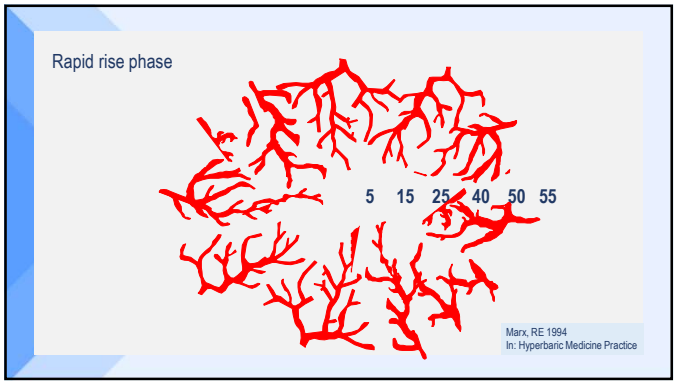
Regulation of wound-healing ● CO_2-O_2 angiogenesis—Effect of oxygen gradients and inspired oxygen concentration

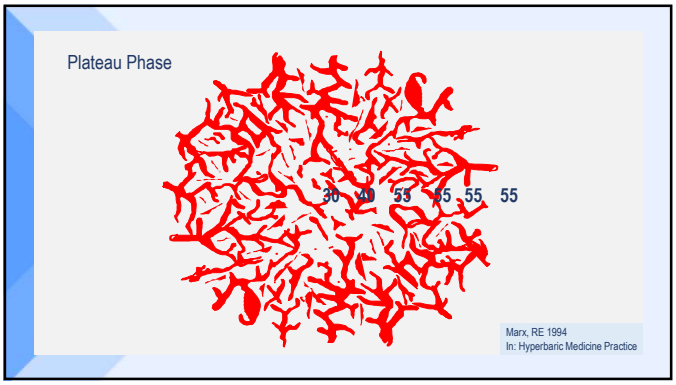
David R. Knighton, M.D., Ian A. Silver, M.A., M.R.C.V.S., and Thomas K. Hunt, M.D., F.A.C.S., San Francisco, Calif.

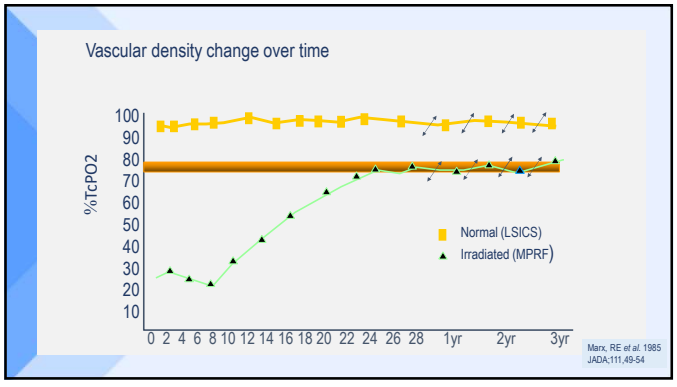
Knighton DR, *et al.* Surgery 1981;90(2)

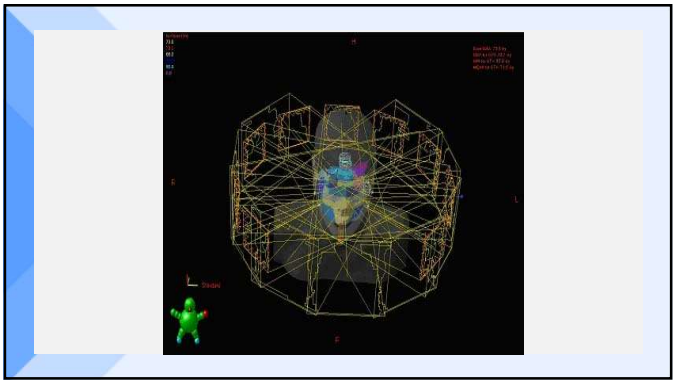

1.0 ATA air
5 10 15 20 35 40 55
10-20 mmHg
Marx, RE 1994
In: Hyperbaric Medicine Practice


HBO at 2.4 ATA
50 50 90 120 350
> 200 mmHg
Marx, RE 1994
In: Hyperbaric Medicine Practice


Rapid rise phase
5 15 25 40 50 55
Marx, RE 1994
In: Hyperbaric Medicine Practice


Plateau Phase
30 40 55 55 55 55
Marx, RE 1994
In: Hyperbaric Medicine Practice


Vascular density change over time
%TcPO2
100
90
80
70
60
50
40
30
20
10
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 1yr 2yr 3yr
Normal (LSICS)
Irradiated (MPRF)
Marx, RE et al. 1985
JADA;111,49-54

