Mandibular Osteoradionecrosis

Dick Clarke, CHT

Mandibular Osteoradionecrosis

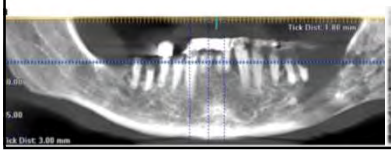
Review & Update

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*

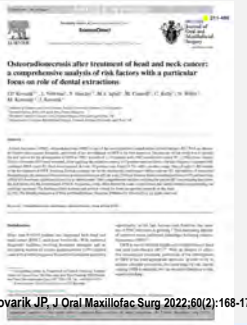
dose-dependent > complex wounds/organ loss

"consequential vs. generic"

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

(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

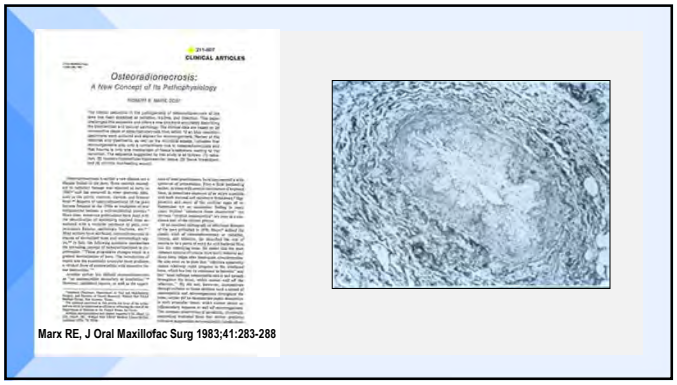
90% traumatically-induced



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

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

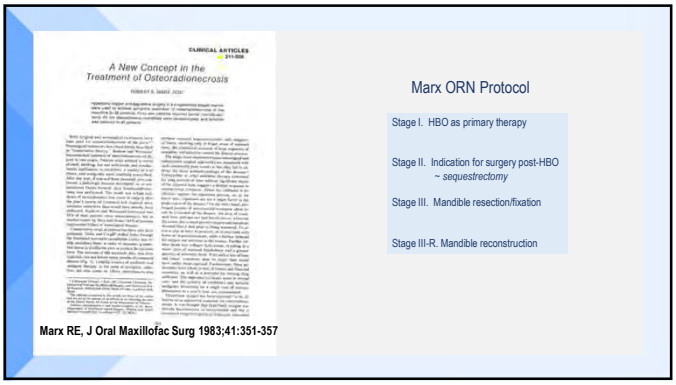
Dose of RT (Gy)	Patients (percentage)
<40	8 (8.8)
40.1 – 45.0	5 (5.5)
45.1 - 50.0	4 (4.4)
50.1 – 55.0	5 (5.5)
55.1 – 60.0	15 (16.5)
>60	54 (59.3)



