Die Hyperbare Sauerstofftherapie im

Therapiekonzept von

Bestrahlungsfolgen an Weichteilen

Strahlenproktitis

Strahlencystitis

in Druckkammerzentren des

Verbandes Deutscher Druckkammerzentren

VD e.V.
Verband Deutscher
Druckkammerzentren

Aufgrund von in vitro und tierexperimentellen Studien ergibt sich eine klare Behandlungsrationale für die adjuvante Anwendung der hyperbaren Sauerstofftherapie (HBO) bei durch Strahleneinwirkung veränderten Geweben. Die bestrahlten Gewebe sind im Zeitverlauf nach Radiatio zunehmend hypozellulär, hypovaskulär und damit immer auch hypoxisch.
Sauerstoff und hier insbesondere hyperbarer Sauerstoff ist aber in der Lage schlecht perfundierte Weich- und Knochengewebe zu oxygenieren. Damit werden schlecht versorgte Gewebe erhalten und dem Fortschritt von Nekrosen Einhalt geboten. Zusatzbelastungen wie Operationen und Verletzungen werden besser toleriert.

Die an der Heilung beteiligten Zellsysteme werden aktiviert und die Heilung der defekten Knochen und Weichteile beschleunigt bzw. erst ermöglicht.

In der Folge bieten wir eine Zusammenstellung von Literatur zu diesem Thema ohne Anspruch auf Vollständigkeit. Auch auf dem Gebiet der Hyperbarmedizin werden laufend neue Erkenntnisse veröffentlicht und zunehmend die positiven klinischen Erfahrungen durch gute Studien untermauert. Mittlerweile liegen Studien bis zur Evidenzklasse 1b vor.

Die hyperbare Sauerstofftherapie bietet insbesondere bei unzureichender Wirkung der üblichen Behandlungsmethoden einen weiteren Therapieansatz, der häufig mit Erfolg eingesetzt wurde. Die HBO Therapie erfolgt bei den therapieresistenten Weichteilläsionen adjuvant unter Fortführung der etablierten Maßnahmen.

Die Frage nach einer möglichen **Förderung von Tumorwachstums-beschleunigung**, Förderung von Metastasierung und Förderung von Rezidiven wurde eingehend in vitro, tierexperimetell und in klinischen Studien untersucht (Literatur bitte anfordern).

Schlussfolgerung aus den Tierversuchen mit einer großen Bandbreite von Tumor Typen und Histologie:
kein oder sogar reduzierender Effekt der HBO auf Tumorwachstum oder Metastasierung

Schlussfolgerung aus klinischen Untersuchungen zur Tumoracceleration:
Studien, die einen wachstumsfördernden Effekt der HBO zeigen umfassen 72 Patienten.
Studien mit keinem oder wachstumshemmendem Effekt der HBO umfassen
> 3000 Patienten. (Sminia 2006)
Wegen Bedenken, dass die HBO die Wahrscheinlichkeit von Tumorrezidiven oder Metastasen bewirken könnte, sollte man Patienten die Aussicht auf Linderung durch HBO haben diese Therapie nicht vorenthalten' (Feldmeier et al., UHM 30, 1-18, 2003 (Metaanalyse))

Der Evidenzlevel für Strahlenproktitis ist 1b
Der Evidenzlevel für Strahlencystitis ist 2
bei drohender Cystektomie ist er 1

sonstige Einsatzgebiete der adjuvanten HBO in der Radio – Onkologie:
radiogenes Mammaödem (Evidenzlevel = 3)
Strahlennekrosen im ZNS (Evidenzlevel = 3)
Glioblastome zur Strahlensensibilisierung (Evidenzlevel = 3)
Strahlensensibilisierung spez. bei Rezidivcarcinomen (Evidenzlevel = 3)
rez. Neuroblastom IV (mit G-BA Akzeptanz) (Evidenzlevel = 1a)
Vor Dental-Implantation und Impantation von Knochenankern im bestrahlten Gebiet
Osteoradionekrose speziell Mandibula (Evidenzlevel = 2)
Osteoradionekrose sonst (Evidenzlevel = 3)

Inhaltsverzeichnis:

Die Hyperbare Sauerstofftherapie (HBO) als Behandlungsmethode im Rahmen des Therapiekonzeptes bei

Strahlenproktitis

Der Einsatz der Hyperbaren Sauerstofftherapie (HBO) nach den Qualitätsstandards der GTÜM (Ges. f. Tauch- u. Überdruckmedizin e.V.) und des VDD e.V. (Verband Deutscher Druckkammerzentren e.V.) ist bei der oben genannten Indikation in folgenden Fällen sinnvoll:

- bei konservativ nicht zu beherrschenden Schmerzen und anorektalen Dysfunktionen
- als Alternative zu chirurgischen Primärbehandlungen bei Komplikationen wie Blutungen, Entzündungen und Fistelungen.
- als Vorbehandlung bei geplanten Operationen in strahlengeschädigtem Gewebe.

Inhaltsübersicht:

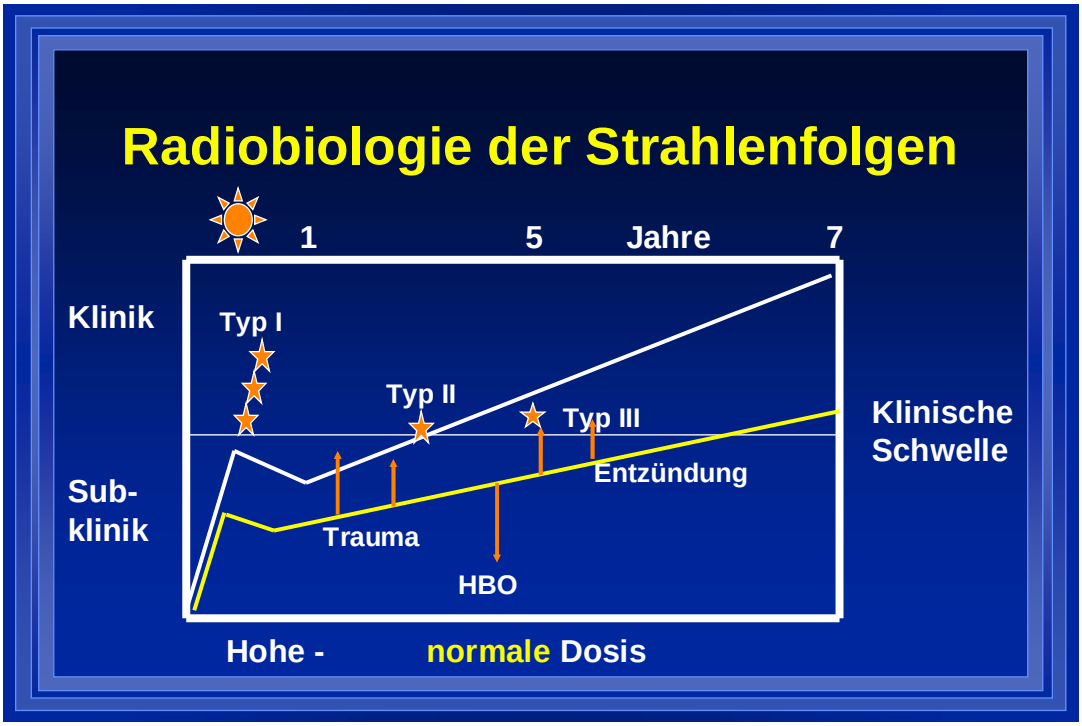
1. Behandlungsindikation

1.1 Epidemiologie

Bei der Strahlentherapie des Collum- und Corpus-, des Ovarial-, Blasen- und Prostatakarzinoms sind aktinische Schädigungen der Nachbarorgane nicht zu vermeiden. Ihre Häufigkeit wird im Rektum und Sigma mit 2-5% angegeben [24]. Die Strahlenproktitis steht dabei in direkter Beziehung zu Dosis, Dauer und Strahlenart. Sie ist ferner abhängig von der individuellen Gewebssensibilität, der Tumorausdehnung und seinem Metastasierungsgrad, von vorausgegangenen chirurgischen Eingriffen im kleinen Becken sowie vom Alter und Allgemeinzustand des Patienten [5]. Bei einer Gesamtdosis von bis zu 30 Gy sind normalerweise keine Spätfolgen zu erwarten. Bei Dosen zwischen 45 - 55 Gy weisen circa 5% der Patienten innerhalb von 5 Jahren eine entsprechende Spätsymptomatik auf und ab 60 Gy ist mit einem erheblichen Ansteigen der Spätkomplikationen in Form der chronischen Strahlenproktitis zu rechnen [24]. Bei zunehmender Häufigkeit von Strahlentherapie bei malignen Prozessen im kleinen Becken und Steigerung der Gesamtdosen ist trotz Optimierung weiter mit Bestrahlungsfolgen zu rechnen, die sich auch noch nach Jahren manifestieren können.

1.2 Pathogenese

Nach dem zeitlichen Intervall zwischen Beginn der Radiatio und dem Auftreten von Symptomen wird wie bei allen Bestrahlungsfolgen ein akutes von einem chronischen Stadium der Strahlenproktitis unterschieden. Aufgrund der hohen Zellproliferation ist die Colonmukosa relativ strahlensensibel. Die direkte Strahleneinwirkung auf die Mukosazelle ist verantwortlich für das akute Stadium der Strahlenproktitis, welche nach Dosen von 20 - 30 Gy schon während oder kurz nach Abschluß der Strahlentherapie auftritt [14,20].



Das chronische Stadium manifestiert sich nach einer Latenzperiode von einigen Monaten bis Jahren und entsteht durch eine Kombination von Ischämie und Fibrose, verursacht durch Strahleneffekte an Blutgefäßen und Bindegewebe [9,13]. In Arteriolen und kleinen Arterien kommt es zur initialen Endothelschwellung und zum Ödem der glatten Muskulatur.

Es folgt eine Endothelproliferation und die subendotheliale Ablagerung von Hyalin. Das Bindegewebe reagiert mit Schwellung und charakteristischer Atypie der Fibroblasten. Die schleichende, progressive Endarteriitis sorgt mit ihren chronisch ischämischen Veränderungen für die Ausbildung der charakteristischen Strahlenfibrose [10]. In der Regel hat die Ischämie der Darmwand innerhalb von 2 Jahren derart zugenommen, daß die Mukosa atrophiert, ihre Schutzfunktionen nicht länger voll wahrnehmen kann und stellenweise von erosiven bis ulcerösen Entzündungen zerstört wird. Während das histologische Bild im Frühstadium von pathologischen Veränderungen an Mukosa und Submukosa geprägt ist,

findet sich im chronischen Stadium neben ulcerösen und atrophischen Veränderungen der Mukosa eine diffuse Fibrinosierung der Darmwand und ihrer Umgebung mit fortschreitender Gefäßsklerose [23].

1.3 Klinik

Während des akuten Stadiums der Strahlenproktitis klagen die Patienten über Tenesmen, Diarrhoe, Meteorismus sowie Schleimabgang und in vereinzelten Fällen auch über Blutbeimengungen im Stuhl. In den meisten Fällen klingt das Beschwerdebild innerhalb von einigen Wochen ab, ohne Spätfolgen nach sich zu ziehen.

Die Symptomatologie des chronischen Stadiums beinhaltet Schmerzen, Diarrhoen, Obstipationen sowie Blut- und Schleimabgänge. Typische Spätfolgen sind Ausbildung von Darmstrikturen und Stenosen mit entsprechenden Subileusbeschwerden sowie Fisteln und schmerzhafte Ulzera [15]. Auch die Ausbildung einer akuten Peritonitis nach spontaner Darmperforation ist möglich.

Die Diagnosestellung einer Strahlenproktitis erfolgt endoskopisch und bioptisch. Rektoskopisch findet sich im akuten Stadium eine ödematöse Mukosaaufquellung mit verwaschener bis aufgehobener Gefäßzeichnung und erhöhter Vulnerabilität.

Im chronischen Stadium sieht man zusätzlich weißliche Mukosaatrophien, im ehemaligen Bestrahlungsfeld lokalisierte Erosionen und oftmals tiefe Ulcerationen mit schmutzigem Grund und glatten, nicht aufgeworfenen Rändern. Pathognomonisch für Strahlenulcera sind Teleangiektasien in der Umgebung, während fibröse narbige Strukturen und Stenosen oftmals nur histologisch von einem Neoplasma zu unterscheiden sind [27].

Wegen des erhöhten Risikos der sekundären Carzinombildung durch Strahlen sind endoskopische Überwachungen in zweijährigem Abstand angezeigt [7,22].

Schwere chronische Verlaufsformen stellen den Arzt häufig vor nahezu unlösbare Probleme. Die spontane Remissionsrate innerhalb der ersten 6 Monate beträgt lediglich 10 %. Nach Ausschöpfung der lokalen und konservativen Therapie, die in Verordnung von Antidiarrhoika, Spasmolytika, Sedativa, Salicylazosulfapyridin sowie hydrokortisonhaltigen Suppositorien und Klysmen besteht, können Ileusbeschwerden infolge von Stenosen oder Strikturen, Ulzera, Fisteln oder das Auftreten massiver Blutungen einen operativen Eingriff notwendig werden lassen [24]. Wird das Krankheitsbild von alleiniger Hämorrhagie mit meist chronischen Blutverlusten bestimmt, kommt eine ableitende doppelläufige Kolosstomie in Betracht [11]. Eine zunehmende Stenosesymptomatik erfordert bei kurzstreckigen Stenosen die Resektion oder bei ausgedehnten Prozessen mit Blutungen, Fistelbildung und Begleitentzündung die Exstirpation des Rektums mit Anlage eines Kunstafters [28]. Wegen der schlechten Wundheilungstendenz nach Bestrahlung und der damit erhöhten Gefahr einer Nahtinsuffizienz müssen derartige Resektionen immer weit im Gesunden erfolgen. Die Mortalität chirurgischer Interventionen bei Strikturen, Fisteln, Perforationen, Ulcera und Hämorrhagien wird mit 12 - 50 % beziffert [2,8]. Mortalität und Morbidität der chirurgischen Eingriffe werden zwischen 10 - 80 % angegeben [6,17].

2. Therapeutischer Nutzen und Vorzüge der HBO

2.1 Übersicht

Zur Vermeidung der hohen Operationsmorbidität und Mortalität bietet sich bei medikamentös nicht zu beherrschender chronischer Strahlenproktitis mit rezidivierenden Blutungen und rektalen Dysfunktionen die HBO als schonende und risikoarme adjuvante Behandlungsmethode an, denn der zentrale pathogene Faktor bei Strahlenspätschäden ist die Ischämie mit Hypoxie. Bei Sauerstoffpartialdrücken unter 30 - 40 mmHg gibt es keine effektive Wundheilung und Infektabwehr [16].

Die Ischämie der strahlengeschädigten Darmwand ist der kausale Angriffspunkt der HBO. Der während der Druckkammerbehandlung vermehrt im Blutplasma gelöste Sauerstoff gelangt in Gefäßbezirke, die in Folge endangitischer Lumeneinengung für Erythrozyten bereits nicht mehr passierbar sind. Verkürzte Diffusionszeiten und verlängerte Diffusionswege tragen zur Beseitigung der Gewebshypoxie bei. Makrophagen, Fibroblasten und Granulozyten, die unter Sauerstoffmangel lediglich ihren Strukturstoffwechsel aufrecht erhalten konnten, erwachen unter den

intermittierend angehobenen und zum Zentrum der Läsionen steil abfallenden Sauerstoffpartialdrücken zu neuer Funktion und initiieren Reparaturvorgänge und Infektabwehr [1]. Dazu ist die HBO in der Lage eine Neoangiogenese zu induzieren, die eine Steigerung auf bis zu 80% der Kapillardichte von Normalgewebe erreicht (Marx 85).

Die mit der HBO bei anderen Strahlenspätschäden der Weichteile gesammelten positiven Erfahrungen wurden erstmals 1986 von HART und STRAUSS für die Strahlenproktitis bestätigt [12]: Bei 10 von 12 Patienten heilten die rektalen Ulzera und cirka 1 Jahr nach adjuvanter HBO wurde der doppelläufige Anus praeter zurückverlegt.

Bei 2 weiteren Patienten, vorgestellt von NAKADA 1993 und SCHNEIDER und Mitarbeitern 1992, waren fäkale Diversionen erst nach adjuvanter HBO erfolgreich [18,26].

1991 wurde von CHARNEAU und Mitarbeitern erstmals ein Behandlungskonzept veröffentlicht, welches die HBO vor offenen chirurgischen Maßnahmen einsetzte [4]:
Bei einem 74jährigen Patienten entwickelte sich 3 Jahre nach Radiatio eines Prostatakarzinoms eine Strahlenproktitis mit rezidivierenden Blutungen, die mit Neodym YAG-Laserbehandlung nicht beherrscht werden konnten und transfusionsbedürftig waren. Vor der geplanten ableitenden Colostomie entschloß sich das Ärzteteam aus Chirurgie, Intensivmedizin und Gastroenterologie der Universität Angers zur HBO, die bei 2,5 bar zweimal täglich über 90 Minuten in einer Mehrplatzkammer durchgeführt wurde. Nach 15 Tagen nahm die Darmblutung ständig ab, so daß die stationäre Behandlung am 21. Behandlungstag beendet wurde und die restlichen 40 Behandlungen ambulant erfolgten. Bei Rektoskopiekontrolle 5 Monate später fanden sich nur noch Teleangiektasien.

Brandon et al. (31) setzten die HBO 1998 vor Operationen im bestrahlten Gebiet erfolgreich zur Prävention von Komplikationen ein.
1990 präsentierte das gleiche universitäre Zentrum 8 weitere Fälle [3], die in der klinischen Klassifikation nach GILINSKY der Gruppe III zugeordnet wurden, welche üblicher Weise keine Spontanremissionen erwarten läßt und somit chirurgischer Behandlung vorbehalten ist [9]. Sechs dieser 8 Patienten wurden ohne Operation geheilt, das heißt, im Anschluß an die HBO bestanden weder Blutungen noch rektale Dysfunktionen. Bei einem Patienten rezidivierten die Blutungen nach 6 Monaten und blieben auch durch Wiederholung der HBO unbeeinflußt. Ein weiter Patient verstarb an

hepatozellulärer Insuffizienz. Während 4jähriger Nachsorge traten bei den geheilten 6 Patienten keine weiteren Blutungen auf.
Seither sind etliche weitere Studien publiziert worden, die bis zum Evidenzgrad 1b reichen (siehe Clarke 2008) (30). Damit ist die Anwendung der HBO bei Strahlenproktitis inzwischen gut abgesichert.