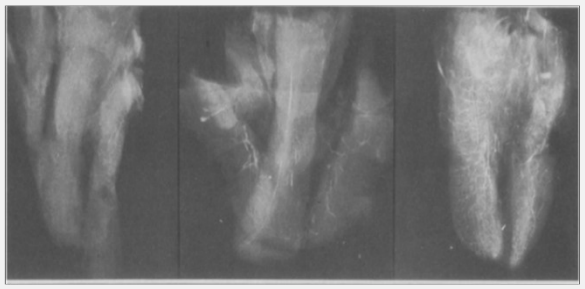


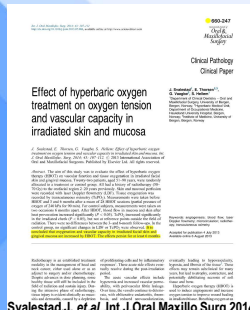
Micro-angiogenic vascular density

	Normobaric Air (N=7)	Normobaric Oxygen (N=14)	Hyperbaric Oxygen (N=14)
Maximum VDE	18	19	99
Minimum VDE	6	6	78
Mean VDE	13	13	93

Normobaric air vs. Normobaric O2 p < 0.89
Normobaric O2 vs. Hyperbaric O2 p < 0.01
Normobaric air vs. Hyperbaric O2 p < 0.01

Marx RE, *et al.* 1990
Am J Surgery; 160





Effect of hyperbaric oxygen treatment on oxygen tension and vascular capacity in irradiated skin and mucosa

Clinical Pathology
Clinical Paper

20 pts hx H/N RT 50-70 Gy.
ORN or ORN prophylaxis

Randomly allocated HBO vs. no-HBO

Skin & mucosal tissue perfusion measurements
Transcutaneous oximetry & Doppler flowmetry

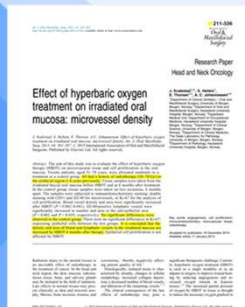
pre-HBO & 6 months post-HBO
controls 6 months apart

Svalestad J, *et al.* Int J Oral Maxillo Surg 2014;43

tcpO2 measurements pre/post HBO vs. controls

		HBO group Baseline	3 months	6 months	Controls Baseline	6 months
Forehead	*Basal*	39.8 +/-15.75	39.87 +/-11.25	41.3 +/-10.5	41.3 +/-12	43.6 +/-10.5
	O2	140.3+/-71.3	135.8 +/-37.5	137.3 +/-38.3	127.5 +/-55.5	113.3 +/-39.8
Cheek	*Basal*	29.3 +/-13.5	42.8 +/-15.7 *	42.8 +/-7.5 *	31.5 +/-9	29.3 +/-11.3
	O2	105.0 +/-43.5	150.85 +/-63.8 *	148.5 +/-48.8 *	105.0 +/-37.5	95.3 +/-34.5
Intercostal	*Basal*	54.0 +/-13.5	54.8 +/-15	59.3 +/-9.75	64.5 +/-18	62.3 +/-14.3
	O2	148.2 +/-52.5	156.8 +/-52.5	156.8 +/-43.5	116.3 +/-33	145.5 +/-45.0

** P < 0.05 compared to baseline*



Effect of hyperbaric oxygen treatment on irradiated oral mucosa: microvessel density

Research Paper
Head and Neck Oncology

Same 20 pts hx H/N

Buccal oral mucosa tissue samples

pre-HBO & 6 months post-HBO

controls 6 months apart

Svalestad J, *et al.* Int J Oral Maxillo Surg 2015;44

Vascularization & cell proliferation

	HBO Group			Controls		
Blood vessels	Baseline	6 months	p	Baseline	6 months	p
Sub-epithelial						
MVD	45.4 +/- 13.9	98.0 +/- 15.9	0.002	45.6 +/- 15.7	49.3 +/- 10.5	NS
MVA	1.5 +/- 0.6	4.4 +/- 1.9	0.003	1.5 +/- 0.6	1.6 +/- 0.5	NS
Deeper connective tissue						
MVD	30.4 +/- 10.1	45.1 +/- 16.4	0.01	28.1 +/- 9.6	34.4 +/- 7.8	NS
MVA	2.5.+/- 1.3	3.7 +/- 1.3	0.041	2.2 +/- 0.9	2.7 +/- 1.4	NS
Lymph vessels						
Sub-epithelial						
MVD	18.3 +/- 8.1	36.1 +/- 12.6	0.002	19.4 +/- 6.2	16.9 +/- 8.8	NS
MVA	1.3 +/- 0.7	2.7 +/- 1.8	0.019	1.2 +/- 0.6	1.5 +/- 0.7	NS