Osteoradionecrosis:
A New Concept of Its Pathophysiology

CLINICAL ARTICLES

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



A New Concept in the Treatment of Osteoradionecrosis

CLINICAL ARTICLES

Marx ORN Protocol

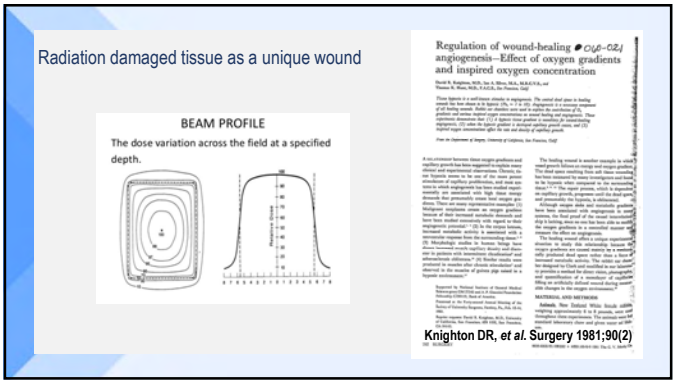
Stage I. HBO as primary therapy

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

Stage III. Mandible resection/fixation

Stage III-R. Mandible reconstruction

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



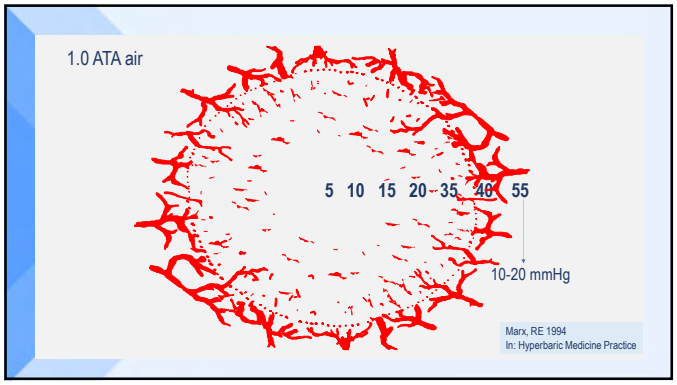
Radiation damaged tissue as a unique wound

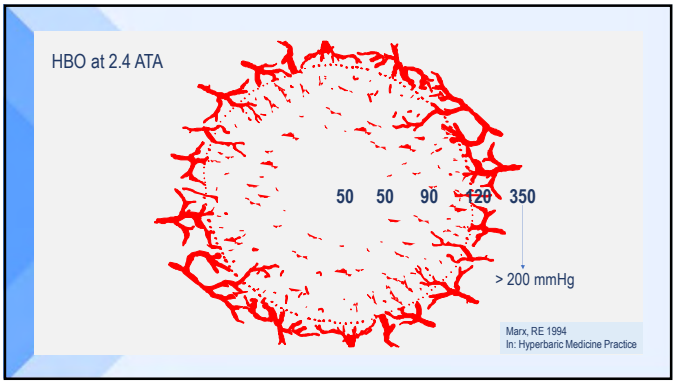
BEAM PROFILE

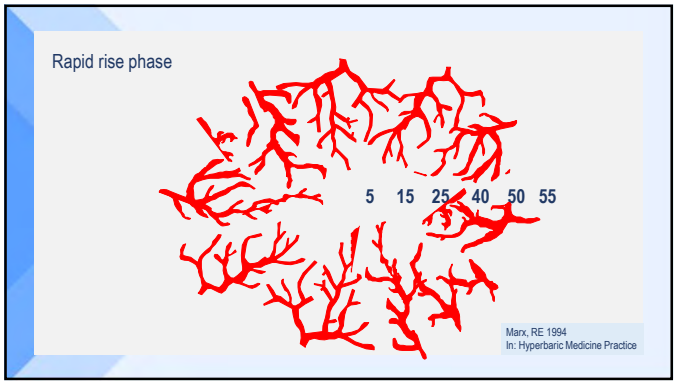
The dose variation across the field at a specified depth.

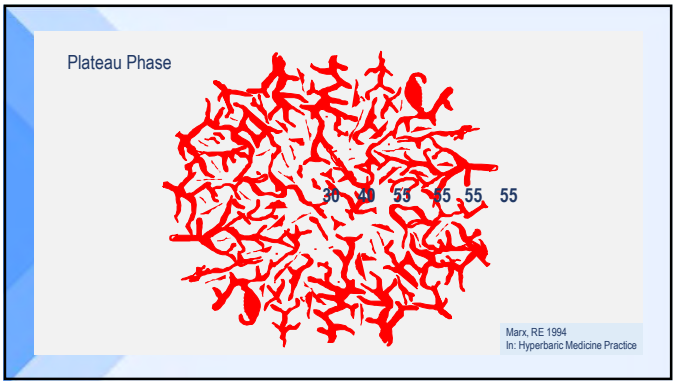
Regulation of wound-healing angiogenesis—Effect of oxygen gradients and inspired oxygen concentration

