

# **Radiation-Induced Soft Tissue Injuries**

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**Dick Clarke, CHT**

# Radiation-Induced Soft Tissue Injuries

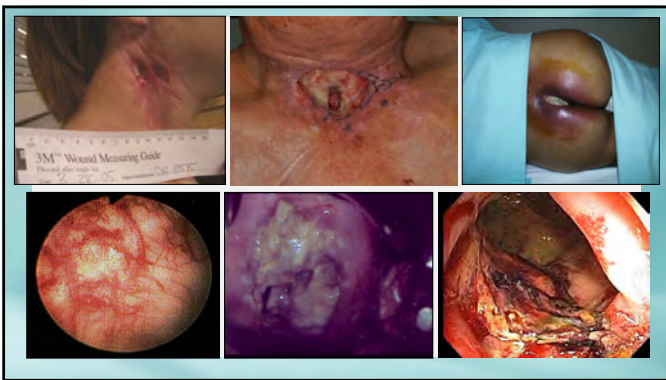
## Hyperbaric Oxygen as Standard of Care?

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

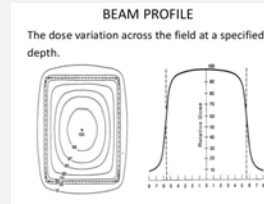


### Radiation Tissue Injury: "Non-Target" Tissues

- Acute effects: mucosa, other rapidly proliferating cells
- usually benign +/- RT pause
- Late effects: chronic oxidative stress
- dose-dependent
- complex wounds/organ loss



Greenwood TW, Gilchrist AG. Brit J Surgery 1973;60(5)



### Regulation of wound-healing • $O_2$ • $Ca^{2+}$ angiogenesis—Effect of oxygen gradients and inspired oxygen concentration

**Background and objectives:** The healing of a wound is a complex process involving many factors, including oxygen tension, growth factors, and cell proliferation. The regulation of wound-healing by oxygen gradients and inspired oxygen concentration is a topic of increasing interest. This study aims to investigate the effect of oxygen gradients and inspired oxygen concentration on wound-healing in a rat model.

**Methods:** The study involved the use of a rat model of wound-healing. The wound was created by a standardized method, and the wound was treated with different concentrations of inspired oxygen. The wound-healing was monitored by measuring the wound area and the time to complete healing.

**Results:** The study found that the wound-healing was significantly faster in the group that received inspired oxygen compared to the control group. The wound area was significantly smaller in the inspired oxygen group, and the time to complete healing was significantly shorter.

**Conclusions:** The study demonstrates that inspired oxygen significantly accelerates wound-healing in a rat model. This finding has important implications for the treatment of wounds in clinical practice.

**Keywords:** wound-healing, oxygen gradients, inspired oxygen, angiogenesis, wound-healing, rat model.

Knighon DR. et al. Surgery 1981;90(2)

### Evolution of radiation-induced soft tissue injuries

- Some minor symptoms resolve spontaneously *others with conservative care*
- Remitting-relapsing characteristics
- Other seemingly minor symptoms prove refractory *disease progression despite 'standard' care*
- New forms of injury may evolve > advanced care *leading in some cases to loss of organ or death*

### Rectal RT injury complex

Microscopic hemorrhage  
Macroscopic hemorrhage  
Mucosal loss  
Pain/tenesmus  
Frequency  
Loss of sphincter control  
Stricture  
Ulceration  
Ulceration  
Death

*Trial design*

- 226 screened for eligibility
- 150 enrolled/analyzed (1:1)
- 66% ratio
- 120 evaluable
- 64 HBO, 20 ATA O2
- 56 Sham, 13 > 1 ATA O2

*Objective & subjective criteria*

- HBO higher response rates
- SGM4-p=0.019
- clinical assessment p=0.0009
- bowel bother
- bowel function

All differences abolished at cross-over

Elimination of remitting/relapsing sequence = "disease modification"