Marx ORN protocol

Marx Stage I: Localized/early disease

30 HBO treatments

Stage I responder

decreased amount of exposed bone

resorption or spontaneous sequestration

softening of exposed bone

PENTOCLO

Pentoxifylline - Tocopherol - Clodronate

PENTO

Pentoxifylline - Tocopherol

Delanian S, *et al.* Int J Rad Oncol Biol Phys 2011

Kolokythas A, *et al.* Oral & Maxillofac Surg.2019; 48

Zhang Z, *et al.* Oral Surg Oral Med Oral Path Oral Radio 2020;129

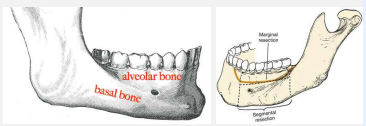
D'Souza J, *et al.* B J Oral Maxillo Surg 2014;52

d'Hauthuille C *et al.* Review de Stomatologie et de Chirurgie Maxillo-Faciale 2009;110(1)

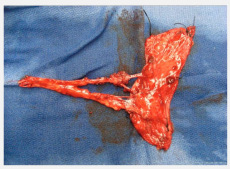
Bettoni J, *et al.* Br J Oral Maxilla Surg 2019;57(6)

Notani Stages

1. ORN confined to alveolar bone
2. ORN limited to alveolar bone and/or above level of inferior alveolar canal
3. ORN under lower part of inferior alveolar canal, with fistula or bone fx.



Haffey T, *et al.* Am J Otolaryngol 2019;40



First description of this flap type for ORN

8 pts with clinical & radiological evidence of ORN

6/8 had underdone debridement & HBO
- *persistent sx's*

Low donor site morbidity - ease of harvest

Overview and Emerging Trends in the Treatment of Osteoradionecrosis

Joseph R. Peleca MD
Emily Zhang MD
Michael A. Fritz MD
Peter J Cobb MD

Meleca JB, *et al.* Curr Treat Options in Oncol 2021;22

Hyperbaric Oxygen Therapy

Standard procedure: *Pressures often vary between 2.0 & 2.5 ATA for 60-120 minutes once or twice daily for 30-60 sessions*

Contraindications: *Tumor recurrence; history of HBO complications*

Complications: *Tumor recurrence (theoretical, not substantiated by evidence); visual disturbance, barotrauma, oxygen toxicity*

Special points: *Evidence for HBO treatment & prevention of ORN mixed. Smaller uncontrolled studies have shown recovery with HBO alone or combined with surgery, however, few randomized controlled trials exist. The first showed ORN prevention for dental procedures. Subsequent RCTs have not supported HBO treatment or prevention efficacy. Cochrane Review suggested moderate-quality evidence for increased likelihood to achieve mucosal coverage & prevent post-op breakdown.*

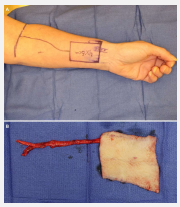
Cost-effectiveness: *Expensive (often more expensive that surgery given number of visits required and cost of equipment/staffing).*

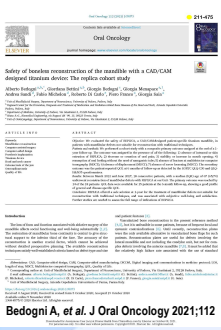
Fasciocutaneous Flaps for Refractory Intermediate Stage Osteoradionecrosis of the Mandible—Is It Time for a Shift in Management?

Gigliotti J, *et al.* J Oral Maxillofac Surg 2021;79

"Marx pioneered HBO, no RCTs have replicated his results"
"Appears little benefit to addition of HBO for advanced stages"

Concept of RT-induced fibro-atrophic theory
Use of PENTO/PENTOCLO promising - better data required



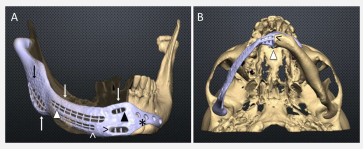


Safety of bespoke reconstruction of the mandible with a CAD/CAM designed titanium device: The replics cohort study

18 pts over 5 yrs

Primary outcomes at 1 yr. achieved in 14/18 (78%)
- *absence of extrusion*
- *decrease/cessation of pain*
- *stability/increase in mouth opening*
- *resumption of oral feeding*
- *absence of fracture/displacement/screw loosening*