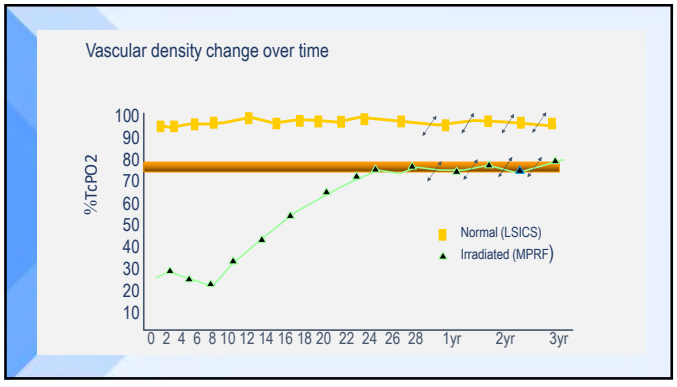
Knighton DR, *et al.* Surgery 1981;90(2)

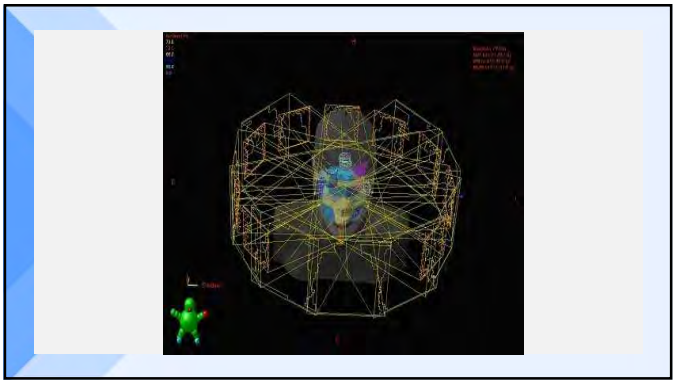

1.0 ATA air
5 10 15 20 35 40 55
10-20 mmHg
Marx, RE 1994
In: Hyperbaric Medicine Practice


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)



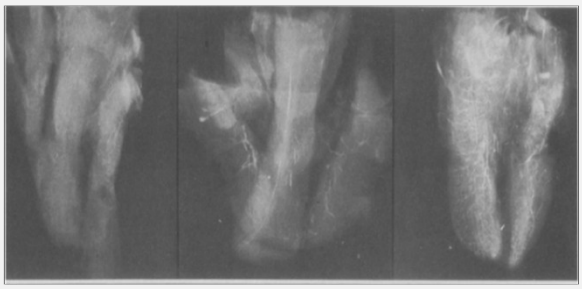
Micro-angiogenic vascular density

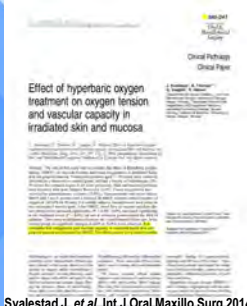
	Normobaric Air (N=7)	Normobaric Oxygen (N=14)	Hyperbaric Oxygen (N=14)
Maximum VDE	18	19	99
Minimum VDE	6	6	78
Mean VDE	13	13	93

Normobaric air vs. Normobaric O_2 $p < .89$
Normobaric O_2 vs. Hyperbaric O_2 $p < .01$
Normobaric air vs. Hyperbaric O_2 $p < .01$

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

1.0 ATA air | 1.0 ATA oxygen | 2.5 ATA oxygen





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

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

Randomly allocated HBO vs. no-HBO

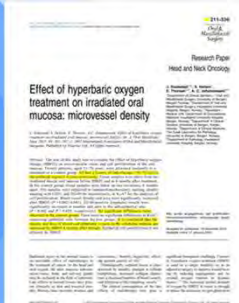
Skin & mucosal tissue perfusion measurements
Transcutaneous oximetry & Doppler flowmetry

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

$tcpO_2$ 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*



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

Same 20 pts hx H/N

Buccal oral mucosa tissue samples

pre-HBO & 6 months post-HBO

controls 6 months apart

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

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

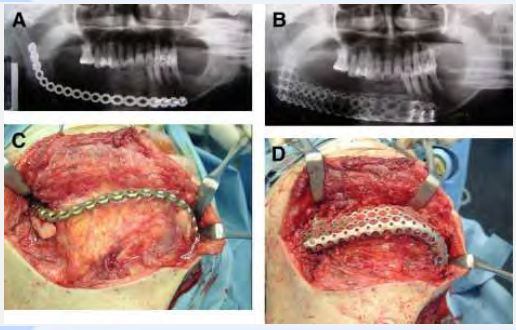
Resection of RT damaged soft tissue & skin flap repair

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

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)

Study design

97 ORN pts randomized
12 centers; 2008-2017

Required removal necrotic bone
"some pts reconstructed"

Randomly assigned per ITT
51 Surg. + HBO vs. 46 Surg.