Clarke RE, et al. Int. J Rad Oncol Biol Phys 2008;72

RADIATION PROCTITIS		EVAL BY: PRINT NAME: _____		DATE: _____		HORTS IV	
PT NAME	HORTS ID	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORE	ACTIVITY CODE
<b>Subjective</b>							
Tenesmus	Occasional urgency	Frequent urgency	Persistent urgency	Severe	Severe	1-4	1-4
Mucosal loss	Occasional	Intermittent	Persistent	Extensive	Extensive	1-4	1-4
Sphincter control	Occasional	Intermittent	Persistent	Severe	Severe	1-4	1-4
Stool frequency	2-4 per day	4-8 per day	8 per day	Uncontrolled diarrhea	Uncontrolled diarrhea	1-4	1-4
<b>Objective</b>							
Bleeding	Occasional & minimal	Intermittent & moderate	Persistent & severe	Severe & extensive	Severe & extensive	1-4	1-4
Ulceration	Superficial < 1 cm <sup>2</sup>	Superficial > 1 cm <sup>2</sup>	Deep ulcer	Perforation, Fistulae	Perforation, Fistulae	1-4	1-4
Stricture	< 20 normal diameter	< 20 normal diameter	< 20 normal diameter	Complete obstruction	Complete obstruction	1-4	1-4
<b>Management &amp; stool frequency</b>							
Tenesmus & stool frequency	Occasional < 2 antidiarrheals/week	Regular > 2 antidiarrheals/week	Multiple > 2 antidiarrheals/day	Surgical intervention/Permanent colostomy	Surgical intervention/Permanent colostomy	1-4	1-4
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	Surgical intervention	1-4	1-4
Bleeding	Blood transfusion, not surgery	Occasional transfusion	Frequent transfusions	Surgical intervention/Permanent colostomy	Surgical intervention/Permanent colostomy	1-4	1-4
Ulceration	Diet modification, stool softener	Occasional steroids	Steady per orals, frequent surgery	Surgical intervention/Permanent colostomy	Surgical intervention/Permanent colostomy	1-4	1-4
Stricture	Diet modification	Occasional dilation	Regular dilation	Surgical intervention	Surgical intervention	1-4	1-4
Sphincter control	Occasional use of biofeedback aids	Intermittent use of biofeedback aids	Persistent use of biofeedback aids	Surgical intervention/Permanent colostomy	Surgical intervention/Permanent colostomy	1-4	1-4
<b>Analysis</b>							
Rectal exam	Assessment of lumen and perianal					Y/N	Date
Proctoscopy	Assessment of lumen and mucosal surface					Y/N	Date
CT	Assessment of wall thickness, strict and fistula formation					Y/N	Date
MRI	Assessment of wall thickness, strict and fistula formation					Y/N	Date
Endoanatomy	Assessment of strictures, strict and fistula formation					Y/N	Date
Other	Assessment of wall thickness, strict and fistula formation					Y/N	Date

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**Patient beliefs (blinding)**

72 pts. asked what they thought their randomization was

	HBO	Sham	Don't Know
HBO Group (33)	20	1	12
Sham Group (39)	23	2	14

Chi-square test detects no relationship ( $p=0.9058$ )  
 Ignoring those who did not know, Kappa statistic  $p=0.0299$

**Harms**

Ear barotrauma

19 pts (15.8%) complained of ear pain/discomfort  
 11 unremarkable exam  
 7 TM changes only  
 1 TM change & middle ear effusion  
 decongestants...8 ventilation tubes...7 no tx...4

Sinus barotrauma

1 pt. (0.08%), tx with decongestants

Transient myopia

4 pts. (3.3%)

Confinement anxiety

2 pts. (1.7%) sedative...1 reassurance...1

**Treatment failure**

Local recurrence vs. residual tumor as failed clinical response/relapse risk

45% (3) of those who failed to respond per SOMA dx with cancer

SOMA scores in pts who either failed to respond or improved then relapsed > by average of 9 (4-7) at 1yr when CA dx.