MRONJ - 10 ORN - 2 SCC - 2 Other - 4



Bedogni A, *et al.* J Oral Oncology 2021;112

Platelet-rich fibrin as a treatment option for osteoradionecrosis: A literature review

Harris P, *et al.* J Stomatol Oral Maxillo Surg 2021

Marx Stage II:
Stage I "non-responder"

Local surgical debridement or resection

10 HBO treatments post-operatively

Marx Stage III/III-R:

Extensive mucosal loss & more necrotic bone

Soft tissue fistula; pathologic fracture; bone resorption; Stage II non-responder

Following initial 30 treatments:

Partial jaw resection; fixation; primary closure of any fistulae

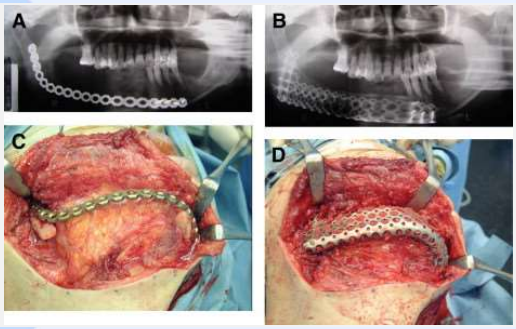
Resection of RT damaged soft tissue & skin flap repair

Ten additional treatments

10-12 weeks after resection > formal reconstruction

Titanium fixation plate; titanium/Dacron tray-filled cancellous bone chips

+/- ten additional treatments



Prospective study; complications within irradiated soft tissue

> 6,400 cGy

Wound Infections	N	Minor	Major	Total
Non-HBO	80	6 (7.5%)	13 (16%)	19 (24%)
HBO	80	3 (3.5%)	2 (2.5%)	5 (6%)

P= 0.001

Wound Dehiscence	N	Minor	Major	Total
Non-HBO	80	12 (15%)	26 (33%)	38 (48%)
HBO	80	6 (7.5%)	3 (3.5%)	9 (11%)

P= 0.001

Delayed Healing	N			
Non-HBO	80	44 (55%)		
HBO	80	9 (11%)		

P= 0.005

Marx, RE 1994
In: Hyperbaric Medicine Practice


Hyperbaric Oxygen Therapy for Radionecrosis of the Jaw: A Randomized, Placebo-Controlled, Double-Blind Trial From the ORN96 Study Group

Study design

134 consecutive ORN pts assessed
12 centers; 1997-2001

68 randomized & analyzed
31 HBO - 37 sham

Study stopped at 2nd interim analysis

HBO 19% healed

Sham 32% healed

"Need for surgery = HBO failure"

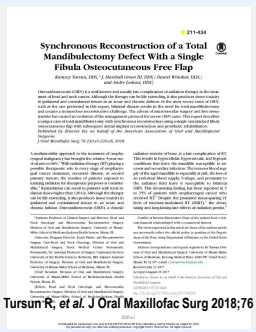
Annane D, *et al.* J Clinical Oncology 2004;22(24)


Challenges threaten, opportunity awaits hyperbaric medicine and the head and neck cancer patient

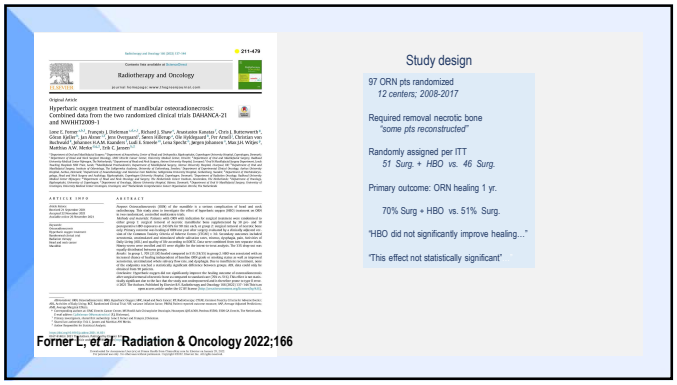
Clarke R. UHM 2019;46(4)


Hyperbaric oxygen is still needed in the management and prevention of mandibular necrosis: a response to Mr. Richard Clarke