Primary outcome: ORN healing 1 yr.

70% Surg + HBO vs. 51% Surg.

"HBO did not significantly improve healing…"

"This effect not statistically significant"

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

PENTOCLO
Pentoxifylline - Tocopherol - Clodronate

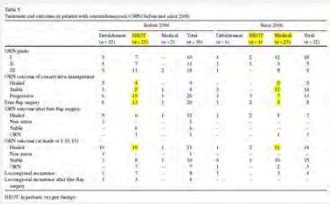
PENTO
Pentoxifylline - Tocopherol

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

Kolokythas A, *et al.* Int.J. 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



Shaw R, *et al.* Trials 2025;26:254

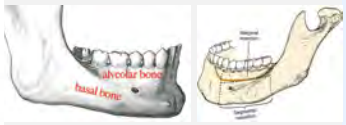
d'Hauthuille,C *et al.* Review de Stomatolgie et de Chirurgie Maxillo-Faciale 2009;110(1)

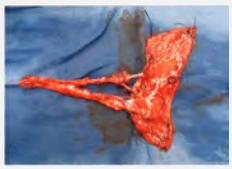
Bettoni J, *et al.* Br J Oral Maxilla Surg 2019;57(6)

Arianpour K, *et al.* JAMA Otol Head Neck Surg 2023;149(7):621-627

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.





50/52 MORN cases successfully managed

2 progressed to fibular free flap

Simple, reliable, low risk

Low donor site morbidity - ease of harvest

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).*

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

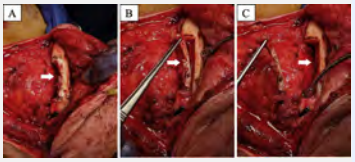
"Marx pioneered HBO, no RCTs have replicated his results"
"Appears little benefit to addition of HBO for advanced stages"

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

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

"The microvascular osteo-myo-cutaneous free flap, such as free fibular flap, has evolved to become a workhorse …"

"Conservative management including the use of pentoxifylline-vit. E should be attempted before surgical procedures"

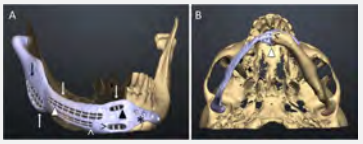


Bedogni A, *et al.* J Oral Oncology 2021;112

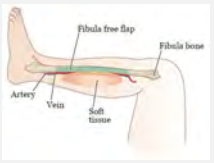
18 pts over 5 yrs

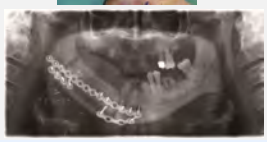
Primary outcomes at 1 yr. achieved in 14/18 (78%)
- *absence of extrusion*
- *decrease/cessation of pain*
- *stability/increase in mouth opening*
- *resumption of oral feeding*
- *absence of fracture/displacement/screw loosening*

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



Modern management mandibular reconstruction





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

Clarke R. UHM 2019;46(4)

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

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"

Fritz MA, *et al.* Otolaryn Head Neck Surg 2024;00:1-13

Where does HBO currently stand for ORN?

Stage I - localized

Four decades clinical practice experience c/w Marx protocol

Widely, although not exclusively reimbursed

Not supported by efficacy/effectiveness evidence

PENTOCLO <100 reported cases; no efficacy evidence

Recent limited reporting of periosteal & ALT/FFF flaps promising

Weight of existing evidence supports HBO **

** Cochrane Database of Systemic Reviews, 2016

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 surgeon


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


HOPDN (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