**Trial design**

241 screened for eligibility  
 84 enrolled/randomized (2:1)  
 35%

Reported  
 40 HBO 2.4 ATR Q2 per mask  
 25 Sham 1.3 ATR air per mask

Subjective primary endpoint  
 change in IBD questionnaire score  
 IBDQ rectal bleeding score at 1 yr

Glover M, et al. Lancet Oncology 2016;17(2):224-233

**Discussion**

**Hyperbaric oxygen therapy for chronic hemiparesis after stroke: a randomized, double-blind, sham-controlled phase 3 trial**

**Background**

Stroke is a leading cause of disability worldwide. Hemiparesis, or weakness of one side of the body, is a common and often debilitating consequence of stroke. Current treatments for hemiparesis include physical therapy, occupational therapy, and pharmacological agents. However, the effectiveness of these treatments is limited, and many patients experience poor functional outcomes. Hyperbaric oxygen (HBO) therapy has been proposed as a potential treatment for stroke, based on its ability to increase oxygen delivery to hypoxic tissues and promote neuroplasticity. However, the efficacy of HBO for stroke remains controversial, and large-scale randomized controlled trials are needed to evaluate its effectiveness.

**Methods**

This phase 3 trial was a randomized, double-blind, sham-controlled trial comparing HBO to a sham treatment in patients with chronic hemiparesis after stroke. The primary endpoint was the change in the Barthel ADL index score at 12 weeks. Secondary endpoints included the change in the Fugl-Meyer Assessment score, the change in the Stroke Impact Scale score, and the change in the modified Rankin Scale score. The trial was conducted in a tertiary care hospital and was approved by the local research ethics committee.

**Results**

The trial included 241 patients who were randomized to either the HBO group (n=160) or the sham group (n=81). The HBO group had a significantly greater improvement in the Barthel ADL index score at 12 weeks compared with the sham group (mean difference, 10.5; 95% CI, 5.5 to 15.5; p<0.001). There were no significant differences between the groups for the other endpoints.

**Conclusions**

Hyperbaric oxygen therapy significantly improved functional outcomes in patients with chronic hemiparesis after stroke compared with a sham treatment. These findings suggest that HBO may be a promising treatment for stroke, and further research is needed to evaluate its long-term effectiveness and safety.

*"This trial is VERY upsetting!*

*We have seen such consistently good results in the patients treated off trial, in terms of healing ulceration & treating bleeding - in fact, there is no one in 10 years who has not responded well to HBO.*

*I must have sent 4 or 5 a year - and it is very difficult to understand our trial results!"*







**Successful hyperbaric oxygen therapy for laryngeal rhabdomyosarcoma after chemoradiotherapy for nasopharyngeal cancer: case report and literature review**

**Abstract** Laryngeal rhabdomyosarcoma (LR) is a rare and aggressive tumor of the head and neck. It is characterized by a high rate of local recurrence and distant relapse. The use of hyperbaric oxygen (HBO) in combination with chemotherapy and radiotherapy is a promising treatment option for LR. This report describes a patient with LR who achieved a complete response after HBO therapy following chemoradiotherapy for nasopharyngeal cancer. The patient's clinical course and imaging findings are discussed, along with a review of the literature on HBO for LR. The authors conclude that HBO may be a valuable adjuvant treatment for LR, particularly in cases where surgery is not feasible or the tumor has recurred.

**Keywords** Laryngeal rhabdomyosarcoma; hyperbaric oxygen; chemoradiotherapy; nasopharyngeal cancer; complete response.

**Case report** A 47-year-old male patient presented with a 3-month history of a rapidly enlarging, painless mass in the larynx. He had a history of nasopharyngeal cancer, treated with chemoradiotherapy 5 years ago. Physical examination revealed a large, fleshy, polypoid mass protruding from the larynx. Imaging studies (CT and MRI) showed a soft tissue mass in the larynx, consistent with LR. The patient underwent a course of HBO therapy (2.0 ATA, 90 minutes, 5 times weekly) in combination with chemotherapy. The mass regressed significantly, and the patient achieved a complete response. The authors discuss the pathophysiology of HBO, its potential mechanisms of action, and its role in the treatment of LR. They also review the literature on HBO for LR, highlighting the benefits and risks of this treatment modality.

**Conclusion** HBO therapy may be a valuable adjuvant treatment for LR, particularly in cases where surgery is not feasible or the tumor has recurred. Further studies are needed to evaluate the optimal dose and duration of HBO for LR.