Aus den vorgestellten Studien kann resümiert werden:

- Die HBO ist als kausale Therapie des chronischen Strahlenschadens am Enddarm zu betrachten. Sie ermöglicht Remissionen und senkt das Risiko von Entzündungen (insbesondere durch Anaerobier), Blutungen und Fistelungen.
- Mit einer Erfolgsrate von zur Zeit 82 % steht die Wirksamkeit der HBO bei chronischer Strahlenproktitis außer Zweifel.
- Angesichts der hohen Operationsmortalität und -morbidität ist die HBO eine risikoarme Alternative zur chirurgischen Primärbehandlung.
- Erforderliche sekundäre operative Eingriffe im vorbestrahlten Gewebe lassen sich nach HBO-Vorbehandlung erfolgreicher durchführen.
- Die Wirtschaftlichkeit der HBO ergibt sich aus der Abkürzung der stationären Behandlung mit Verlagerung der HBO in den ambulanten Bereich und der Vermeidung von Folgekosten.

2.2 Studien und Expertenaussagen

Metaanalysen (Evidenzklasse 1a):

Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. ***Cochrane Database of Systematic Reviews*** **2005,** Issue 3. Art. No.: CD005005. DOI: 10.1002/14651858.CD005005.pub2. (noch vor Clarke et al. siehe unten – Anmerkung des Verfassers)

Main results
Six trials contributed to this review (447 participants). For pooled analyses, investigation ofheterogeneity suggested important variability between trials. From single studies there was a significantly improved chance ofhealing following HBOT for radiation proctitis (relative risk (RR) 2.7, 95% confidence Interval (CI) 1.2 to 6.0, P = 0.02, numbers needed to treat (NNT) = 3), and following both surgical flaps (RR 8.7, 95% CI 2.7 to 27.5, P = 0.0002, NNT = 4) and hemimandibulectomy (RR 1.4, 95% CI 1.1 to 1.8, P = 0.001, NNT = 5). There was also a significantly improved probability ofhealing irradiated tooth sockets following dental extraction (RR 1.4, 95% CI 1.1 to 1.7,P=0.009,NNT=4).

There was no evidence ofbenefit in clinical outcomes with established radiation injury to neural tissue, and no data reported on the use ofHBOT to treat other manifestations of LRTI. These trials did not report adverse effects.

Authors' conclusions

These small trials suggest that for people with LRTI affecting tissues of the head, neck, anus and rectum, HBOT is associated with improved outcome. HBOT also appears to reduce the chance of osteoradionecrosis following tooth extraction in an irradiated field.

P L A I N L A N G U A G E S U M M A R Y

Hyperbaric oxygen (HBO) may improve radiation injuries of the head, neck and bowel. It also appears to reduce the chance of bone death following tooth extraction.

There is a risk of serious complications developing after radiation treatment for cancer (late radiation tissue injury (LRTI). Hyperbaric oxygen therapy (HBOT) involves breathing oxygen in a specially designed chamber. It is used as a treatment to improve oxygen supply to damaged tissue and stimulate healing. We found some evidence that LRTI affecting the head, neck and lower end ofthe bowel can be improved with HBOT. There is little evidence for or against benefit in other tissues affected by LRTI. Our conclusions are based on six randomised trials with a limited number ofpatients. Further research is needed

Randomisierte Kontrollierte Studien (Evidenzklasse 1b):

RICHARD E. CLARKE et al. HYPERBARIC OXYGEN TREATMENT OF CHRONIC REFRACTORY RADIATION PROCTITIS: A RANDOMIZED AND CONTROLLED DOUBLE-BLIND CROSSOVER TRIAL WITH LONG-TERM FOLLOW-UP Int. J. Radiation Oncology Biol. Phys., Vol. •, No. •, pp. 1–10, 2008

120 Patienten mit therapierefraktärer Strahlenproktitis wurden randomisiert in Gruppe 1 für HBO Behandlung mit 2 ATA oder Gruppe 2 für Behandlung bei Luftatmung mit 1,1 ATA (Placebo Gruppe) Die Patienten der Gruppe wurden anschließend ebenfalls wie Gruppe 1 behandelt (cross over). Die Auswertung erfolgte nach vor Behandlung, nach 3 und 6 Monaten und dem 1. – 5. Jahr durch einen Verblindeten Untersucher.

In Gruppe1 war der Soma-Lent Score niedriger als in Gruppe2 (p=0,0150) und das Ausmaß der Besserung doppelt so hoch (p=0,0019 / 5,00 vs 2,61). Nach klinischer Bewertung fanden sich in Gruppe 1 mehr Responder als in Gruppe 2 (88.9% gegen 62,5%; p=0,0009). Aus intention to treat Perspektive verbesserte sich die Signifikanz auf p=0,0006. NNT = 3. Nach dem Cross-Over glichen sich die Unterschiede der Gruppen aus!. Andere Behandlungen wurden während der Studie unterbrochen. Aufwendige Interventionen wurden weitestgehenst vermieden.

Nicht kontrollierte klinische Studien (Evidenzklasse 3)

Bouachour G., Rongeray, J., Ben Bouali, A., Person, B., Boyer, J., Alquier, P.: HYPERBARIC OXYGEN IN THE TREATMENT OF RADIATION-INDUCED PROCTITS. A REPORT ON 8 CASES. Undersea Biomed Res 17s (1990), 171-172
Bouachour et al. berichten über ihre Erfahrung bei der Behandlung der Strahlenproktitis durch HBO bei 8 Patienten. Die vorangegangenen Behandlungen mit Diät und Steroiden blieben ohne Erfolg. Alle Patienten benötigten regelmäßige Bluttransfusionen. Die Patienten erhielten 80 Sitzungen HBO bei einem Druck von 2,5 ATA und einer 100%igen Sauerstoffatmung von 90 Minuten pro Sitzung. 6 Patienten konnten erfolgreich behandelt werden. Auch das Follow-up über 4-20 Monate zeigte keinen erneuten Progress. Ein Patient erlitt 6 Monate nach HBO einen Progress und ein Patient erlitt einen Relaps einen Monat nach HBO bei bestehender Gerinnungsstörung. Bouachour et al. fassen zusammen, daß die HBO einen positiven Effekt in der Behandlng der hämorrhagischen Strahlenproktits zu haben scheint und daß diese Behandlungsform eine Alternative zur chirurgischen Intervention darstellen könnte. (3)

BRANDON D. ItOMEROY, LW. KEIM, RJ. TAYLOR: PREOPERATIVE HYPERBARIC OXYGEN THERAPY FOR RADIATION INDUCED INJURIES JOURNAL OF UROLOGY 1998; 159: 4632, May 1998
Bei 5 Patienten mit Weichteilveränderungen nach Radiotherapie wurde vor präoperativen Interventionen im bestrahlten Abdomen prospektiv HBO eingesetzt. Bei allen Patienten verliefen die Eingriffe ereignislos. Die HBO verbesserte die Operationsergebnisse.

Jones K, Evans AW, Levin W. : RADIATION PROCTITIS TREATEMENT WITH HYPERBARIC OXYGEN . Proc. UHMS ASM 2004
10 Patienten mit Strahlenproktitis wurden der HBO zugeführt:

No. of Patients	Symptoms/Function	Response to HBOT			
		CR	PR	NR	Progressive
9	Bleeding	4	3	1	1
5	Pain/Discomfort	3	1	1	
5	Diarrheoa	1	3	1	

CR = completely resolved; PR = partially resolved; NR = not responsive.

Charneau J., Bouachour G., Person, B., Burtin, P., Rongeray, J., Boyer, J.: SEVERE HEMORRHAGIC RADIATION **PROCTITS** ADVANCING TO GRADUAL CESSATION WITH HYPERBARIC OXYGEN. Digest Dis Sci 36 (1991), 373-375
Charneau und Mitarbeiter berichten über einen Patienten, der aufgrund einer schweren, histologisch gesicherten hämorrhagischen Strahlenproktitis einer HBO zugeführt wurde. Die Behandlung wurde über 82 Sitzungen bei einem Druck von 2,5 ATA und 90minütiger Sauerstoffatmung durchgeführt. Nach 30 Behandlungen kam es zu einer erheblichen Besserung der Blutung. Charneau und Mitarbeiter fassen zusammen: „ ....Diese Therapie (HBO) kann als Alternative zur chirurgischen Intervention bei der Strahlenproktitis vorgeschlagen werden.“ (4)

Mayer,-R; Klemen,-H; Quehenberger,-F; Sankin,-O; Mayer,-E; Hackl,-A; Smolle-Juettner,-F-M : Hyperbaric oxygen--an effective tool to treat radiation morbidity in prostate cancer. Radiother-Oncol. 2001 Nov; 61(2): 151-6
7 Patienten mit Strahlenproktitis, 8 mit Strahlencystitis und 3 Patienten mit Strahlen-Cystitis und –proktitis wurden nach erfolgloser konventioneller Behandlung mit HBO behandelt. Insbesondere bei Strahlenzystitis erwies sich die HBO als hilfreich. Strahlencystitiden sollten möglichst früh der HBO zugeführt werden, um Blasenschrumpfung zu vermeiden.

Hart, G.B., Strauss, M.B.:DIE HYPERBARE SAUERSTOFFTHERAPIE IN DER VERSORGUNG VON BESTRAHLUNGSSCHÄDEN. Reports des ersten Schweizer Symposium für Hyperbare Medizin, Basel (Ch), 13.-14. Oktober 1986, 18-36 p 27, Bestrahlungs**proktitis** oder -enteritis.
Hart und Strauss berichten über 12 Patienten, die aufgrund einer Strahlenproktitis einer HBO zugeführt wurden. Bei 10 Patienten führte die HBO in Kombination mit Antibiotika und Darmspülungen zu einer Ausheilung der Ulcerationen. In 2 Fällen konnten die Ulzera nicht beseitigt werden. (12)

Nakada, T., Kubota Y., Sasagawa, I., et al.: THERAPEUTIC EXPERIENCE OF HYPERBARIC OXYGENATION IN RADIATION **COLITIS**. REPORT OF A CASE. Dis Colon Rectum 36 (1993), 962-965
Nakada et al. berichten über einen Patienten mit einer schweren Darmblutung nach einer Bestrahlung des kleinen Beckens wegen eines Prostatakarzinoms. Histologisch wurde die Diagnose einer Strahlencolitis gesichert. Unter einer HBO bei 2,0 ATA und Sauerstoffatmung über 90 Minuten kam es bei einer Gesamtbehandlung von 30 Sitzungen zu einem Sistieren der Blutung und zu einer Besserung des makroskopisch-endoskopischen Befundes. (18)

Norkool D.M., Hamptom N.B., Gibbons, R.P., Weisman R.M.: HYPERBARIC OXYGEN THERAPIE FOR RADIATION INDUCED HEMORRHAGIC CYSTITS. J Urol 150 (1993), 332-334
Die Arbeitsgruppe um Norkool hat 14 Patienten mit einer hämorrhagischen Strahlencystits der HBO zugeführt. 2 dieser Patienten litten zusätzlich unter

einer Strahlenproktits. Bei beiden Patienten kam es unter der HBO nach 8 beziehungsweise 12 Behandlungen zu einem sisitieren der proktologischen Beschwerden (19)

Schneider, F., Jung, G.M., Lutun, Ph, Aysoy, C., Bilbault, P., Tempe, J.D.: HYPERBARIC OXYGENATION CAN IMPROVE SERVERE HEMORRHAGIC RADIATION **PROCTITS** - A CASE-REPORT, XVIIIth Annual Meeting of EUBS 15.-19. September 1992, Basel, Schweiz, 133
Schneider und Mitarbeiter stellen den Fall eines 59-jährigen Mannes vor, der nach einer Bestrahlung des kleinen Beckens aufgrund eines Prostatakarzinoms unter einer blutenden und sehr schmerzhaften Strahlenproktitis litt. Durch 40 Sitzungen HBO bei 2,5 ATA über jeweils 90 Minuten sistierten die Blutung und die anogenitalen Schmerzen. Sigmoidoskopisch konnte auch makroskopisch eine Befundbesserung dokumentiert werden, die beim Follow-up nach einem Jahr unverändert bestand. Schneider faßt zusammen, daß die HBO bei der Strahlenproktitis ein effektives Mittel in der Spätbehandlung einer Strahlenproktitis darstellt und als Alternative zu chirurgischen Interventionen gesehen werden kann. (26)

Wissenschaftlich begründete Expertenaussagen

HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF RADIO-INDUCED LESIONS IN NORMAL TISSUES CONSENSUS CONFERENCE Jointly held by: EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY – ESTRO AND EUROPEAN COMMITTEE FOR HYPERBARIC MEDICINE – ECHM *October 19-20th, 2001 Lisbon – Portugal*
(noch vor Clarke et al. siehe unten – Anmerkung des Verfassers)

Radiation-induced proctitis and enteritis:
Here there was a considerable literature which had been gathered [I, ii & vi] for review by the conference and the jury. Fifteen papers reporting 256 cases treated with hyperbaric oxygen were found and there were 10 papers reporting 116 cases from 1993 to 2000 (i,ii). The majority of the cases were reported as either cured or improved with regard to the symptoms and/or clinical findings. In their review Dr Roque and his colleagues found 13 papers reporting 107 cases between 1990 and 2000, and gained an even greater impression of improvement (viii). The symptom and findings in these cases were obviously complex, making assessment difficult.
The jury concluded that hyperbaric oxygen could be employed in the management of radiation poctitis and enteritis, however the evidence must be regarded as at **level 3**.

Mayer, E.D.: CHIRURGISCHE UND ANDERE EINSATZGEBIETE DER HYPERBAREN OXYGENATIONSTHERAPIE (HBO). MDK Friedrichshafen, Baden-Württemberg, Juni 1995, 28
Mayer faßt in seinem Gutachten zusammen: „....Konservative schulmedizinische Behandlungsregime versagen in der Regel, die Morbidität der chirurgischen Intervention wird mit 10 bis 80% angegeben. Weitere Berichte geben den Hinweis auf eine mögliche Wirkung der HBO bei

Strahlenproktitis, größere Arbeiten mit breiterer Aussagekraft liegen nicht vor.“ (17)

Williams, J.A., Clarke, D.: PELVIC RADIATION NECROSIS AND RADIATION CYSTITS. In: HYPERBARIC MEDICINE PRACTICE. Ed. Kindwall E.P., Best Publishing Company, 1994, 506-516
Williams zitiert eine Falldarstellung, bei der es 15 Tage nach HBO-Beginn zu einer erheblichen Abnahme der rektalen Blutung bei einem Patienten mit einer therapieresistenten Blutung bei einer Strahlenproktitis kam. (29)

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Die Hyperbare Sauerstofftherapie (HBO) als Behandlungsmethode im Rahmen des Therapiekonzeptes bei Strahlencystitis

Der Einsatz der Hyperbaren Sauerstofftherapie ist bei der oben genannten Indikation in folgenden Fällen sinnvoll:

Subakute und chronische Formen der Strahlencystitis

- mit Komplikationen, wie Blutungen, Fisteln und Entzündungen
- mit medikamentös unbeeinflußbaren Miktionsbeschwerden

Hyperbare Sauerstoffbehandlung (HBO) der Strahlencystitis

Durch HBO bei 2,4 bar werden die Sauerstoffwerte des bestrahlten Gewebes um das 7- bis 10-fache angehoben. Wesentlicher noch als die für die Reaktivierung der Zellfunktionen verantwortlichen absoluten Werte über 30-40 mm/Hg ist der damit verbundene steilere Sauerstoffgradient als treibende Kraft normaler Wundheilung [16,17]. Die intermittierende Hypoxie und Hyperoxie unter Therapiebedingungen fördert Fibroblastenproliferation und Kollagenproduktion als Voraussetzung für die Angioneogenese.

Nach 20tägigen HBO-Anwendungen über 90 Minuten bei 2,4 bar ist der bei normobarer Luftatmung gemessene Sauerstoffpartialdruck im Zentrum des strahlengeschädigten Gewebes von 20-30% auf 80-85% des unbestrahlten Gewebes angehoben. Er ist damit indirekter Hinweis auf die 8- bis 9-fach verbesserte Kapillardichte, zumal er sich durch weitere HBO-Sitzungen nicht steigern und bei Kontrollen nach bis zu 4 Jahren in unveränderter Höhe nachweisen ließ [22].

Die zunächst im kiefer-und gesichtschirurgischen Bereich gesammelten positiven Erfahrungen mit der HBO zur Behandlung von Strahlenspätschäden konnten auf urologischem Gebiet erstmals 1985 von WEISS und Mitarbeitern bestätigt werden [42]. Drei Patientinnen mit therapieresistenter hämorrhagischer Strahlencystitis wurden mit einer Serie von 60 HBO-Sitzungen bei 2 bar über zwei Stunden behandelt und konnten dauerhaft geheilt werden. Mit cystoskopischen Aufnahmen wurde die eindrucksvolle Verbesserung der pathologischen urothelialen Mikrovaskulatur dokumentiert. Nachfolgende Untersuchungen über 8 bis 9 Jahre zeigten, daß die mit HBO erreichte Heilung dauerhaft war und die Patienten symptomfrei blieben [41]. Seitdem wurden in der Literatur 137 Fälle publiziert, bei denen die HBO-Behandlung einer therapieresistenten Strahlencystitis in 60 - 90 % erfolgreich war [1,3,11,14,19,25,27,35,39,41]. Beispielhaft für diese adjunktive Behandlungsmethode sind folgende Anwendungsbeobachtungen:

SCHOENROCK und CIANCI beschrieben 1986 den spontanen Verschluß einer vesicocutanen Fistel bei gleichzeitiger Heilung der ursächlichen hämorrhagischen Cystitis durch 19 HBO-Sitzungen. Während Verlaufskontrollen über 6 Jahre blieb die Patientin symptomfrei [35]. KINDWALL behandelte 1988 eine 67jährige Patientin mit strahleninduzierter Schrumpfblase und konnte ihre miktionsfreien Perioden durch 30 HBO- Behandlungen bei 2,4 bar von 30 Minuten auf 4 Stunden dauerhaft verlängern [14].