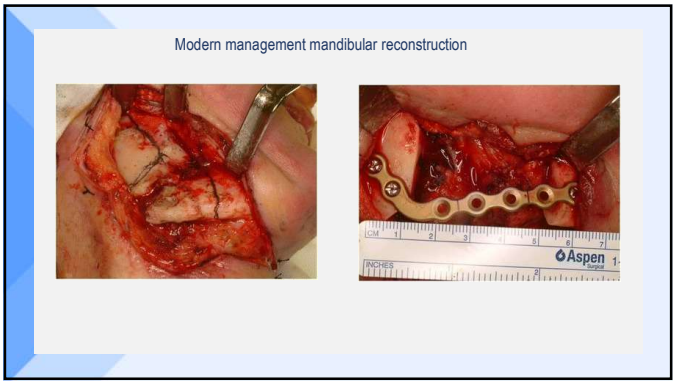
Marx RE, *et al.* UHM 2019;46(4)

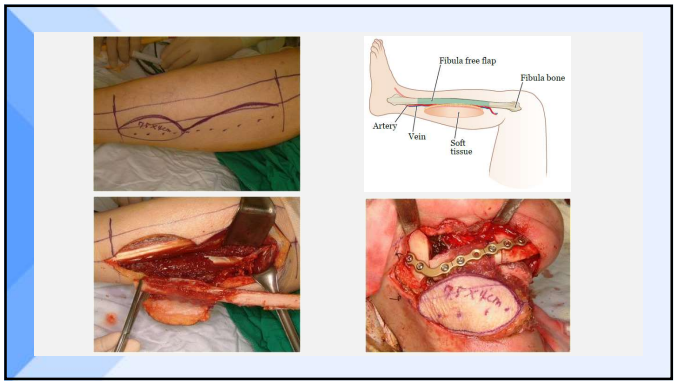

Synchronous Reconstruction of a Total Mandibulectomy Defect With a Single Fibula Osteocutaneous Free Flap

Tursun R, *et al.* J Oral Maxillofac Surg 2018;76



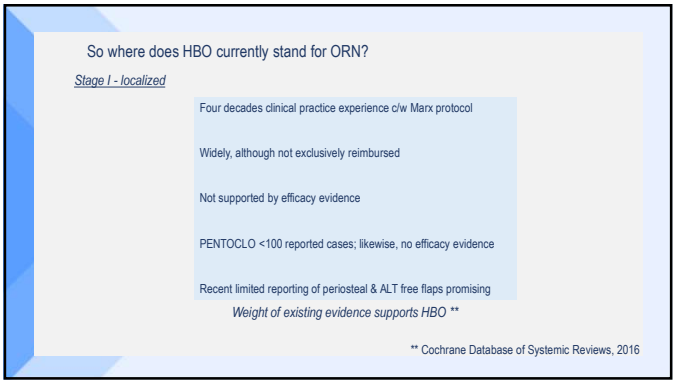
Forner L, *et al.* Radiation & Oncology 2022;166





Kokosis G, *et al.* Arch Plastic Surg 2016;43(1)

Frankart AJ, *et al.* Int J Rad Oncol Biol Phys 2021;109(5)



Stage III 'advanced'

Introduction of Marx Protocol (1983) mandible reconstruction
- ~ *HBO reduced failure rates; optimized healing*
- ~ *essential standard of care ~ two decades*

Advent of microvascular surgery another step change

Single-stage radical resection & myo-cutaneous free fibular flap
- ~ *now considered "gold standard" for advanced ORN since 2000*
- ~ *HBO occasionally employed for post-op complications*

Marx two-stage protocol in absence of microvascular capabilities


217-006

Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin

Marx RE, *et al.* JADA 1985;111:49-54

74 pts randomized to HBO or PCN

All high risk > 6,000 cGy

135 teeth extracted in 37 PCN pts
- ~ *29.9% unhealed sockets at 6 months*

156 teeth extracted in 37 HBO pts
- ~ *5.6% unhealed sockets at 6 months*

ORN prophylaxis protocol

Basis for 20 pre-op. procedures

angiogenesis plateau

Basis for 10 post-op. procedures

reduces dehiscence by promoting collagen production along incision lines


217-047

HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): A Randomized Controlled Trial of Hyperbaric Oxygen to Prevent Osteoradionecrosis of the Irradiated Mandible After Dentoalveolar Surgery

Shaw, RJ, *et al.* Int J Rad Oncol Bio Phys 2019

144 pts randomized; HBO vs. no HBO

10 facilities

55 received HBO + surgery

66 received surgery

Mean RT dose 6,300 cGy

Blinded assessors

Trail halted at interim analysis

Data relates to conformal/IMRT


211-499

Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy: ISOO-MASCC-ASCO Guideline

Peterson DE, *et al.* J Clinical Oncology 2024;May 1

" The use of hyperbaric oxygen in prevention and management of ORN remains largely unjustified, with limited evidence to support its practice"