**References** Abe M, et al. Jpn J Radiol 2012;30(4)

**Hyperbaric dosing**

- Treatment pressure...2.0 ATA oxygen  
*may require a multiplace (mask) pressure of 2.36 ATA*
- Treatment duration...90 minutes at tx pressure  
*typically requires up to 120 minutes in-chamber time*
- Treatment frequency...once daily, five times weekly
- Treatment course...30-40 exposures  
*titrated to clinical response*



**Hyperbaric Oxygen: Does it promote growth or recurrence of malignancy?**

**Abstract** Hyperbaric oxygen (HBO) is a well-established treatment for various medical conditions, including wound healing and radiation-induced tissue damage. However, there is concern that HBO might promote the growth or recurrence of malignancy. This review examines the evidence regarding the potential effects of HBO on tumor biology. The authors discuss the mechanisms of HBO, including its effects on oxygen delivery, cellular metabolism, and the immune system. They also review the literature on HBO and malignancy, highlighting the potential risks and benefits of this treatment modality. The authors conclude that HBO is unlikely to promote the growth or recurrence of malignancy, and it may be a valuable adjuvant treatment for certain types of cancer.

**Keywords** Hyperbaric oxygen; malignancy; tumor growth; recurrence; oxygen delivery.

**Conclusion** HBO is unlikely to promote the growth or recurrence of malignancy, and it may be a valuable adjuvant treatment for certain types of cancer. Further studies are needed to evaluate the optimal use of HBO in the treatment of malignancy.

**References** Feldmeier J et al. UHM 2003;30(1)

**Five-Year Recurrence Rates for SCC**

SCC Stage	Non-HBO	Recurred	HBO	Recurred
I	29	6 (21%)	36	6 (16%)
II	58	14 (24%)	94	17 (18%)
III	50	16 (32%)	92	19 (21%)
IV	23	9 (38%)	23	6 (28%)

**References** Moen I, Stuhr LEB. Targ Oncology 2012;7

**Source** Marx RE, 2008 Hyperbaric Med Practice



**The Therapeutic Effect of Photon Irradiation on Viable Glioblastoma Cells Is Restored by Hyperbaric Oxygen.**

**Abstract:** Radiation therapy (RT) is a standard treatment for glioblastoma (GBM). However, the therapeutic effect of RT is limited by the hypoxic microenvironment of the tumor. Hyperbaric oxygen (HBO) is a potential adjuvant therapy for GBM. In this study, we investigated the effect of HBO on the therapeutic effect of RT on viable GBM cells. We found that HBO significantly increased the number of viable cells after RT, suggesting that HBO may restore the therapeutic effect of RT on viable GBM cells.

**Cell colony survival**

Radiation Dose (Gy)	Survival (Air)	Survival (O <sub>2</sub> )
0	100	100
2	~75	~95
4	~55	~85
6	~35	~75

**Cell colony migration**

Radiation Dose (Gy)	Migrated Cells (Air)	Migrated Cells (O <sub>2</sub> )
0	~10	~10
2	~15	~25
4	~12	~20
6	~8	~15

**Statistical significance:** \*\* p < 0.01, \*\*\* p < 0.001, \*\*\*\* p < 0.0001

Buhler H, et al. Anticancer Research 2015;35

**Radiation-Induced Increase in Cell Migration and Metastatic Potential of Cervical Cancer Cells Operates Via the K-Ras Pathway**

**Abstract:** Radiation therapy (RT) is a standard treatment for cervical cancer. However, the therapeutic effect of RT is limited by the hypoxic microenvironment of the tumor. In this study, we investigated the effect of RT on cell migration and metastatic potential of cervical cancer cells. We found that RT significantly increased cell migration and metastatic potential, and this effect was mediated by the K-Ras pathway.

**Figure 1: Cell Migration and Metastatic Potential**

**Statistical significance:** \*\* p < 0.01, \*\*\* p < 0.001, \*\*\*\* p < 0.0001

Su W-H, et al. Am J Pathology 2012;182(2)