WEISS und NEVILLE stellten 1989 den Fall einer 35-jährigen Patientin mit Streß- und Urgeinkontinenz infolge Strahlenblase vor. Anticholinergika und Sympatomimetika besserten aber beseitigten nicht die Inkontinenz. Nach 60 HBO-Sitzungen bei 2 bar stellte sich bei unveränderter medikamentöser Therapie eine komplette Harnkontinenz ein. Bei der Nachuntersuchung nach 16 Monaten war die Patientin unverändert kontinent, obgleich cystoskopischer Befund und Blasenkapazität sich nur wenig geändert hatten. Ebenso beispielhaft ist in gleicher Publikation der Fall eines 67jährigen Urologen, der nach kontrasexueller und Strahlentherapie eines fortgeschrittenen Prostatacarzinoms eine Strahlenenteritis entwickelte und deshalb mit HBO behandelt wurde. 7 Jahre später offenbarte sich eine Strahlencystitis mit akuter, massiver Makrohämaturie. Erneut wurden 60 hyperbarmedizinische Behandlungen durchgeführt. Nach der 17. Sitzung sistierte die Blutung und trat auch während des 6monatigen Follow up trotz uneingeschränkter sportlicher Aktivität nicht wieder auf [43].

RIJKMANS und BAKKER stellten 1989 erstmals eine Gruppe von 10 Patienten mit therapieresistenter hämorrhagischer Strahlencystitis vor, welche mit HBO bei 3 bar behandelt wurden. Bei 5 Patienten sistierte die Hämaturie nach durchschnittlich 12 Sitzungen. Die übrigen 5 zeigten bei cystoskopischer Kontrolluntersuchung ein Blasentumorrezidiv, welches erst durch die erfolgreiche Strahlencystitisbehandlung demaskiert wurde [32].

NORKOOL und Mitarbeiter teilten 1993 nach Behandlung von 14 Patienten mit hämorrhagischer Strahlencystitis die Erfahrung mit, daß erforderliche Elektrokoagulationen nach HBO erfolgreicher durchzuführen seien [27].

Auf der ersten europäischen Konsensuskonferenz über Hyperbarmedizin am 19. - 21. September 1994 in Lille, Frankreich, faßte BOUACHOUR die bisherigen Behandlungserfahrungen wie folgt zusammen: „ HBO scheint eine effektive und ökonomische Methode der Strahlencystitisbehandlung zu sein. Sie ist die einzige Therapie, die causale Heilung verspricht und sollte vor chemischer Instillations- oder chirurgischer Behandlung in Betracht gezogen werden“ [4]. Die Jury der ersten europäischen Konsensuskonferenz folgte dieser Einschätzung, indem sie für Weichteilradionekrosen die Typ I Rekommendation aussprach: „HBO ist nachdrücklich empfohlen bei der Weichteilradionekrose. Ausgenommen sind die radionekrotischen Läsionen des Intestinums, wo die HBO nur als optional zu betrachten ist (Typ II Rekommendation)“ [30].

Der Committee Report der UHMS von 1996 listet die Strahlencystitis unter den erprobten und anerkannten Indikationen auf. Als Therapieschema sind tägliche HBO-Behandlungen bei 2 bis 2,4 bar über 90 bis 120 Minuten anzuwenden. Nach 60 HBO-Behandlungen wird wie bei allen Strahlenschäden eine Therapiekontrolle für notwendig gehalten [5].

E.D. MAYER interpretiert in seinem umfassenden Gutachten für den MDK Baden-Württemberg, Friedrichshafen, vom Juni 1995 drei Literaturstellen zur HBO bei Strahlencystitis wie folgt: „ Im Einzelfall ist aber eine Wirkung immerhin als möglich zu erachten“ [23].

Indikationen für die adjuvante Behandlung der Strahlenzystitis mit HBO

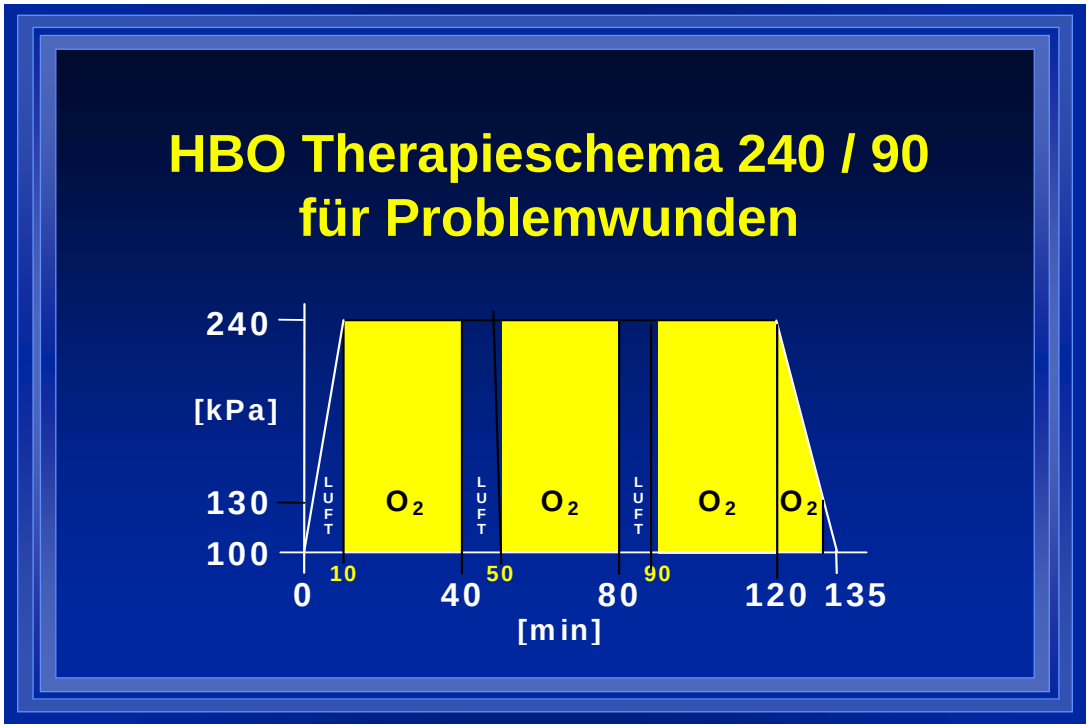
Die Pathogenese liefert das Verständnis für das klinische und histologische Bild der Strahlencystitis. Für die Heilung läßt sich folgerichtig die Forderung nach Beseitigung der Gewebshypoxie ableiten. Diese wird durch keine der konventionellen Therapien, sondern nur durch die HBO verwirklicht [24]. Wie experimentelle Untersuchungen und klinische Erfahrungen bestätigen, schafft die Beseitigung der Gewebshypoxie die Voraussetzungen für eine Neovaskularisation [39].

Die HBO ist damit in der Lage, den dynamischen Krankheitsprozeß der Strahlencystitis in der subakuten und chronischen Periode nach Radiatio zu stoppen und teilweise umzukehren. Die publizierten Erfolge bei der Behandlung von Problempatienten, denen durch konventionelle Maßnahmen nicht geholfen werden konnte, und die einfache Anwendung, die vergleichsweise wenig Risiken und Nebenwirkungen beinhaltet [25], machen die HBO der Strahlencystitis zur Therapie der Wahl [1]. Mit den beispielhaft aufgeführten Kasuistiken lassen sich folgende therapeutische Empfehlungen belegen:

1.) Behandlungsprotokoll

Problemwundenschema mit täglicher 90-minütiger 100%iger Sauerstoffatmung bei 2,4 bar über maximal 60 Tage (siehe Committee Report der UHMS).

Die experimentellen Untersuchungen von MARX zur Verbesserung der Kapillardichte finden ihre klinische Bestätigung in der Beobachtung, daß sich die Symptomatik nach etwa 3 Wochen täglicher HBO-Behandlungen bessert. Da eine dauerhafte Beschwerdefreiheit vom Ausmaß der mikrovaskulären Umbauvorgänge abhängt, sollte die Behandlung über den Zeitpunkt der Symptombeseitigung hinaus bis maximal 60 Tage fortgeführt werden.



2.) Patientenauswahl

a) Patienten mit Komplikationen, wie Blutungen, Fisteln und Entzündungen.

Diffuse Blutungen lassen sich nicht durch cystoskopische Kauterisation stillen. Jeder offene chirurgische Eingriff bedeutet eine zusätzliche Noxe mit der Gefahr des großflächigen Gewebsuntergangs. Instillationsbehandlungen sind angesichts der Gefäßrupturen und zumeist vorhandenen Ostiuminsuffizienzen gefährlich durch Resorption und Reflux. Sie können ebenso wie Hydrodilatationen die Entwicklung zur Schrumpfblase beschleunigen. Hämostyptika vermögen am ursächlichen Krankheitsprozeß nicht zu ändern. Unter HBO sistiert die radiogene Hämaturie nach 2-4 Wochen, anscheinend in Abhängigkeit vom Ausmaß der pathohistologischen Veränderungen. Persistierende Hämaturien müssen endoskopisch kontrolliert werden, denn nach HBO sind sie entweder lokalisiert und damit besser koagulierbar oder demaskiert als Malignomblutung und damit risikoärmer resezierbar [27]. Ein Blasentumorrezidiv stellt für die HBO keine

Kontraindikation dar, denn HBO läßt das Tumorwachstum unbeeinflußt [31]. Die intermittierende Hyperoxie unter Therapiebedingungen ermöglicht die Ausbildung eines vitalen Granulationsgewebes und damit den Spontanverschluß von Blasenfisteln.

Entzündungen eines hypoxischen, hypovaskulären und hypozellulären Gewebes sind bekanntlich therapieresistent, führen in der Blase zu Konkrementbildungen und beschleunigen die Entwicklung der Schrumpfblase. Üblicherweise resigniert der Urologe nach wiederholten frustranen Versuchen testgerechter Infektsanierung und beschränkt sich auf die Ansäuerung des Urins. HBO schafft mit der Verbesserung der Perfusion, Beseitigung des Ödems, Restaurierung des Urothels und Verbesserung der körpereigenen Abwehr die Voraussetzungen für eine effektive Antibiose [15].

b) Unbefriedigend medikamentös zu beeinflussende strahlenbedingte Miktionsbeschwerden

Das Spektrum der Miktionsbeschwerden auf dem Weg zur Schrumpfblase ist unspezifisch und reicht von erschwertem Wasserlassen bis zur Harninkontinenz. Hochgradige diurne und nokturne Pollakisurie oder Drang- und Streßinkontinenz können zur sozialen Isolierung führen. Dass Patienten, die vor der Wahl einer Cystektomie mit Urindeviation oder Blasenersatzplastik standen, nach HBO infolge vergrößerter Blasenkapazität wieder zu einer normalen Miktionsfrequenz fanden beziehungsweise auch ohne objektivierbare Blasenveränderungen wieder verbessert auf die Basismedikation ansprachen, ist ein Beweis für die Wirksamkeit der HBO bei konservativ nicht beeinflußbaren strahlenbedingten Miktionsbeschwerden [11,45].

Nach BEVERS und Mitarbeitern sollte die HBO „nicht nur für schwer Betroffene und konventionell therapieresistente Patienten reserviert sein“ [3].

c) Bei geplanten operativen Eingriffen im vorbestrahlten Gebiet

Aus den pathophysiologischen Erkenntnissen der Kieferchirurgie bei prophylaktischer HBO zur Verhütung der Osteoradionekrose nach Zahnextraktionen und Implantationen im vorbestrahlten Kiefer kann gefolgert werden, dass sich die HBO generell zur Prävention von Wundheilungsproblemen im vorbestrahlten Gewebe eignet, beziehungsweise eine rekonstruktive Chirurgie in vorbestrahltem Gebiet erst durch HBO ermöglicht wird [20,10]. Die Länge des Intervalls zwischen HBO und Operation ist dabei bedeutungslos, denn die HBO-induzierten Gewebsveränderungen sind dauerhafter Natur [22].

d) Rezidive nach vorangegangener HBO

Bei Rezidivkomplikationen von Strahlenspätschäden kann die HBO auch als Wiederholungsbehandlung erfolgreich eingesetzt werden [43].

2.3 Studien und Expertenaussagen

Bei der relativ seltenen Erkrankung ist es bisher nur in Ausnahmefällen möglich gewesen randomisierte kontrollierte Studien zu fertigen.

Expertenmeinungen:

HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF RADIO-INDUCED LESIONS IN NORMAL TISSUES CONSENSUS CONFERENCE Jointly held by: EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY – ESTRO AND EUROPEAN COMMITTEE FOR HYPERBARIC MEDICINE – ECHM *October 19-20th, 2001 Lisbon – Portugal* (noch vor Clarke et al. siehe unten – Anmerkung des Verfassers)

Radiation cystitis:

The jury were however impressed that in patients resistant to conservative treatment and where the only measure to be considered was cystectomy, there was a high rate of response to hyperbaric oxygen; while recurrence of bleeding did occur in some, there were a considerable number where the improvement was maintained long term. The jury therefore considered that there was convincing evidence (**level 2**) tha in this situation hyperbaric oxygen should be employed in management.

Randomisierte controllierte Studien (Evidenzklasse 1 - 2):

Lewis,-L; Hardy,-K-R; Huang,-E-T; Bolotin,-T; Clark,-J-M; Thom,-S-R **:** HYPERBARIC OXYGEN THERAPY DECREASES GROSS HEMATURIA AND IMPROVES QUALITY OF LIFE IN PATIENTS WITH RADIATION CYSTITIS. Undersea and hyperbaric medical society scientific meeting; 16-19 June 2005, Las Vegas, Nevada

HBOT had a significant effect on resolving gross hematuria and improving quality of life in patients with RC N = 26. Additionally, there were improvements in symptom severity, which did not reach significance. This study supports the role of HBOT in the treatment of RC, however further study to improve the statistical power of these observations is indicated.

CAPELLI-SCHELLPFEFFER et al.: THE USE OF HYPERBARIC OXYGEN IN UROLOGY. J. Urology 1999; 162: 647-645

In the acute setting hyperbaric oxygen is an effective form of therapy for the majority of patients with radiation cystitis and may also offer significant benefit to those with hemorrhagic cystitis from chemical exposure. While further research is needed to determine the role of hyperbaric oxygen with time in patients with radiation tissue damage, shortterm followup suggests that hyperbaric oxygen appears to lead to good outcomes, a high rate of bladder preservation and few serious side effects in radiation cystitis patients.

In einer **Metaanalyse** weisen die Autoren die Wirksamkeit der HBO besonders bei radiogener Cystitis hin.

Feldmeier et al.: A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: An evidence based approach. UHM 2002; 29 No 1: 4 – 30
In 17 eingeschlossenen Studien wurden insgesamt 190 Strahlencystitis-Patienten mit HBO behandelt, 145 (76,3%) werden als Therapieerfolg registriert. 16 der 17 Studien haben für die HBO positive Ergebnisse (Ausnahme : Del Pizzo 1998). Obwohl keine RCT´s vorhanden sind, begründet die Konsistenz der Studienergebnisse aus verschiedenen Ländern in 3 Kontinenten die **AHA-Bewertung IIa** („Acceptable and Usefull“) und die BMJ-Bewertung „Likely to be Beneficial“ für die HBO bei Strahlenzystitis
Guter systematischer Review mit qualitativer Bewertung anhand dreier Bewertungsschemata (AHA, NCI, BMJ) mit nachvollziehbarer positiver Bewertung der HBO-Therapie.

Nicht kontrollierte klinische Studien (Evidenzklasse 3)

Bakker, D.J, Niinikoski, J.: CHRONIC HYPERBARIC OXYGEN THERAPY INDICATIONS - FINAL REPORT. In: HANDBOOK ON HYPERBARIC MEDICINE. G. Orianai, A. Marroni, F. Wattel, Eds., Springer, Berlin, Heidelberg, New York, 1996, 115
Bakker benutzte ein Behandlungsprotokoll mit 100 %igem Sauerstoff bei 2,8 - 3 bar über 2 h mit insgesamt 20 Sitzungen. Die Gewebsantwort wird nach 20 Sitzungen cystoskopisch bewertet. Wenn kein Resttumor vorhanden und die Geweberestauration noch nicht befriedigend ist, können 10 zusätzliche Behandlungen erfolgen. Von der Gesamtzahl (54), der zwischen 1989 und 1993 mit HBO behandelten Patienten waren 80 % (44) beschwerdefrei oder deutlich gebessert.

Bevers, R.F.M., Bakker, D.J., Kurth,K.H.: HYPERBARIC OXYGEN TREATMENT FOR HEMORRHAGIC RADIATION CYSTITIS. Lancet 346 (1995), 803-305
Prospektive nicht kontrollierte Studie.
Hingegen ist der Einsatz der HBO bei der Strahlencystitis in der Lage, sowohl die Hämaturie als auch die pathophysiologischen Veränderungen direkt zu beeinflussen. In ihrer Arbeit stellen sie die Ergebnisse einer prospektiven Studie dar, in der 40 Patienten mit einer bioptisch gesicheten Strahlencystits und Hämaturie über 90 Minuten bei 3 bar während 20 Sitzungen mit 100%igem Sauerstoff therapiert wurden. Die Hämaturie sistierte vollständig oder erheblich bei 37 Patienten nach Beendigung der Therapie. Sie schließen mit der Aussage, daß HBO einen festen Platz in der Behandlung der Strahlencystits verdient und nicht nur den schweren oder therapieresistenten Fällen vorbehalten werden sollte.

Chong KT, Hampson NB, Corman JM: Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. J Urology 2005; 65(4):649-53
A total of **60 patients** (55 men and 5 women), mean age 70 years, received an average of 33 HBO2 treatments (range 9 to 63). Of the 60 patients, 48 (80%) had either total or partial resolution of hematuria. When treated within 6 months of

hematuria onset, 96% (27 of 28) had complete or partial symptomatic resolution (P = 0.003). All 11 patients with previous clot retention had clinical improvement if treated within 6 months of hematuria onset (P = 0.007). Prior intravesical chemical instillation did not affect the clinical outcome. Patients who had undergone primary, adjuvant, or salvage external beam pelvic radiotherapy showed response rates of 81%, 83%, and 78%, respectively (P = 0.950). Our results show that delivery of HBO2 therapy within 6 months of hematuria onset is associated with a greater therapeutic response rate. Treatment efficacy was independent of prior intravesical therapy and the timing of radiotherapy.

Hart, G.B., Strauss, M.B.:DIE HYPERBARE SAUERSTOFFTHERAPIE IN DER VERSORGUNG VON BESTRAHLUNGSSCHÄDEN. Reports des ersten Schweizer Symposium für Hyperbare Medizin, , Basel (Ch), 13.-14. Oktober 1986, 18-36
- Seite 26 Urogenitale Weichteilnekrosen -
Die Autoren berichten über 15 Patienten, die wegen einer Bestrahlungszystitis mit Hyperbarem Sauerstoff behandelt wurden. Symptomatisch waren eine erhöhte Miktionsfrequenz, Tenesmen und Hämaturie. Unter der Therapie mit HBO bei 2 bar für 2 Stunden täglich über 28 Tage mit 2 mal wöchentlich erfolgender Instillation von DMSO konnten die Symptome bei 11 Patienten erfolgreich behoben werden.

Hendricks, DM, Kraft, KL, Moon, RE , Piantadosi, Stolp, BW: CA DOSE-RESPONSE FOR HYPERBARIC OXYGEN TREATMENT OF RADIATION CYSTITIS (RC). 2000 Undersea and Hyperbaric Medical Society, Inc. (http://www.uhms.org)
A total of 20 patients (mean age 72.2 years) with cystoscopically or biopsy demonstrated RC, who had failed other treatment modalities, received HBO treatment (2 ATA/2h, 2 x daily, 5-6 days/week)
Hematuria resolved completely in 14 of 20 patients (70%) in our series (mean 34.2 treatments). Six patients failed to resolve (mean 38.7 treatments) and required surgical intervention. This response rate was comparable to results obtained from previous studies at similar follow-up times. Examination of the pooled data revealed that the resolution rate was correlated with the number of treatment days (P=0.4) and concentration-time product (P=0.2), but not the daily dose of oxygen. (Graphs on page 39 of supplement.) These findings strongly suggest that both total oxygen dose and duration of treatment affect the resolution of RC. Because the two variables were highly correlated, their independent effects cannot be established from these data. Generally, optimal results appear to occur at oxygen doses of >100 ATA-hours O2 and 40 treatment days.

JOSPEHSON-L; WOODWARD-C; LEWIS-D; ET-AL: Radiation Cystitis: Outcomes Review 1991-1995. Undersea and Hyperbaric Medical Society Gulf Coast Chapter Annual Scientific Meeting, Panama City, FL 1997 Mar 6-9.
N = 17 All except two patients (that received hyperbaric treatments 16 and 25 years after radiation) showed significant improvement. Improvements were measured by decreased hematuria as well as follow up cystoscopy per their urologist. Cystoscopy exams revealed average 75-90% healing of bladder

tissue. The patients that were 6, 7, and 9 years post radiation treatments revealed the same healing rate as the patient that were seen with 1-3 years. Adjunctively, hyperbaric treatment for radiation cystitis appears to be of significant benefit, particularly if treated within a reasonable time.

Kindwall, E.P.,MD: HYPERBARIC OXYGEN TREATMENT OF RADIATION CYSTITIS. Clin Plast Surg 3 (1993) 20: 589-592
Kindwall stellt zwei eigene erfolgreich behandelte Patienten vor und fasst in seiner Arbeit zusammen: Es gibt bisher nur sehr wenige Berichte über die HBO-Behandlung einer Strahlencystits. Bisher wurde in der Literatur über 53 Patienten berichtet. HBO scheint die einzige Behandlungsform zu sein, welche die durch die Bestrahlung veränderte ursprüngliche Gefäßarchitektur wiederherstellen kann. In allen bisher veröffentlichten Berichten und in allen Fällen, die durch persönliche Mitteilung bekannt sind, ist es in keinem Fall zu einer Verschlechterung durch die HBO gekommen. Insgesamt sind 4 Therapieversager, alle aus dem gleichen Zentrum, beschrieben worden. In allen anderen veröffentlichten Fällen ist eine erhebliche Verbesserung oder sogar eine komplette, lang anhaltende Remission eingetreten.

Lee, H.C., Liu, C.S., Chiao, C., Lin, S.N.: HYPERBARIC OXYGEN THERAPY IN HEMORRHAGIC RADIATION CYSTITIS: A REPORT OF 20 CASES. Undersea & Hyperbaric Medicine 3, 1994, 21, 321-327
und
Lee, H.C., Liu, C.S., Chiao, C., Lin, S.N.: HYPERBARIC OXYGEN THERAPY IN HEMORRHAGIC RADIATION CYSTITIS: A REPORT OF 40 CASES. Proceedings of the International Joint Meeting on Hyperbaric and Underwater Medicine, 4. - 8. September 1996, Mailand, Italien, 85-87.
N = 40 Nur eine dieser Patienten sprach auf die Behandlung nicht an und musste sich einer Harnableitung durch Ileum conduit unterziehen. Bei 33 Patienten (82,5%) trat eine vollständige und bei weiteren 3 Patienten (7,5%) eine erhebliche Besserung der Hämorrhagie ein. 3 Patienten (7,5%) bei denen keine Hämorrhagie bestand, zeigten unter der HBO eine erhebliche Verbesserung der cystitschen Beschwerden. Bei einem Patienten konnte ein Anstieg des maximalen und mittleren Flows und eine Verkürzung der Miktionszeit urodynamisch verifiziert werden. Bei den zwei weiteren Patienten reduzierte sich die Miktionsfrequenz. Zusammenfassend wird die HBO als wirksame und sichere Behandlung der hämorrhagischen Strahlencystitis angesehen.

Mayer R. et al.: Hyperbaric oxygen — an effective tool to treat radiation morbidity in prostate cancer Radiotherapy and Oncology 6 (2001) 151-156

N = 18 men (median age 71 years) with radiation proctitis (n = 7), cystitis (n = 8), and combined proctitis/cystitis (n = 3) underwent HBO therapy in a multiplace chamber for a median of 26 sessions (range 2-60). The treatment schedule (2.2-2.4 atmospheres absolute, 60 min bottom time, once-a-day, 7 days a week) was set at a lower limit of 20 sessions; the upper limit was left open to symptom-related adjustment. Prior to HBO treatment, RTOG/EORTC late genitourinal (GU) morbidity was Grade 2 (n = 3), Grade 3 (n = 6) or Grade 4 (n = 2); modified RTOG/EORTC late gastrointestinal (GI) morbidity was either

Grade 2 (n = 4) or Grade 3 (n = 6). Sixteen patients underwent an adequate number of sessions. RTOG/EORTC late GU as well as modified GI morbidity scores showed a significant improvement after HBO (GI, P = 0.004; GU, P = 0.004; exact Wilcoxon signed rank test); bleeding ceased in five out of five patients with proctitis and in six out of eight patients with cystitis; one of those two patients, in whom an ineffective treatment outcome was obtained, went an to have a cystectomy. HBO treatment seems to be an effective tool to treat those patients with late GI and GU morbidity when conventional treatment has led to unsatisfactory results. Particularly in patients with radiation cystitis, HBO should not be delayed too long, as in the case of extensive bladder shrinkage improvement is hard to achieve.

Nakada, T., Yamaguchi, T., Sasagawa, I., Kubota, Y., Suzuki, H., Izumiya, K.: SUCCESSFUL HYPERBARIC OXYGENATION FOR RADIATION CYSTITiS DUE TO EXCESSIVE IRRADIATION TO UTERUS CANCER. Eur Urol (1992) 22, 294-297.
Nakada et. al. berichten über 6 Frauen, die aufgrund einer Strahlencystitis nach vorangegangener Bestrahlung des Beckens wegen eines Uteruskarzinoms mit HBO behandelt wurden. Mit Ausnahme von einer Patientin kam es bei allen Frauen zu einer Besserung der Beschwerden und des cystoskopischen Befundes. Nebenwirkungen traten nicht auf. Während des follow-up über 1 Jahr kam es in keinem Fall zur erneuten Strahlencystitis. Daraus folgern die Autoren, daß die Hyperbare Sauerstofftherapie einen positiven Effekt auf die Strahlencystitis ausübt und in der Behandlung der Strahlencystitis eingesetzt werden sollte.

Norkool D.M., Hamptom N.B., Gibbons, R.P., Weisman R.M.: HYPERBARIC OXYGEN THERAPIE FOR RADIATION INDUCED HEMORRHAGIC CYSTITS. J Urol 150 (1993), 332-334
Die Arbeitsgruppe um Norkool hat 14 Patienten mit einer cystoskopisch und bioptisch gesicherten hämorrhagischen Strahlencystits, die therapieresistent auf alle anderen Behandlungsmethoden waren, keinen bakteriellen Infekt und keinen Rezidivtumor hatten, mit Hyperbarem Sauerstoff behandelt. Während des follow-up über 10 bis 42 Monate hatten 8 Patienten (57%) eine vollständige Remission und weitere 2 Patienten (14%) eine erhebliche Besserung der Symptomatik. Somit fand sich bei 10 Patienten (71%) ein positives Ergebnisse der Hyperbaren Sauerstoffbehandlung. Von den 4 Patienten (29%) mit einem negativen Behandlungsergebnis konnte bei 3 Patientin nach der Therapie ein Rezidivtumor, der vor Behandlung cystoskopischh nicht nachweisbar war, diagnostiziert werden. Ein Patient musste die Behandlung aufgrund einer Erkrankung abbrechen. Sie kommen zu dem Ergebnis, dass die Hyperbare Sauerstofftherapie bei einer Strahlencystits eine effektive Behandlungsmethode auch nach Versagen der Initialtherapie darstellt.

Rijkmans B.G., Bakker, D.J., Dabhoiwala N.F., Kurth, K.H.: SUCCESSFUL TREATMENT OF RADIATION CYSTITS WITH HYPERBARIC OXYGEN. Eur Urol (1989) 16, 354-356
Rijkmans et. al. beschreiben in ihrer Arbeit die Ergebnisse der Hyperbaren Sauerstofftherapie bei 10 Patienten mit einer Strahlencystits. Bei allen Patienten

bestand eine für konventionelle Therapie resistente Makrohämaturie. Vorangegangen war die Radiation mit 60 Gy bei 8 Patienten wegen eines Blasenkarzinoms und bei 2 Patienten wegen eines Prostatakarzinoms. Die Hyperbare Sauerstofftherapie wurde über 20 Sitzungen mit 100%iger Sauerstoffgabe über 90 Minuten bei 3 bar durchgeführt. Bei 6 Patienten sistierte die Makrohämaturie vollständig, bei den restlichen Patienten kam es zu einer erheblichen Besserung. Bei diesen 4 Patienten konnte nach der HBO ein Tumorrezidiv beziehungsweise eine Tumorpersistenz als Blutungsursache nachgewiesen werden.

Shoung, G., Chiao, C.S., Liu, C.S., Lee, H.C.: HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF RADIATION-INDUCED CYSTITS. Undersea Hyperbaric Med 20 (1993) Suppl., 43-44
Shoung und Mitarbeiter berichten über die Behandlung über 15 Patienten, die aufgrund einer Strahlencystitis mit HBO therapiert wurden. Nach einer durchschnittlichen HBO-Anwendung von 44 Sitzungen sistierte die Makrohämaturie in 12 Fällen vollständig und in 2 Fällen erheblich. Die nach der Behandlung durchgeführte Cytoskopie zeigte makroskopisch eine signifikante Abnahme von Hämorrhagien und Teleangiektasien der Blasenschleimhaut. Die Autoren halten aufgrund der klinischen und cystoskopischen Ergebnisse bei der Behandlung ihrer 15 Patienten die HBO für eine sinnvolle Behandlung bei der Strahlencystitis.

Velu, S.S., Myers R.A.M.: HYPERBARIC OXYGEN TREATMENT FOR RADIATION INDUCED HEMORRHAGIC CYSTITS. Undersea Biomed Res (1992) 199, 85
Velu et. al. berichten über 4 Patienten, die wegen einer Strahlencystitis mit persistierender Hämaturie mit HBO behandelt wurden. Das Behandlungsschema beinhaltete bei 2 bar die Atmung von Sauerstoff über 90 Minuten, anfänglich zweimal täglich, später reduziert auf täglich einmalige Behandlung. Alle Patienten zeigten schon nach 10 Behandlungen eine erhebliche Besserung der Symptomatik. 2 Patienten erhielten 60 Anwendungen, einer 35 Anwendungen und bei dem vierten Patienten mußte wegen einer Begleiterkrankung die Behandlung nach 28 Expositionen abgebrochen werden. Im follow-up fand sich bei 3 der 4 Patienten cystoskopisch ein unauffälliger Befund. Zusammenfassend hält Velu die HBO für effektiver als andere Behandlungen bei der Strahlencystits. Dies begründet er unter anderem damit, dass die Neovaskularisation den Hauptfaktor der Wundheilung darstellt, der zu einer Verminderung der Symptome der Strahlencystits führt.

Weiss J.P., Neville E.C.:HYPERBARIC OXYGEN: PRIMARY TREATMENT OF RADIATION-INDUCED HEMORRHAGIC CYSTITS: J Urol (1989) 142, 43-45
Weiss und Neville berichten erstmalig über 3 Patienten, die aufgrund einer therapieresistenten Strahlencystitis erfolgreich mit HBO - 2 Stunden 100% Sauerstoffatmung bei 2 bar, 60 Sitzungen - behandelt wurden. In allen drei Fällen trat eine vollständige Remission auf.

Weiss J.P., Neville E.C.:TREATMENT OF RADIATION-INDUCED CYSTITS WITH HYPERBARIC OXYGEN: J Urol (1985) 134, 352-354
Weiss und Neville fassen ihre Ergebnisse 1985 folgendermaßen zusammen: „ Von 8 Patienten, die mit den Symptomen einer fortgeschrittenen Cystitis infolge

einer Bestrahlung des kleinen Beckens mit HBO behandelt wurden, zeigten 7 bei Verlaufsbeobachtung eine Langzeitbesserung der Symptome. Alle 6 Patienten, die aufgrund einer Makrohämaturie einer stationären Behandlung bedurften, waren nach der Behandlung im Durchschnitt 24 Monate (6 bis 43 Monate) beschwerdefrei. ..... Diese Erfahrung legt nahe, dass die Hyperbare Sauerstofftherapie bei der Behandlung einer hämorrhagischen Strahlencystits initial eingesetzt werden sollte und sich die Morbidität durch den frühzeitigen HBO-Einsatz senken läßt.“ (siehe Anlage, Kat. 4, Nr. 14)

Weiss, JP, Mattei, DM, Neville, EC, Hanno, PM: PRIMARY TREATMENT OF RADIATION-IDUCED HEMORRHAGIC CYSTITIS WITH HYPERBARIC OXYGEN: 10-YEAR EXPERIENCE, J Urology, 1994, 151: 1514-1517
Obwohl es ihnen möglich erscheint, dass durch frühzeitigere HBO schwere Krankheitsverläufe vermieden werden können, betonen die Autoren, dass ihre Patienten nur in die Studie aufgenommen wurden, wenn die strahlenbedingte Hämaturie eine Klinikaufnahme mit in den meisten Fällen Transfusionsbehandlung und/oder Blaseninstillationen oder Koagulation erforderte. „In diesem Sinne glauben wir, dass unsere Daten dem Wert einer prospektiven randomisierten Studie nahekommen.“

Wissenschaftlich begründete Expertenaussagen

Bouachour, G.: PATHOPHYSIOLOGIC BASES FOR THE USE OF HYPERBARIC OXYGEN IN SOFT TISSUE RADIONECROSIS. 1st European Consensus Conference on hyperbaric Medicine, Lille (F), 19.-21.September 1994, 196-203
Bouachour fasst zusammen, dass HBO bei der Strahlencystitis eine effiziente und ökonomische Behandlungsform darstellt. HBO ist die einzige Therapie, welche die Heilung unterstützt und die auch vor Instillation von chemischen Präparaten oder Operationen angewandt werden sollte.

Camporesi, E. (Ed.): HYPERBARIC OXYGEN THERAPY, A COMMITTEE REPORT. Undersea and Hyperbaric Medical Society, Kensington, MD, USA, 1996, 42
Die Strahlencystits wird im COMMITTEE REPORT unter Punkt 10 der anerkannten Indikationen aufgeführt. Eine Therapiekontrolle ist spätestens nach 60 Behandlungen indiziert. Die Behandlungen sollen täglich bei einem Druck zwischen 2,0 und 2,4 bar über 90 bis 120 Minuten mit Hyperbarer Sauerstoffatmung erfolgen.

Jain, K.K.:RADIATION NECROSIS OF THE GENITOURINARY TRACT. In:“TEXTBOOK OF HYPERBARIC MEDICINE“, Hogrefe & Huber Publisher, Toronto, Lewiston, Bern, Göttingen, Stuttgart, (1990), 211
Jain weist auf die gemeinsamen pathologischen Merkmale der Strahlencystitis und Weichteil-Radionekrose hin und fasst die Ergebnisse einiger Studien mit der Aussage zusammen, dass die einzelnen Autoren die HBO bei der Behandlung der hämorrhagischen Strahlencystitis als primäre Behandlung ansehen.

Mayer, E.D.: CHIRURGISCHE UND ANDERE EINSATZGEBIETE DER HYPERBAREN OXYGENATIONSTHERAPIE (HBO). MDK Friedrichshafen, Baden-Württemberg, Juni 1995, 28-29
Mayer kommt in seiner Stellungnahme zu dem Schluss, dass die HBO bei der hämorrhagischen Radiozystitis hinsichtlich eines Behandlungserfolges nach den geforderten schulmedizinisch-wissenschaftlichen Kriterien nicht „wahrscheinlich“, im Einzelfall aber eine Wirkung immerhin als möglich zu erachten ist.

Noordzij, J.W., Dabhoiwala, N.F: HEMORRHAGIC RADIATION CYSTITIS, INT. UROGYNECOL J, (1994), 4, 160 - 167
Das Übersichtsreferat endet mit der Feststellung: „Wenngleich einige der Möglichkeiten den Beweis erbrachten, bei wenigstens temporärer Besserung oder sogar Beseitigung der Hämaturie sehr wirksam zu sein, behandeln die meisten Therapien lediglich die Symptome, während die zugrundeliegende Pathologie fortbesteht. In dieser Hinsicht hat lediglich die HBO ihre Nützlichkeit bewiesen, denn sie fördert die Neovaskularisation und die Bildung von Granulationsgewebe. Die Behandlungsauswahl sollte vom Wissen bestimmt sein, dass viele der wirksamen kauterisierenden Agenzien weiteren Schaden an der zarten Mucosa verursachen und die Fibrose verstärken, womit weitere Blutungen gefördert und die Drangsymptome verschlimmert werden. Wirksame Behandlung hat daher so schonend und ‘blasenmukosafreundlich’ wie möglich zu sein.“

Tschuschke, Ch.: RADIOGENE ZYSTITS. In: „UROLOGISCHE THERAPIE“. Hrsg.: Hertle & Pohl, Urban & Schwarzenberg (1993): 230 - 231.
Tschuschke äußert sich zur HBO-Therapie bei radiogener Zystitis wie folgt: „Einen möglichen kausalen Therapieansatz bietet die hyperbare Oxygenierung in einer Überdruckkammer. ..... Die veröffentlichen Ergebnisse sind gut; sogar Fistelbildungen konnten durch diese Behandlungsform verschlossen werden.“

Williams, J.A., Clarke, D.: PELVIC RADIATION NECROSIS AND RADIATION CYSTITS. In: HYPERBARIC MEDICINE PRACTICE. Ed. Kindwall E.P., Best Publishing Company, 1994, 506-516
Zusammenfassend berichtet Williams, dass ein deutlicher Benefit durch die Anwendung der HBO bei der Strahlencystitis besteht. In den meisten Berichten wurde die HBO erst nach Versagen der konventionellen Behandlung erfolgreich angewandt. Allerdings scheint durch frühzeitige Anwendung der HBO die Morbidität weiter gesenkt werden zu können.

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Purpose: Cancer patients who undergo radiotherapy remain at life-long risk of radiation-induced injury to normal tissues. We conducted a randomized, controlled, double-blind crossover trial with long-term follow-up to evaluate the effectiveness of hyperbaric oxygen for refractory radiation proctitis.

Methods and Materials: Patients with refractory radiation proctitis were randomized to hyperbaric oxygen at 2.0 atmospheres absolute (Group 1) or air at 1.1 atmospheres absolute (Group 2). The sham patients were subsequently crossed to Group 1. All patients were re-evaluated by an investigator who was unaware of the treatment allocation at 3 and 6 months and Years 1–5. The primary outcome measures were the late effects normal tissue-subjective, objective, management, analytic (SOMA-LENT) score and standardized clinical assessment. The secondary outcome was the change in quality of life.

Results: Of 226 patients assessed, 150 were entered in the study and 120 were evaluable. After the initial allocation, the mean SOMA-LENT score improved in both groups. For Group 1, the mean was lower ($p = 0.0150$) and the amount of improvement nearly twice as great (5.00 vs. 2.61, $p = 0.0019$). Similarly, Group 1 had a greater portion of responders per clinical assessment than did Group 2 (88.9% vs. 62.5%, respectively; $p = 00009$). Significance improved when the data were analyzed from an intention to treat perspective ($p = 0.0006$). Group 1 had a better result in the quality of life bowel bother subscale. These differences were abolished after the crossover.

Conclusion: Hyperbaric oxygen therapy significantly improved the healing responses in patients with refractory radiationproctitis, generating an absolute risk reduction of 32% (number needed to treat of 3) between the groups after the initial allocation. Other medical management requirements were discontinued, and advanced interventions were largely avoided. Enhanced bowel-specific quality of life resulted. © Int J Radiation Oncology Biol. Phys.;2008, Elsevier Inc: 1- 10

Hyperbaric oxygenation, Controlled trial, SOMA-LENT, Late radiation injury, Quality of life.

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Supplementary material (Table 3) for this article can be found at www.redjournal.org.

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Conflict of interest: R. E. Clarke provides hyperbaric medicine support services; and S. D. Rodrigues was compensated for lectures by Roche in 2007 and sat on the pain management board of Jansen Cilag in 2006.

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INTRODUCTION

Radiotherapy is a major nonoperative treatment and commonly used in the management of a number of different malignancies. During the past decade, significant developments in the delivery of radiotherapy have improved the efficacy and tolerance (1). Despite such advances, adverse effects continue to complicate its use (2, 3). These effects are commonly categorized as either acute effects, representing those that occur during or soon after radiotherapy completion, or late effects that manifest many months to several years later.

Acute toxicity is usually mild, frequently self-limiting, and often responds to brief interruptions in radiotherapy (3–5). Severe acute effects can lead to later excluded ones from "consequential"effects (6). Late toxicity is largely a function of the total radiation dose and fraction size and tends to be dose limiting in curative settings (7, 8). The resulting injuries are frequently refractory to a wide range of therapeutic interventions, can proceed to surgical removal of damaged organs, and are the cause of some mortality (2, 3, 9).

Late radiation proctitis is a particularly difficult condition to treat and for patients to live with (10–13). The reported incidence varies from 4% to 22% (5, 14), yet because of a frequent lack of recognition and insufficient long-term follow-up, its true incidence is unknown (14, 15). No recommended standard treatment exists, and current management is often unsatisfactory (11, 16). This shortcoming is readily apparent given the large number of medical and surgical therapies in common use (Table 1).

Hyperbaric oxygen (HBO) therapy has been used in the treatment of pelvic radiation injuries for several decades (Table 2) and has been reported to be beneficial (16–18). It has not, however, been studied in a sufficiently rigorous manner to determine its precise therapeutic effect. We conducted a multicenter, randomized, controlled, double-blind trial with crossover and long-term follow-up to evaluate the effect of HBO therapy for patients whose radiation proctitis had proven refractory to other interventions.

Table 1. Late radiation proctitis treatment options (in alphabetical order)

5-ASA
Antidiarrheal agents
Argon laser
Cautery
Corticosteroids
Dilation and stenting
Elemental diet
Formalin
Heat probe
Hormonal therapy
Hyperbaric oxygen therapy
Iron supplementation
Low-residue, low-fat diet
Metronidazole
Nd:YAG laser
Pain control
Pentosan
Resection
Replacement transfusion
Short-chain fatty acids
Sucralfate
Surgical repair

Abbreviations: ASA = acetylsalicylic acid (aspirin); Nd:YAG = neodymium:yttrium-aluminium-garnet (laser) ($Nd:Y_3Al_5O_{12}$).

METHODS AND MATERIALS

Patients

Patients from the Instituto Nacional de Cancerologica, Mexico City, Mexico, the University of Pretoria Medical Centre, Pretoria, Republic of South Africa, Department of Underwater and Hyperbaric Medicine, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, Wesley Medical Centre, Brisbane, Australia, and the Royal Hobart Hospital, Tasmania, Australia were enrolled in the trial. Each participating center's institutional review board approved the study protocol. Referring physicians agreed to participate as blinded assessors. The trial registration numbers were NCT00134628 and ISRCTN85456814.

Patients were eligible for enrollment if they had undergone pelvic radiotherapy and had subsequently developed evidence of rectal late radiation tissue injury. The diagnosis had to have been present for ≤3 months and to not have responded sufficiently to other therapies. Eligibility screening confirmed the absence of unacceptable patient-specific risks to HBO therapy. All patients or their surrogate provided written informed consent before enrollment. On patient enrollment, the best supportive care was maintained.

Before beginning treatment, patients were evaluated with the late effects normal tissue-subjective, objective, management, analytic (SOMA-LENT) scale, an anatomic-specific morbidity scoring system (19). It provides an ascending order of severity of radiation-induced complications. It is particularly well suited to multicenter trials, because of its standardized application, reproducibility, and accuracy. A standardized clinical assessment was also included with both screening tools conducted by a physician unaware of the allocation. Patients also completed the Expanded Prostate Cancer Index Composite (20) quality of life (QOL) instrument at this time and at every other follow-up stage.

Randomization

Biostatisticians at the University of South Carolina generated the randomization sequence, which was uploaded into, and concealed within, the study database software. The patients were randomly assigned (1:1) to receive HBO or normobaric air, using a "blocking" process. The block size was four and was equally stratified with two of each treatment options (A or B). The randomization sequence became available to the unblinded local principal investigator only on irretrievable entry of each patient's demographic information, medical history, and clinical characteristics. Group 1 (active treatment) was randomized to receive 2.0 atmospheres absolute (ATA) oxygen. Group 2 (sham) patients were randomized to receive 1.1 ATA air.

Treatment procedure

Group 1 was treated with 100% oxygen at 2.0 ATA for 90 min, once daily, five times weekly. Group 2 were treated with 21% oxygen (normal air) at 1.1 ATA, once daily, five times weekly. For patient blinding purposes, Group 2 patients underwent a brief compression to 1.34 ATA at the beginning of each treatment. The chamber was then slowly decompressed from 1.34 to 1.1 ATA.

Table 2. Reported hyperbaric oxygen dosing and outcomes for radiation proctitis

		Hyperbaric treatment			
Investigator	Patients (n)	Pressure (ATA)	Time (min)	Treatment sessions (n)*	Overall improvement (%)
Bouachour et al. (31), 1990	8	2.5	90	80 ± 10	75
Charneau et al. (28), 1991	1	2.5		80	Healed
Nakada et al. (35), 1993	1	2.0	90	30	Healed
Hamour et al. (36), 1996	1	2.5	90	49	Healed
Feldmeier et al. (37), 1996	7	2.4	90	3–50 (24)	57
Woo et al. (38), 1997	18	2.0	90	12–40	>50
Warren et al. (39), 1997	14	2.0–2.5	90–120		59
Ugheoke et al. (40), 1998	8	2.5	90	20–40 (28)	62.5
Carl et al. (41), 1998	2	2.4	90	38–40 (39)	50
Gouello et al. (42), 1999	36	2.5	90	Mean 67	56–65
Kitta et al. (43), 2000	4	2.0	60	30–60 (38)	75
Bem et al. (44), 2000	2	2.4	90	60	100
Roque et al. (45), 2001	6	2.5	90	20–60 (37)	85
Mayer et al. (46), 2001	7	2.2–2.4	60	20–60 (33)	85
Boyle et al. (47), 2002	19	2.0	120	27–80 (59)	68
Jones et al. (48), 2006	10	2.0–2.5	90	36–41 (40)	>70
Dall'Era et al. (49), 2006	27	2.4	90	29–60 (36)	48
Fink et al. (50), 2006	4	2.4	90	20–50 (33)	50
Girnius et al. (51), 2006	9	2.5	90	22–80 (58)	78
Nakabayashi et al. (52), 2006	1	2.4	90	40	Healed
Marshall et al. (53), 2007	65	2.36	90	30–60	25–73

Abbreviation: ATA = atmospheres absolute.
* Average number of treatment sessions in parentheses.

Group 2 patients remained for the sum of the time taken to treat the Group 1 patients. Reassessment, after 30 treatment sessions, was undertaken by the referring physician, who remained unaware of the allocation. Ten additional treatment sessions were provided to selected patients, depending on the individualized responses. Patients repeated their QOL survey and were screened to determine the effectiveness of the blinding process. Unblinding took place at this point.

Those who had been allocated to Group 1 were entered into follow-up, with repeat evaluations scheduled at intervals of 3 and 6 months and Years 1–5. For Group 2, all but 3 accepted crossover to the active treatment arm.

Data collection at inclusion

Once a patient was enrolled, their local principal investigator collected the following data: age and gender; comprehensive medical history; current medications and any history of tobacco use; cancer-related history, including tumor type, location, stage, and treatment; and late radiation proctitis signs and symptoms, including treatment sessions to date.

Statistical analysis

The primary outcome was a change in the SOMA-LENT (Fig. 1) score, a numeric variable measured at all periods. Four other numeric values were derived from a QOL survey completed by patients in conjunction with their clinical evaluations. From this survey, using the Expanded Prostate Cancer Index Composite Bowel Domain, the Bowel Function and Bowel Bother subscales were obtained. Also obtained were the physical and mental results using the SF-12 General Health Function Survey. The SOMA-LENT score was analyzed using a repeated measures model containing patient type, period, their interaction, and six covariates: gender, tobacco use, external beam radiotherapy and brachytherapy, interval between radiotherapy and symptoms, interval between symptoms and treatment, and country of residence.

A sixth, ordinal categorical outcome, was the clinical evaluation measured at all periods, except at initialization. The evaluations made immediately after completion of the initial treatment allocation and crossover were coded as healed, significant improvement, modest improvement, or no improvement. For the remaining periods, they were coded as healed, improved, unchanged, or recurrence. For analysis purposes, these evaluations were dichotomized. After the initial treatment allocation and crossover, healed, significant improvement, and modest improvement were collapsed into one category and no improvement and recurrence into the other. For the follow-up evaluations, healed and improved were collapsed into one category and no improvement and recurrence into the other. The outcomes were compared for the two patient types using Fisher's exact test and logistic regression analysis containing the same variables as the repeated measures model for SOMA-LENT. Additionally, a Jonckheere-Terpstra test for trend was used with the original calculations.

RESULTS

A total of 226 patients were assessed for eligibility. Of these 226 patients, 76 were excluded and 150 enrolled. Of the 150 patients, 120 completed the protocol (Fig. 2). At 1 year, 5 patients (4%) had died and 9 (8%) had been lost to follow-up.

Descriptive statistics

Data were available for 120 patients. The minimal follow-up period for all patients was 1 year (average, 2.09). Of the 120 patients, 106 (88.33%) were women, and 101 (84.17%)

SOMA LENT scoring system for radiation proctitis

RADIATION PROCTITIS EVAL. BY: PRINT NAME:_____ HORTIS IV
PT. NAME_____HORTIS I.D._____ DATE: _____
SIGNATURE: _____

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORE	FACILITY CODE: _____
Subjective						
Tenesmus	Occasional urgency	Intermittent urgency	Persistent urgency	Refractory	____	
Mucosal loss	Occasional	Intermittent	Persistent	Refractory	____	Scoring Instructions:
Sphincter control	Occasional	Intermittent	Persistent	Refractory	____	
Stool frequency	2 - 4 per day	4 - 8 per day	> 8 per day	Uncontrolled diarrhea	____	Score the 14 SOM parameters with 1-4 and total all 14 to
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	____	generate the
Objective						1st LENT Score
Bleeding	Occult	Occasionally >2/week	Persistent/daily	Gross hemorrhage	____	
Ulceration	Superficial ≤ 1 cm^2	Superficial > 1 cm^2	Deep ulcer	Perforation, Fistulae	____	(Score = 0 if there are no toxicities)
Stricture	> 2/3 normal diameter with dilation	1/3 - 2/3 normal diameter with dilation	< 1/3 normal diameter	Complete obstruction	____	
Management						
Tenesmus & stool frequency	Occasional, ≤ 2 antidiarrheals/week	Regular, > 2 antidiarrheals/week	Multiple, > 2 antidiarrheals/day	Surgical intervention/ Permanent colostomy	____	1st LENT Score_____
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	____	Divide the 1st LENT Score by 14 to provide the 2nd LENT Score
Bleeding	Stool softener, iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention / Permanent colostomy	____	
Ulceration	Diet modification, stool softener	Occasional steroids	Steroids per enema, hyperbaric oxygen	Surgical intervention / Permanent colostomy	____	
Stricture	Diet modification	Occasional dilatation	Regular dilatation	Surgical intervention	____	2nd LENT Score_____
Sphincter control	Occasional use of incontinence pads	Intermittent use of incontinence pads	Persistent use of incontinence pads	Surgical intervention / Permanent colostomy	____	
Analytic						
Barium enema	Assessment of lumen and peristalsis				Y/N	Date:
Proctoscopy	Assessment of lumen and musosal surface				Y/N	Date:
CT	Assessment of wall thickness, sinus and fistula formation				Y/N	Date:
MRI	Assessment of wall thickness, sinus and fistula formation				Y/N	Date:
Anal manometry	Assessment rectal compliance				Y/N	Date:
Ultrasound	Assessment of wall thickness, sinus and fistula formation				Y/N	Date:

Fig. 1. Late effects normal tissue-subjective, objective, management, analytic (SOMA-LENT) scoring system for radiation proctitis.

reported never having smoked. Because of the small number of current (n=8) and former (n=11) smokers, the tobacco variable was dichotomized into ever/never. Of the 120 patients, 11 (9.17%) were from Australia, 85 (70.83%) from Mexico, and 12 (10.00%) from both South Africa and Turkey. The baseline comparisons of the covariates for the two groups resulted in no significant differences, indicating that the randomization process had worked well. The patient demographics and clinical characteristics are detailed in Table 3 (appears online only at www.redjournal.org). The mean SOMA-LENT values for the two patient types at each period are displayed in Fig. 3. The mean SOMA-LENT score decreased considerably between the initial value and completion of HBO therapy in Group 1, with a much smaller change in Group 2. For the latter group, however, a substantial decrease occurred after crossover, when they received HBO therapy.

Numeric outcomes

SOMA-LENT score. Adjusting for covariates, a significant ($p < 0.0001$) decrease (improvement) occurred in Group 1 of 5.00 (95% confidence interval, 3.96–6.03), as well as a significant ($p < 0.0001$) decrease in Group 2 of 2.61 (95% confidence interval, 1.51–3.70) after completion of the initial allocation. The decrease was greater in Group 1 than in Group 2 ($p = 0.0019$). At initialization, no difference was detected between the two groups ($p = 0.5597$). However, after the initial allocation, Group 1 had significantly ($p = 0.0150$) lower average scores than Group 2, with an estimated difference of 1.93 (95% confidence interval, 0.38–3.48). After completion of the crossover, no differences were detected ($p = 0.6594$). The mean scores remained relatively stable through 1 year and showed a trend to additional and sustained improvement through Year 5.

Clinical evaluation. The frequencies for clinical evaluations are given in Table 4. The most notable result was after completion of the initial allocation, at which 56 (88.9%) of the 63 patients in Group 1 were assessed to have either healed or had some improvement, and 32 (62.5%) of the 56 patients in Group 2 were assessed to have had at least some improvement. Fisher's exact test ($p = 0.0009$) and logistic regression

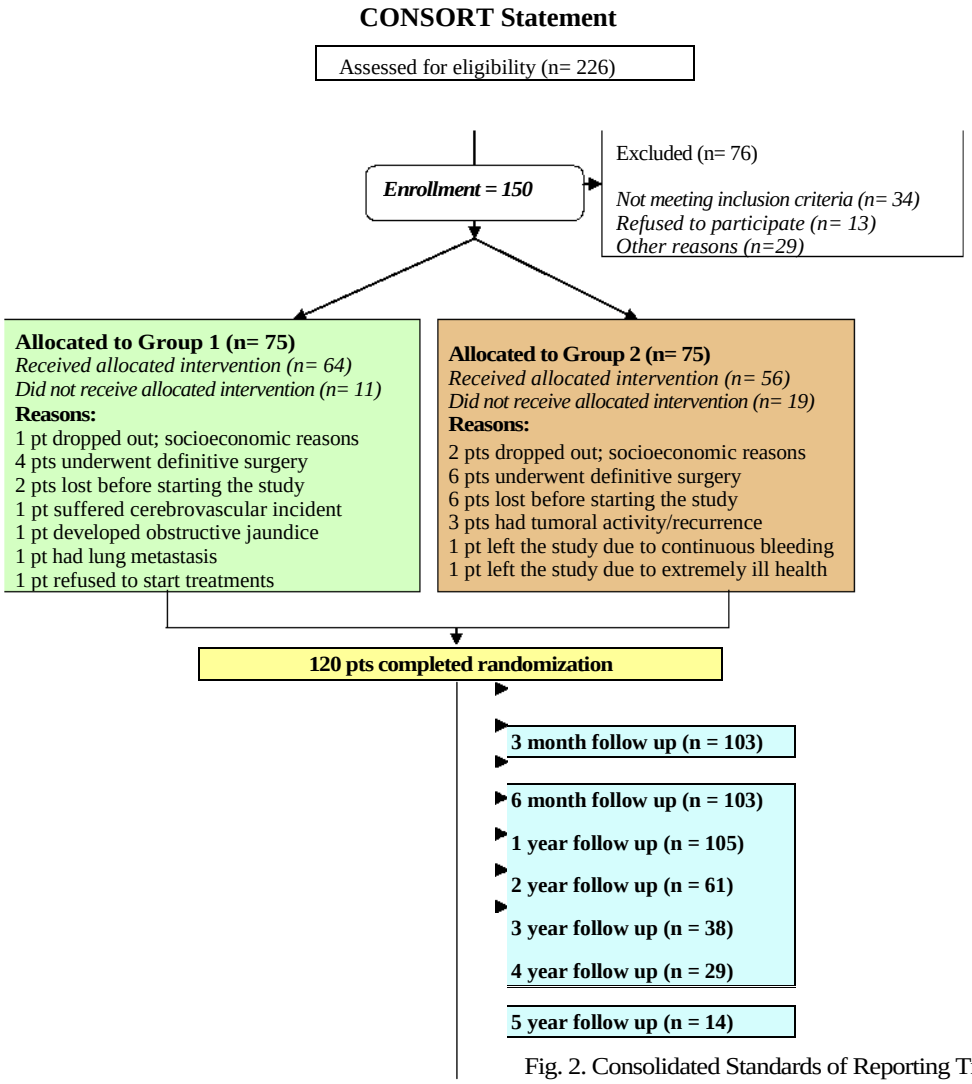
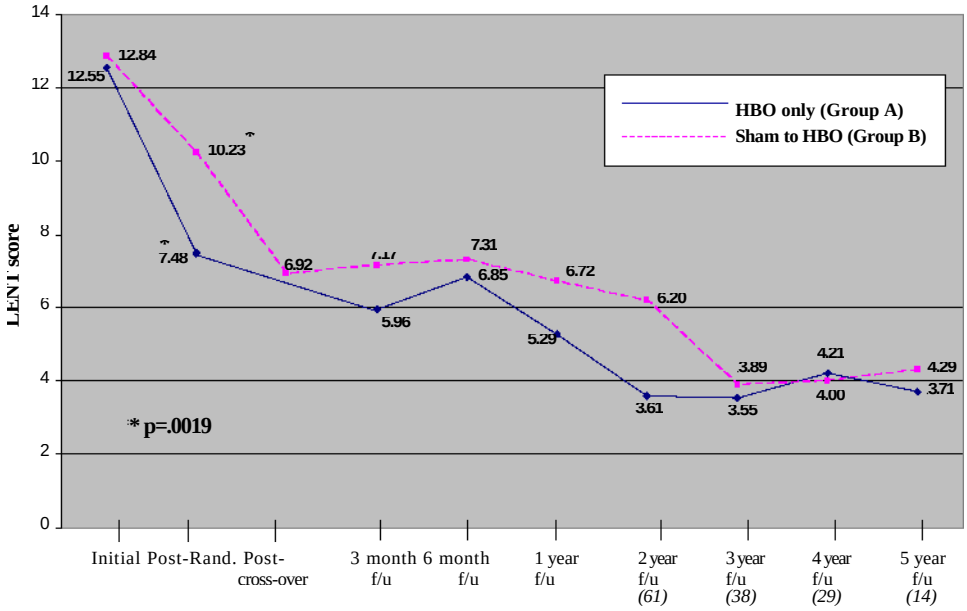


Fig. 2. Consolidated Standards of Reporting Trials (CONSORT) statement.

analysis ($p = 0.0011$) both indicated that Group 1 had a significantly greater proportion of healing/improvement at that time. For logistic regression analysis, the corresponding odds ratio was 5.93 (95% confidence interval 2.04–17.24). From this, we estimated that Group 1 was about six times more likely to have an evaluation that indicated at least some type of improvement than was Group 2. Furthermore, the Jonckheere-Terpstratestfortrend was significant ($p = 0.0008$), indicating that better outcomes were more common in Group 1. On the basis of the clinical evaluation outcomes, an absolute risk reduction of 0.32 (32%) was generated, resulting in a number needed to treat of 3.

From an intention to treat perspective, we considered what would have happened if (1) all those for whom we had no results had had improvement, (2) all those for whom we had no results had not had improvement, and (3) for each patient type, one-half of those for whom we had no results had improvement and one-half had not. In all cases, the results still indicated that Group 1 had a significantly greater proportion of improvement than did Group 2 ($p = 0.0057$, $p = 0.0007$, and $p = 0.0036$, respectively).

Quality of life. Marked improvement was noted in the bowel-specific QOL assessment for Group 1 after treatment but not for Group 2 (14% for Bowel Bother and 9% for Bowel Function vs. 5% and 6%, respectively). After crossover, Group 2 showed notable improvement, with an increase to 13.6 for bowel bother and 10% for bowel function. Both groups showed additional improvement at 1 year. For the bowel bother subscale, a significant improvement was seen between initialization and randomization in Group 1 (estimated change, 14.14; $p = 0.0007$, adjusting for covariates), but not in Group 2 (estimated change, 5.75; $p = 0.1521$). However, Group 2 experienced a significant improvement after crossover (estimated change, 14.27; $p = 0.0002$). The scores for both groups were stable or tended to improve further throughout follow-up. Similar trends were seen in the bowel function subscale. No differences were observed in the general well-being assessment.



Mean SOMA LENT Scores

Fig. 3. Mean late effects normal tissue-subjective, objective, management, analytic (SOMA-LENT) scores. HBO = hyperbaric oxygen.

Patient beliefs

Of the 120 patients, 72 (33 in Group 1 and 39 in Group 2) were surveyed to determine which randomization allocation they had received. In Group 1, 20 said "HBO,"1 said "sham,"and 12 "could not say."In Group 2, these numbers were 23, 2, and 14. A chi-square test detected no relationship ($p = 0.9058$) between the patient opinions and what they had actually received. When patients who "could not say"were ignored, a Kappa statistic was $p = 0.0299$, indicating essentially no agreement beyond chance.

Harms

Consistent with hyperbaric practice, ear pain/ear discomfort (ear barotrauma) was the most common complaint. Ear barotrauma represents the clinical manifestation of an imbalance of pressure between the external and middle ear spaces. It is usually limited to the tympanic membrane, occasionally involves the middle ear, and only rarely involves the inner ear. Nineteen patients (15.8%) complained of ear pain or discomfort. The otologic examination was unremarkable in 11, 7 had tympanic membrane changes consistent with barotrauma, and 1 had both tympanic membrane injury and middle ear effusion. Decongestants were effective in 8 patients, 7 underwent ventilation tube placement, and 4 did not require treatment. One patient (0.8%) complained of sinus barotrauma and was successfully treated with decongestants.

Four patients (3.3%) experienced transient myopia. This is a poorly understood process and although thought to represent an oxidative stress-induced temporary alteration in the shape of the lens (21), its exact mechanism remains obscure.

Two patients (1.7%) complained of confinement anxiety. One was treated with reassurance alone; the other required mild sedation. No cases of acute central nervous system oxygen toxicity occurred. None of these harms compromised a patient's participation in the study, and all patients completed their prescribed treatment course.

DISCUSSION

Radiation proctitis is a common unfortunate complication of pelvic radiotherapy (22). Its reported incidence ranges from 4% to 22% (5, 7, 14) and can reach 36% after combination external beam radiotherapy and brachytherapy (23). More severe forms, some of which are life-threatening, have been reported to range from 4.3% to 22% (14, 24) with resulting mortality rates of 2–8% (3, 7, 24).

Most late cases occur within 3 years of radiotherapy completion, although latencies in excess of 10 years are not uncommon (14, 22). The natural history of late radiation proctitis is unpredictable. Minor symptoms can resolve either spontaneously (4) or with conservative management (2, 25). Other seemingly minor symptoms will prove refractory to standard care, resulting in disease progression despite increasingly aggressive interventions (24), and new forms of this complication can evolve (22). Minor complaints of pain and bleeding, therefore, cannot be characterized as harmless manifestations. Serious manifestations can necessitate high-risk surgery; high risk because tissues within the operative site might have been rendered hypoxic and poorly able to support oxygen-dependent wound repair. Ultimately, and having survived cancer, some patients will die of these complications (3, 7, 24).

The clinical presentation can involve any combination of tenesmus, urgency, diarrhea, constipation, sphincter dysfunction, mucoid or bloody discharge per rectum, frank bleeding, and ulceration, which can be localized, diffuse, or full thickness. The mucosa can appear granular, friable, edematous, and pale, with prominent submucosal telangiectatic

Table 4. Frequencies of clinical evaluations by patient type

Evaluation point	Clinical evaluation findings	Group 1	Group 2
Randomization*	Healed	5	0
	Significant improvement	24	15
	Moderate improvement	27	20
	No improvement	7	21
Crossover	Healed	1	3
	Significant improvement	0	33
	Moderate improvement	1	11
	No improvement	1	6
3-mo	Healed	5	2
	Improved	31	26
	Unchanged	18	18
	Cancer recurrence	1	2
6-mo	Healed	4	3
	Improved	30	24
	Unchanged	19	17
	Cancer recurrence	2	4
1-y	Healed	5	2
	Improved	32	30
	Unchanged	17	16
	Cancer recurrence	1	2
2-y	Healed	6	1
	Improved	21	12
	Unchanged	8	11
	Cancer recurrence	1	1
3-y	Healed	2	3
	Improved	15	12
	Unchanged	3	3
	Cancer recurrence	0	0
4-y	Healed	2	2
	Improved	12	10
	Unchanged	0	3
	Cancer recurrence	0	0
5-y	Healed	1	0
	Improved	4	6
	Unchanged	1	0
	Cancer recurrence	0	1

* p Values comparing groups after randomization were 0.0009 for Fisher's exact test, 0.0011 for logistic regression analysis, and 0.0008 for Jonckheere-Terpstra test for trend.

vasculature. Pain is common, ranging from occasional and minimal to refractory and excruciating.

The histologic findings can include microvascular compromise, endothelial cell degeneration, and formation of fibrin plugs (26). Submucosal fibrosis and obliteration of small blood vessels is additional evidence of late radiation injury. This process is usually progressive and irreversible. Computed tomography can demonstrate wall thickening, edema, ulcers, stricture, and fistula (27).

The medical treatment is not well defined and, in the absence of recommendations, management is often unsatisfactory (3, 8, 12, 22). One should do everything possible to avoid disease progression, however, because abdominopelvic operations (unavailable in the presence of perforation, obstruction, and fistula) within or through irradiated tissues are fraught with complications (8, 28).

High failure rates with conventional treatment led to the use of HBO therapy. Its beneficial effect, involving mandibular osteoradionecrosis, was first reported in 1973 (29). Resulting pathologic evidence of a progressive and obliterative endarteritis in mandibular osteoradionecrosis contrasted sharply with earlier assumptions of an osteomyelitic-like process (30). The finding that HBO therapy induced angiogenesis, suggested a disease-modifying mechanism, in contrast to more conventional medical and surgical therapies directed at relief of symptoms (16, 17).

Hyperbaric oxygen therapy was first reported to have efficacy in the treatment of late radiation proctitis in 1990 (31). Since then, numerous studies have been published (Table 2). In most instances, they represented small series or single case reports, did not use a specified toxicity scale, and lacked sufficient follow-up. However, the results from this accumulated work do suggest that HBO therapy is likely to be beneficial (16, 18).

We used SOMA-LENT scoring as a primary outcome measure. This numeric evaluation of radiation morbidity is simple, widely applicable, reproducible, and provides an ascending order of severity (19). Given that several different physicians would evaluate outcomes in this multicenter study, such uniform scoring was considered essential. The radiation proctitis SOMA-LENT process scores symptoms on a severity scale of 1–4 for each of five possible symptoms and three related objective clinical signs. Six management options, scored in increasing complexity, represent the final scoring element. The analytic measures used during the diagnostic workup can be recorded but are not scored.

Often, the outcome assessment is a function of clinical impression alone. This, however, opens evaluations to differences in interpretation and has the potential for bias. We elected to include this approach as a second primary outcome measure. Perhaps not surprisingly, the resulting percentage of clinical assessments determined as healed was lower than those reported in several previous studies. The specificity of the SOMA-LENT scale is such that an excellent healing response does not always result in a score of 0 (healed). A final response score of 2–3 might reflect a patient who, on presentation had a score of 15 for ulceration, intense pain, and persistent bleeding, required treatment with narcotics, occasional transfusions, and steroids, and whose post-treatment status became one of diet modification, twice-daily stool frequency, and an occasional non-narcotic analgesic. The clinical impression of this case would be one of "healed"by many. In the present trial, however, the clinical assessor also conducted each SOMA-LENT analysis. Recognizing that the score was not 0, the assessor might have been inclined to categorize the clinical outcome as something less than healed (e.g., significantly improved).

The effect of HBO therapy, scored through the SOMA-LENT process, throughout the 5-year study period is shown in Fig. 3. Although the number of patients at Years 2–5 was 58%, 36%, 27%, and 13% of those at Year 1, respectively, a clear trend was seen toward continued and enduring healing.

A patient's perception of how effective a particular treatment is now represents one important element of the modern application of evidence-based medicine (32). The QOL effect of eliminating pain, minimizing hemorrhage, and normalizing stool frequency is obviously important. This effect was

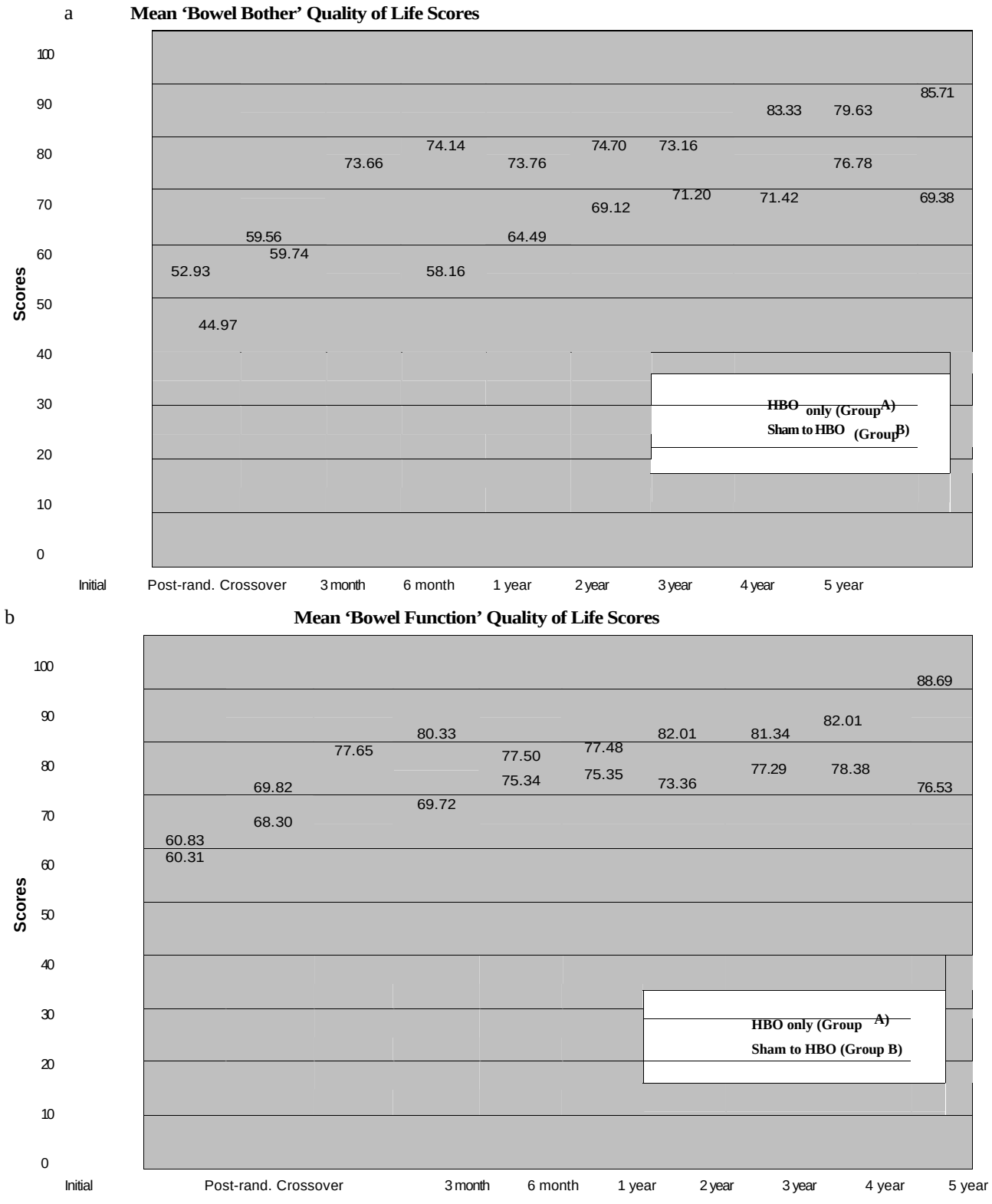


Fig. 4. (a) Bowel bother and (b) bowel function quality of life scores. HBO = hyperbaric oxygen.

evidenced by a significant improvement in the QOL recorded after receipt of HBO therapy in each group. The values continued to improve in Group 1 throughout the 5-year study period for bowel bother and bowel function. In Group 2, bowel bother continued to improve, and bowl function stabilized at its 1 year value throughout the remainder of the study (Fig. 4).

One final observation of some importance was an association between failure to respond and a finding of local recurrence or residual tumor. Three patients were diagnosed

with recurrence during the treatment phase. Eleven others were diagnosed during follow-up, for a recurrence rate of 11.7%. The SOMA-LENT scores in these patients had either remained elevated or improved, only to acutely deteriorate, by an average of 9 points (range, 4–17), by the time the recurrence was diagnosed.

In our study, approximately 45% of those patients without a treatment response were diagnosed with local recurrence. This finding argues for a measured approach to hyperbaric dosing. Ordering an initial hyperbaric course of more than 40 sessions is inadvisable. If little or no subsequent improvement occurs, workup for cancer recurrence should occur before any further hyperbaric treatments.

Hyperbaric oxygen therapy was well tolerated and its safety profile proved encouraging. These findings are consistent with standard practice, with hyperbaric medicine considered low risk. Predictably, no cases of oxygen toxicity developed. This was one of our study's safety goals, with the resulting treatment pressure selection of 2.0 ATA.

A patient's perception of how well, or otherwise, a specific therapy effects their daily living and overall QOL has only recently been recognized as an important outcome measure (32). In our study, patients considered HBO therapy to have an important positive effect on their QOL when measured against their primary complaint.

When numerous therapeutic options exist for a given condition, responsible resource expenditure assumes increasing importance. Although hyperbaric medicine's costs are not insignificant, its employment has resulted in an overall lowering of a patient's total healthcare financial burden (33, 34). Much of this cost reduction is achieved by avoiding repeated hospitalizations and surgeries, because greater disease resolution rates are effected. Such savings support a preference for disease-modifying interventions rather than those directed at relief of symptoms. The immediate and enduring effect of HBO therapy on the resolution or reduction in the degree of radiation proctitis would be expected to have a corresponding positive effect on the overall cost of care. Although we did not incorporate an economic analysis in this trial, several assumptions can be made. First, because disease progression is not uncommon (2, 9), avoiding it would be expected to result in a corresponding decrease in the healthcare costs necessary to manage advancing degrees of morbidity and the costs associated with management failure. Second, a reduction in disease severity, or its resolution, likewise would reduce the subsequent costs. Using the example of the mean improvement in SOMA-LENT change at 1 year in our trial, an index patient's requirements would change from repeated rectal examinations, regularly administered narcotics, multiple daily antidiarrheal agents and steroid enemas to occasional antidiarrheal agents, diet modification, and perhaps a stool softener. The financial implications related to this change in medical management are readily calculable.

CONCLUSION

The results of our study have shown that the provision of HBO therapy for patients with chronic refractory radiation proctitis resulted in significantly improved and enduring healing responses and enhanced QOL. Our results support the role of HBO therapy for soft-tissue radionecrosis.

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APPENDIX

The clinical evaluation team included Dr. Fulya Yaman Agaoglu, Dr. Ridvan Avul, Dr. Robyn Cheuk, Dr. Yavuz Dizdar, Dr. Aaron Gonzalez, Dr. Susan Houldsworth, Dr. Esra Kaytan, Dr. Everine Klopper, Mr. Robert Lincacre, Dr. James Mackean, Dr. Robbie de Meulenare, Dr. Aida Mota, Dr. Gonzalo Montalvo, Dr. Browwyn Mueller, Dr. Binnur Pinarbasi, Dr. Ken Purdie, Dr. Marlene Soares, Dr. John Stephenson, Dr. Colin Tang, Dr. Cherian Varughese, Dr. Albert Verbeek, Dr. Margaret Wallington, and Dr. Alida Wolvaardt. The study monitors included Ms. Guillermina Silva, Lic.Enf., Dr. Baris Pekicten, Mr. Stephen Goble, and Ms. Surita Fitchat, R.N.

Table 3. Patient demographics

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments: Surgery (type)	Cancer treatments: Chemotherapy (type/dose)	Cancer treatments: RT/dosage	Time to LENT diagnosis (mo)*	LENT presentation	Previous LENT treatment[y]	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
PROC 001B	F	3/16/1998	Uterine cervix	SCC/IIIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,031.75 cGy	12	Diarrhea, hemorrhage, stricture	2, 5	Never	No	No	No
PROC 002B	F	2/26/1999	Uterine cervix	AC/IIb	Hysterectomy + BSO	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,500 cGy	16	Hemorrhage	2	Never	No	No	No
PROC 003A	F	12/8/1999	Uterine cervix	SCC/IIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 2,689 cGy	12	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 004A	F	11/26/1998	Uterine cervix	AC/Ib2	Hysterectomy + BSO	No	X-ray, 4,600 cGy (200 cGy x 23 fractions) Brachytherapy, 3,344 cGy	16	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 005A	F	6/9/1999	Uterine cervix	SCC/IIIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,961 cGy	13	Pain, hemorrhage	2	Never	No	No	No
PROC 006A	F	11/4/1999	Uterine cervix	SCC/IIa	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,695 cGy	13	Hemorrhage	2	Never	No	No	No
PROC 007B	F	2/11/2000	Uterine cervix	AC/IIb	Extrafascial hysterectomy	No	X-ray, 5,000 cGy (200 cGy x 16 + 300 cGy x 8) Brachytherapy, 2,571 cGy	10.5	Pain, hemorrhage, ulceration, stricture	2, 12 (Diet)	Never	No	No	Yes
PROC 008B	F	8/11/1995	Uterine cervix	SCC/Ib2	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 2,848 cGy	14	Hemorrhage	1, 2, 12 (Sucralfate)	Never	No	No	Yes
PROC 009A	F	8/24/1999	Uterine cervix	SCC/IIIb	No	Cisplatin/ 250 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,841 cGy	6	Hemorrhage	2	Never	No	No	No

(Continued)

PROC 010B	F	12/17/1999	Uterine cervix	SCC/IIIb	No	Cisplatin/ 360 mg	X-ray, 5600 cGy (200 cGy x 28 fractions) Brachytherapy, 3,600 cGy	12	Hemorrhage	2	Never	No	No	No
PROC 011A	F	10/24/1994	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,653 cGy	13	Hemorrhage	2	Never	No	No	No
PROC 012B	F	12/1/1999	Uterine cervix	SCC/IIa	No	Cisplatin/ 420 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,335 cGy	14	Hemorrhage, wall changes (fibrotic)	1				
PROC 013A	F	1/19/2000	Uterine cervix	SCC/IIb	No	No	X-ray, 4800 cGy (300 cGy x 16 fractions) Brachytherapy, 3,000 cGy	14	Hemorrhage	4	Never	No	Yes	No
PROC 014B	F	4/21/1998	Uterine cervix	SCC/Ib1	Hysterectomy + BSO	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,885 cGy	35	Pain, hemorrhage, Unspecific chronic colitis	2, 12 (Diet, steroid enema)	Never	Yes	No	No
PROC 015A	F	4/13/2000	Uterine cervix	SCC/Ib2	Radical hysterectomy and pelvic lymphadenectomy	No	X-ray, 4,900 cGy (300 cGy x 7 fractions + 200 cGy x 14 fractions) Brachytherapy, 3,673 cGy	14	Diarrhea, pain, hemorrhage, stricture, mild chronic colitis	2	Never	No	No	Yes
PROC 016B	F	8/20/1998	Uterine cervix	SCC/Ib1	Abdominal hysterectomy	No	X-ray, 5,040 cGy (180 cGy x 28 fractions) Brachytherapy, 2,904 cGy	14.5	Hemorrhage, Chronic cystitis	11, 12 (Sucralfate and cystitis after RT with dimethyl sulfoxide)	Never	No	No	Yes
PROC 017B	F	11/8/1999	Uterine cervix	SCC/IIIb	No	Cisplatin/ 360 mg	X-ray, 6,520 cGy (200 cGy x 29 fractions + 180 cGy x 4 fractions) Brachytherapy, 2,031 cGy	19	Diarrhea, pain, hemorrhage, ulceration	2, 11, 12 (Steroids, Bicap)	Never	No	No	No
PROC 018B	F	6/29/2000	Uterine cervix	SCC/Ib2	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 4,329 cGy	11.5	Pain, hemorrhage, ulceration, Chronic mild colitis.	2	Never	No	No	No
PROC 019A	F	4/4/2000	Uterine cervix	SCC/Ib2	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 4,685 cGy	8	Diarrhea, hemorrhage, chronic ileocolitis, enteritis	2, 12 (Sucralfate)	Never	No	No	Yes

(Continued)

Table 3. Patient demographics (continued)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments			Time to LENT diagnosis (mo)*	LENT presentation	Previous LENT treatment†	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
					Surgery (type)	Chemotherapy (type/dose)	RT/dosage							
PROC 020A	F	10/1/1998	Uterine cervix	AC/IIb	Complementary TAH	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,503 cGy	17.5	Hemorrhage	2, 11	Never	Yes	No	No
PROC 021A	F	7/21/1999	Uterine cervix	ASCC/IIIb	Complementary TAH	Cisplatin/ 300 mg	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 3,808 cGy	15.5	Hemorrhage	2	Current use	Yes	Yes	Yes
PROC 022B	F	9/8/1999	Uterine cervix	SCC/IIb	No	Cisplatin/ 360 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,276 cGy	13	Hemorrhage	2	Never	No	No	No
PROC 023B	F	11/1/1999	Uterine cervix	SCC/IIb	No	No	X-ray, 4,600 cGy (200 cGy x 23 fractions) Brachytherapy, 6,696 cGy	17	Hemorrhage	2	Never	Yes	Yes	No
PROC 024A	F	4/23/1999	Uterine cervix	SCC/IIb	No	Irinotecan/ 1,478 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,853 cGy	27	Diarrhea, hemorrhage	2, 5	Never	Yes	No	No
PROC 025A	F	3/16/2000	Uterine cervix	SCC/Ib2	No	No	X-ray, 4,599.9 cGy (242.1 cGy x 19 fractions) Brachytherapy, 3,239.5 cGy	17.5	Hemorrhage, ulceration	2	Current use	No	Yes	No
PROC 026A	F	6/12/2000	Uterine cervix	SCC/IIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,500 cGy	12	Hemorrhage, ulceration	2, 12 (Diet)	Never	No	No	No
PROC 027B	F	7/4/2000	Uterine cervix	SCC/IIIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,729 cGy	10.5	Hemorrhage, ulceration	12 (Pentoxyphiline, tocopherol)	Past use	No	No	No
PROC 028B	F	7/3/2000	Uterine cervix	SCC/IIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,577 cGy	14.5	Pain	2	Never	No	No	No

(Continued)

Table 3. Patient demographics (continued)

PROC 029A	F	11/1/1999	Uterine cervix	SCC/Ib2	No	Cisplatin/ 300 mg	X-ray, 4,600 cGy (200 cGy x 23 fractions) Brachytherapy, 3300 cGy	4.5	Hemorrhage, ulceration, Concurrent cystitis	2	Never	Yes	No	Yes
PROC 030B	F	8/2/1999	Uterine cervix	SCC/Ib2	No	Cisplatin/ 50 mg	X-ray, 5,200 cGy (400 cGy x 3 + 200 cGy x 20 fractions) Brachytherapy, 3,500 cGy	21	Diarrhea, hemorrhage	2, 12 (Diet)	Never	No	No	No
PROC 031A	F	5/15/2000	Uterine cervix	SCC/IIb	No	No	X-ray, 4,800 cGy (300 cGy x 16 fractions) Brachytherapy, 3,500 cGy	15.5	Hemorrhage, ulceration	12 (Ferrous sulfate and diet)	Never	Yes	No	No
PROC 032B	F	7/24/2000	Uterine cervix	SCC/IIIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,227 cGy	8	Hemorrhage, stricture	2, 12 (Diet and metronidazole)	Never	No	No	No
PROC 033A	F	6/29/2000	Uterine cervix	SCC/IIIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,500 cGy	8	Diarrhea, pain, hemorrhage	2	Past use	Yes	Yes	No
PROC 034A	F	1/24/2000	Uterine cervix	SCC/IIb	No	Cisplatin/ 360 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 4,352 cGy	10	Hemorrhage	11	Never	No	Yes	No
PROC 035B	F	5/2/2000	Uterine cervix	SCC/Ib2	No	No	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 3,119 cGy	13.5	Hemorrhage, ulceration, stricture	2, 11	Never	No	No	Yes
PROC 036B	F	11/11/1999	Uterine cervix	SCC/IIIb	No	Cisplatin/ 360 mg	X-ray, 5600 cGy (200 cGy x 28 fractions) Brachytherapy, 3,800 cGy	2.5	Hemorrhage	2	Never	No	No	No
PROC 037B	F	10/20/1999	Uterine cervix	SCC/IIIb	No	No	X-ray, 6,000 cGy (200 cGy x 30 fractions)	22	Hemorrhage	2	Current use	No	No	No
PROC 038B	F	4/14/2000	Uterine cervix	SCC/IIa	TAH	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,928 cGy	14.5	Hemorrhage	2, 12 (Diet)	Never	No	No	Yes
PROC 039A	F	2/12/2001	Uterine cervix	ASCC/Ib2	TAH	No	X-ray,5,000cGy (200 cGy x 19 + 400 cGy x 3 fractions)	11	Hemorrhage, ulceration, stricture	12 (Ferrous Sulfate)	Never	No	No	No

Table 3. Patient demographics (continued)

	Brachytherapy, 3,500 cGy

(Continued)

Table 3. Patient demographics (continued)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer treatments: Cancer type/stage	Surgery (type)	Chemotherapy (type/dose)	RT/dosage	Time to LENT diagnosis (mo)*	LENT presentation	Previous LENT treatment[y]	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
PROC 040A	F	9/9/1999	Uterine cervix	SCC/IIb	No	No	X-ray, 5200 cGy (200 cGy x 20 + 400 cGy x 3 fractions) Brachytherapy, 3,792 cGy	14	Hemorrhage	2, 11	Never	No	No	Yes
PROC 041B	F	12/13/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 7,000 cGy (200 cGy x 35 fractions)	6	Pain, hemorrhage	2	Never	No	No	No
PROC 042B	F	8/25/1997	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,600 cGy (200 cGy x 28 fractions) Brachytherapy, 3,000 cGy	53.5	Hemorrhage, ulceration	2	Never	Yes	No	Yes
PROC 043A	F	2/28/2001	Uterine cervix	SCC/IIb	No	Cisplatin/ 350 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2162 cGy	13.5	Hemorrhage	12 (Diet)	Past use	No	No	No
PROC 044A	F	2/28/2001	Uterine cervix	SCC/IIb	No	Cisplatin/ 350 mg	Brachytherapy, 3654 cGy	15.5	Hemorrhage	2	Past use	No	No	Yes
PROC 045B	F	10/29/1999	Uterine cervix	SCC/IIIb	No	No	X-ray, 6,600 cGy (200 cGy x 33 fractions) Brachytherapy, 3,500 cGy	44.5	Diarrhea, hemorrhage	2, 5	Past use	No	No	Yes
PROC 046A	F	7/23/2001	Uterine cervix	SCC/IIb	No	Cisplatin/ 360 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2879 cGy	10.5	Diarrhea, pain, hemorrhage, ulceration, stricture	3	Past use	No	No	No
PROC 047A	F	4/18/2000	Uterine cervix	ASCC/Ib1	No	No	X-ray, 7,000 cGy (200 cGy x 25 + 200 cGy x 10 fractions)	26.5	Bleeding, metabolic disorder	12 (Diet)	Never	Yes	No	Yes
PROC 048B	M	10/7/2000	Prostate	AC	No	No	X-ray, 6,840 cGy (180 cGy x 38 fractions)	17	Diarrhea, pain, hemorrhage, fistula, edematous wall changes	2, 3	Current use	No	Yes	No
PROC 049A	F	6/1/2001	Uterine cervix	SCC/IIIb	No	Cisplatin/ 200 mg	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 3,704 cGy	13	Diarrhea, pain, hemorrhage, ulceration, stricture	2	Never	No	No	Yes

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PROC 050B	F	6/23/1997	Uterine cervix	SCC/IIa	No	No	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 3,493 cGy	51.5	Hemorrhage	2, 12 (Diet)	Never	No	No	Yes
PROC 051B	F	4/30/2001	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,956 cGy	12.5	Pain, ulceration	1	Never	No	No	Yes
PROC 052A	F	5/7/2001	Uterine cervix	SCC/IIa	No	Cisplatin/ 350 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,331 cGy	18.5	Diarrhea, pain, hemorrhage, ulceration	2	Past use	No	No	Yes
PROC 053B	F	4/14/2000	Uterine cervix	SCC/IIb	TAH	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,670 cGy	20	Hemorrhage	2	Never	No	Yes	No
PROC 054A	F	12/3/2002	Uterine cervix	Cancer epidermoid/IIb	No	No	X-ray, 7600 cGy (200 cGy x 38 fractions) Brachytherapy, 2,486 cGy		Hematuria	12 (Diet)	Never	No	No	No
PROC 055A	F	3/14/2001	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,578 cGy	12	Hemorrhage	2	Never	No	No	No
PROC 056B	F	3/3/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,100 cGy (300 cGy x 17 fractions) Brachytherapy, 3,400 cGy	16.5	Hemorrhage	1	Never	No	No	No
PROC 057A	F	9/3/1984	Uterine cervix	SCC/IIa	No	No	X-ray, 4,600 cGy (200 cGy x 23 fractions) Brachytherapy, 3,456 cGy	28	Hemorrhage	12 (Diet)	Never	No	No	No
PROC 058A	F	11/8/2000	Uterine cervix	SCC/Ib2	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,785 cGy	12.5	Hemorrhage	12 (Steroid use)	Never	No	No	Yes
PROC 059B	F	11/14/2000	Uterine cervix	SCC/Ib1	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,777 cGy	18	Hemorrhage	12 (Steroid use)	Never	No	Yes	Yes
PROC 060B	F	11/30/2000	Uterine cervix	SCC/IIIb	No	Cisplatin/ 240 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,022 cGy	16.5	Cramping, pain, hemorrhage	2, 12 (Diet, steroid enema)	Never	No	No	No

(Continued)

Table 3. Patient demographics (continued)

Patient ID	Gender	Cancer diagnosis date	Cancer Tumor location	Cancer type/stage	Cancer treatments Surgery (type)	Chemotherapy (type/dose)	RT/dosage	Time to LENT diagnosis (mo)*	LENT presentation	Previous LENT treatment†	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
PROC 061A	F	1/3/2001	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 4,238 cGy	16	Diarrhea, hemorrhage, cramping	2	Never	No	No	No
PROC 062B	F	11/26/1998	Uterine cervix	SCC/Ib2	No	No	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 3,562 cGy	10.5	Hemorrhage	2	Never	No	Yes	Yes
PROC 063A	F	12/13/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,517 cGy	19.5	Hemorrhage	2	Never	No	No	Yes
PROC 064B	F	9/24/1999	Uterine cervix	SCC/IIb	No	Cisplatin/ 420 mg	X-ray, 5600 cGy (200 cGy x 28 fractions) Brachytherapy, 3,122 cGy	14	Diarrhea, pain, hemorrhage	2	Never	No	No	No
PROC 065A	F	11/6/2001	Uterine cervix	SCC/IIb	Radical hysterectomy	Cisplatin/ 420 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions)	8.5	Hemorrhage, edematous wall change	2	Never	No	No	Yes
PROC 066A	M	5/1/2001	Prostate	AC	No	No	X-ray, 6840 cGy (180 cGy x 38 fractions)	19	Hemorrhage, ulceration, Wall changes (Mucosal thickening)	2	Current use	No	Yes	No
PROC 067B	F	7/16/2001	Uterine cervix	SCC/IIb	No	Cisplatin/ 390 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,549 cGy	9	Pain, hemorrhage, ulceration, stricture	2	Never	No	No	No
PROC 068B	F	11/21/2001	Uterine cervix	SCC/IIIb	No	Carboplatin/ 450 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,488 cGy	16	Hemorrhage, ulceration, edematous wall changes	2	Never	Yes	No	Yes
PROC 069A	F	12/11/2001	Uterine cervix	SCC/IIb	No	Cisplatin/ 300 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,321 cGy	8.5	Diarrhea, hemorrhage	2	Never	No	Yes	Yes
PROC 070B	F	9/20/2002	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 4,027 cGy	13.5	Constipation, hemorrhage, ulceration	2	Never	No	Yes	No

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PROC 071A F 11/21/2001 Uterine cervix	SCC/IIb	No	Cisplatin/ 350 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,209 cGy	13.5	Hemorrhage	2	Never	No	No	No
PROC 072B F 6/20/2001 Uterine cervix	SCC/IIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,529.68 cGy	3.5	Hemorrhage	12 (Diet)	Never	Yes	No	Yes
PROC 073B M 10/28/1998 Rectum	AC	Low anterior resection + end-to-end anastomoses	FU (400 mg) + FA (20 mg)	X-ray, 5040 cGy (180 cGy x 28 fractions)	44	Pain, hemorrhage, stricture, wall changes (edematous, fibrotic)	NA	Past use	No	Yes	No
PROC 074B F 4/5/2002 Uterine cervix	Other (glassy cells)/IIb	Hysterectomy + BSO	PVC (before RT, platinum 150 mg, after RT vincristine 400 mg 400 mg with platinum 40 mg)	X-ray, 5,312 cGy (180 cGy x 29 fractions) Brachytherapy, 6,804 cGy	17.5	Hemorrhage	2	Never	No	No	No
PROC 075A F 7/26/2000 Uterine cervix	SCC/IIb	No	Cisplatin/300 mg	X-ray, 5,000 cGy (200 cGv x 25 fractions) Brachytherapy, 3,085 cGy	16.5	Hemorrhage, ulceration, stricture	2, 12 (Dilatation)	Never	No	No	No
PROC 076A F 4/18/2002 Uterine cervix	ASCC/IIIb	No	Cisplatin/300 mg	X-ray, 6,000 cGy (200 cGy x 30 fractions)	16	Hemorrhage	2	Never	No	No	Yes
PROC 077A F 5/3/2002 Uterine corpus	AC	TAH	Cisplatin/ 450mg+ Cyclophosphamide/ 4,500 mg	X-ray, 5400 cGy (200 cGy x 27 fractions) Brachytherapy, 3,486 cGy	17.5	Constipation, hemorrhage ulceration	2, 12 (Metronidazole)	Never	No	No	No
PROC 078B F 6/11/2000 Uterine cervix	SCC/IIIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,781 cGy	9.5	Hemorrhage	2, 12 (Diet)	Never	No	No	Yes
PROC 079A F 3/3/2003 Uterine cervix	SCC/IIIa	No	Cisplatin/350 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,750 cGy	10	Diarrhea, Constipation, pain, Hemorrhage, wall changes (edematous, mucosal thickening), other (hyperemia, erosions)	2, 3, 5, 12 (Steroid enema)	Never	No	No	Yes
PROC 080B F 5/20/2002 Uterine cervix	SCC/IIIb	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,077 cGy	19	Hemorrhage	2, 12 (Steroid enema)	Never	No	No	No

(Continued)

Table 3. Patient demographics (continued)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments: Surgery (type)	Cancer treatments: Chemotherapy (type/dose)	Cancer treatments: RT/dosage	Time to LENT diagnosis (mo)*	LENT presentation	Previous LENT treatment[y]	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
PROC 081A	F	5/10/2001	Uterine corpus	AC	Hydrothermal ablation	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,751 cGy	14	Hemorrhage	2	Never	No	No	No
PROC 082A	F	1/7/2002	Uterine corpus	AC	TAH	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,462 cGy	22	Hemorrhage	2	Never	Yes	Yes	No
PROC 083B	F	9/2/2002	Uterine cervix	SCC/IIIb	No	Gemzar/ 2700 mg	X-ray, 5,600 cGy (200 cGy x 28 fractions) Brachytherapy, 2,132 cGy	11.5	Hemorrhage	2	Never	No	No	Yes
PROC 084B	F	2/15/2003	Uterine corpus	AC	TAH	No	X-ray, 5040 cGy (180 cGy x 28 fractions) Brachytherapy, 1,800 cGy	12.5	Cramping, constipation, pain, hemorrhage, ulceration, endarteritis, wall changes (edematous)	3, 12 (Coagulation by adrenaline injection and heater probe)	Never	No	No	Yes
PROC 085A	F	1/25/2002	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,817 cGy	19.5	Hemorrhage	2	Never	No	No	No
PROC 086B	F	1/21/2003	Uterine corpus	AC	TAH + BSO, node sampling	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 5,000 cGy	10.5	Pain, hemorrhage, ulceration	NA	Never	No	No	Yes
PROC 087B	F	7/2/2002	Uterine corpus	AC	TAH	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,775 cGy	8	Hemorrhage	2	Never	No	No	No
PROC 088A	F	7/5/2002	Uterine cervix	SCC/IIa	No	Carboplatin/ 200 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,827 cGy	8.5	Hemorrhage	2	Never	Yes	Yes	Yes
PROC 089B	F	5/24/2002	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,153 cGy	19.5	Hemorrhage	2	Never	No	No	No

(Continued)

PROC 090A	F	5/20/2001	Uterine cervix	SCC/IIIa	Cone biopsy	Cisplatin/390 mg	X-ray, 5,500 cGy (183.33cGy x 30 fractions) Brachytherapy, 2,000 cGy	14	Cramping, pain, stricture, Perforation	12 (Diet)	Current use	No	No	No
PROC 091B	F	3/26/2001	Uterine cervix	SCC/IIIb	No	No	Co60 (pendulum), 6,750 cGy (250 cGy x 27 fractions)	29.5	Pain, hemorrhage, ulceration	5	Never	No	No	Yes
PROC 092A	M	3/28/2003	Prostate	AC	No	No	X-ray, 7,200 cGy (200 cGy x 36 fractions)	11	Pain, hemorrhage, ulceration	2, 5	Past use	No	Yes	No
PROC 093B	F	10/1/1990	Uterine corpus	Carcinosarcoma (mixed malignant mullerian tumor)	TAH + BSO, lymphadenectomy	Cisplatin Adriamycin (dose unknown)	X-ray, 4,500 cGy (1.8cGy x 25 fractions) Brachytherapy, 6,000 cGy	106	Diarrhea, vomiting, pain, Cramping, hemorrhage	3, 4, 5	Past use	No	No	No
PROC 094A	F	4/4/2003	Uterine cervix	SCC/IIb	No	Cisplatin/280 mg	X-ray, 5,000 cGy (400 cGy x 3 + 200 cGy x 19 fractions) Brachytherapy, 3,147 cGy	8.5	Hemorrhage, ulceration	2	Past use	No	No	No
PROC 095A	F	4/24/2002	Uterine corpus	Adenosarcoma	TAH + BSO	No	X-ray, 6,400 cGy (200 cGy x 32 fractions)	11	Pain, hemorrhage, wall changes (edematous)	1, 2	Never	No	No	Yes
PROC 096B	F	1/7/2000	Uterine cervix	SCC/IIIb	No	No	X-ray,5,600cGy (200 cGy x 28 fractions) Brachytherapy, 3,100 cGy	27	Hemorrhage	2, 12 (Diet)	Never	No	No	No
PROC 097B	M	5/28/1999	Prostate	AC	No	No	X-ray, 7,400 cGy (200 cGy x 37 fractions)	61	Constipation, pain, hemorrhage, endarteritis	2, 5	Past use	No	Yes	No
PROC 098A	M	2/13/2002	Prostate	AC	No	Neoadjuvant hormonal therapy	X-ray, 7,200 cGy (180 cGy x 40 fractions)	10.5	Cramping, pain, hemorrhage, hypocellularity, hypovascularity, wall changes (edematous)	2, 5	Past use	No	No	No
PROC 099A	F	12/6/2000	Uterine cervix	SCC/IIb	No	Cisplatin/ 170 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,990 cGy	16	Diarrhea, pain, hemorrhage	2	Never	No	No	No
PROC 100A	F	11/7/2002	Uterine cervix	AC	No	Cisplatin/ 360 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,521 cGy	10.5	Hemorrhage, ulceration	2	Never	No	No	Yes
PROC 101A	F	9/3/2002	Uterine cervix	SCC/IIb	No	Cisplatin/ 190 mg	X-ray, 4,230 cGy (176.2cGy x 24 fractions)	20.5	Diarrhea, cramping, pain	2, 3, 5	Current use	Yes	No	No

Table 3. Patient demographics (continued)

	Brachytherapy, 4,500 cGy

(Continued)

Table 3. Patient demographics (continued)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments			Time to LENT diagnosis (mo)*	LENT presentation	Previous LENT treatment[y]	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
					Surgery (type)	Chemotherapy (type/dose)	RT/dosage							
PROC 102A	M	1/28/2003	Prostate	AC	No	No	X-ray, 7,000 cGy (200 cGy x 35 fractions)	18	Constipation, pain, hemorrhage, ulceration	1, 2, 3	Current use	No	No	No
PROC 103B	F	4/26/2003	Uterine cervix	SCC/IIIb	No	Cisplatin/ 55 mg	X-ray, 6,750 cGy (250 cGy x 27 fractions)	17	Cramping, pain, hemorrhage	2	Past use	No	No	Yes
PROC 104B	F	1/1/2000	Uterine cervix	AC	TAH, pelvic node dissection and omental biopsy	No	X-ray, 5,250 cGy (175 cGy x 30 fractions)	8	Diarrhea, cramping, ulceration, stricture, Endarteritis, hypocellularity, hypovascularity.	2, 5, 7	Never	No	Yes	No
PROC 105B	F	9/1/2000	Uterine cervix	SCC/Ib1	TAH + BSO	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,000 cGy	13	Diarrhea, cramping, pain, hemorrhage, wall changes (edematous, fibrous), other (telangeictasia, regional atrophy)	1, 2	Current use	No	No	No
PROC 106A	F	12/21/2003	Endometrium	AC	Radical hysterectomy + bilateral iliac lymph node dissection	No	X-ray, 5,000 cGy (200 cGy x 25 fractions)	9	Vomiting, constipation, pain, hemorrhage, ulceration, stricture, wall changes (edematous, fibrotic)	NA	Past use	No	Yes	Yes
PROC 107B	F	2/19/2003	Uterine cervix	SCC/IIa	No	No	X-ray, 5,800 cGy (200 cGy x 25 fractions + 800 cGy) Brachytherapy, 2,959 cGy	15.5	Hemorrhage	2, 12 (Diet)	Never	No	No	Yes
PROC 108A	F	2/8/2002	Uterine corpus	AC	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,660 cGy	12.5	Hemorrhage	2	Never	No	No	Yes
PROC 109A	F	6/10/2002	Uterine corpus	AC	TAH + BSO	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,200 cGy	28.5	Vomiting, cramping, pain, Constipation, hemorrhage, ulceration, wall changes (edematous, fibrotic)	1, 2	Never	No	Yes	Yes

(Continued)

Table 3. Patient demographics (continued)

PROC 110A	F	2/13/2002	Uterine cervix	SCC/IIb	Radical hysterectomy	Cisplatin/55 mg & Gemzar/175 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,585 cGy	21.5	Hemorrhage	2	Never	No	No	No
PROC 111B	F	2/20/2003	Uterine cervix	AC	Radical hysterectomy	Carboplatin/ 350 mg	X-ray, 7,000 cGy (200 cGy x 35 fractions)	12.5	Hemorrhage	2	Never	No	No	Yes
PROC 112B	F	8/8/2003	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,547 cGy	17.5	Hemorrhage	2	Never	No	No	No
PROC 113B	F	5/14/2003	Uterine cervix	SCC/IIIa	No	Cisplatin/ 300 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,954 cGy	10.5	Hemorrhage	2	Never	No	Yes	No
PROC 114B	F	1/16/2003	Uterine cervix	SCC/IIIb	No	No	X-ray, 6,750 cGy (250 cGy x 27 fractions)	17	Diarrhea, pain, hemorrhage	2, 3, 5	Never	No	No	Yes
PROC 115A	F	4/14/2003	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,250 cGy (250 cGy x 21 fractions)	16	Diarrhea, pain, hemorrhage	2, 5	Never	No	No	Yes
PROC 116A	M	5/1/2002	Prostate	AC	No	Hormonal therapy	X-ray, 7,000 cGy (200 cGy x 35 fractions)	23.5	Hemorrhage, wall changes (edematous)	NA	Never	No	No	No
PROC 117A	M	8/1/1987	Colon	AC	Resection with colostomy	No	X-ray, dosage unknown	126	Diarrhea, cramping, pain, Constipation, hemorrhage	3, 5, 7, 9	Never	No	No	No
PROC 118B	M	5/1/2003	Prostate	AC	Transurethral resection	Casodex/50 mg lucrin depot 3 M/ 11.25 mg	X-ray, 6,480 cGy (180 cGy x 36 fractions)	17	Constipation, pain, Hemorrhage, ulceration, Wall changes (Pale, edematous, Fibrotic)	2	Never	Yes	No	No
PROC 119B	F	1/24/2004	Uterine cervix	SCC/Ib1	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,900 cGy	10.5	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 120A	M	NA	Prostate	AC	No	No	X-ray, 6600 cGy (200 cGy x 33 fractions)	NA	Diarrhea, cramping, pain	NA	Never	No	No	No
PROC 121B	F	6/6/2003	Uterine cervix	SCC/Ib2	TAH	Cisplatin/330 mg	X-ray, 5199cGy (173.3cGy x 30 fractions) Brachytherapy, 1,800 cGy	17.5	Diarrhea, cramping, pain, constipation, ulceration, stricture, wall changes	5, 12 (Analgesic: morphine)	Never	No	No	No

Table 3. Patient demographics (continued)

										(edematous, mucosal thickening)	

(Continued)

Table 3. Patient demographics (continued)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments: Surgery (type)	Cancer treatments: Chemotherapy (type/dose)	Cancer treatments: RT/dosage	Time to LENT diagnosis (mo)*	LENT presentation	Previous LENT treatment[y]	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
PROC 122A	F	1/14/2002	Uterine cervix	SCC/IIIb	No	Carboplatin/ 1505 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,860 cGy	18	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 123A	F	3/14/2002	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,750 cGy	18.5	Diarrhea, pain, hemorrhage, ulceration, wall changes (fibrotic)	1, 2, 3, 5	Never	No	Yes	Yes
PROC 124B	F	9/22/2003	Uterine cervix	SCC/IIb	No	Carboplatin/ 600 mg	X-ray, 5,000 cGy (400 cGy x 3 + 200 cGy x 19 fractions) Brachytherapy, 3,311 cGy	7.5	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 125B	F	1/27/1987	Uterine cervix	SCC/IIIb	Staging laparotomy, debulking of enlarged nodes in pelvis and transposition of left ovary	No	X-ray, 5220 cGy (180 cGy x 29 fractions) Brachytherapy, 2,100 cGy	155	Diarrhea, cramping, pain, wall changes (edematous)	1, 2, 5	Current	No	No	No
PROC 126B	F	7/15/2003	Uterine cervix	SCC/IIa	TAH + BSO	Cisplatin/ 120 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,000 cGy	12	Cramping, pain, hemorrhage	2, 3, 5	Never	No	Yes	Yes
PROC 127A	F	1/1/2004	Uterine cervix	SCC/IIIb	No	No	X-ray, 6,750 cGy (250 cGy x 27 fractions)	9	Pain, hemorrhage	2, 3, 5	Never	Yes	Yes	Yes
PROC 128A	F	8/1/2003	Uterine cervix	SCC/Ib2	No	Cisplatin/ 330 mg	X-ray, 5,600 cGy (200 cGy x 28 fractions) Brachytherapy, 3039 cGy	14	Constipation, hemorrhage	2	Never	No	No	No
PROC 129B	F	10/8/2003	Uterine cervix	ASCC/IIIb	No	Cisplatin/ 330 mg	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 2879 cGy	11.5	Hemorrhage	2	Never	No	No	No
PROC 130A	F	4/4/2004	Uterine cervix	SCC/IIb	No	Cisplatin/ 240 mg	X-ray, 5,000 cGy (400 cGy x 3 + 200 cGy x 19 fractions) Brachytherapy, 3,167 cGy	10	Pain, hemorrhage, ulceration	2	Never	No	No	Yes

(Continued)

PROC 131A	F	3/25/2002	Uterine cervix	SCC/IIIb	No	Cisplatin/ 175 mg	X-ray, 6,750 cGy (250 cGy x 27 fractions)	12.5	Cramping, pain, hemorrhage	2, 5, 10	Never	No	No	Yes
PROC 132B	F	2/7/1993	Uterine cervix	SCC/IIa	TAH	No	X-ray, 4000 cGy (160 cGy x 25 fractions) Brachytherapy dosage unknown	16.5	Diarrhea, cramping, pain, hypovascularity, wall changes (fibrotic, mucosal thickening)	2, 3, 5	Never	No	No	No
PROC 133B	F	11/19/2003	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,400 cGy (200 cGy x 27 fractions)	15	Pain, hemorrhage	2	Never	No	No	Yes
PROC 134A	F	7/28/2003	Uterine cervix	SCC/IIb	No	Carboplatin/ 900 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,156 cGy	19	Wall changes (edematous)	2	Never	No	No	No
PROC 135B	F	9/16/2003	Uterine cervix	SCC/IIIb	No	Cisplatin/90 mg	X-ray, 6,750 cGy (250 cGy x 27 fractions)	-	Pain, hemorrhage	2	Never	No	No	Yes
PROC 136A	F	3/8/2004	Uterine cervix	SCC/?	No	No	X-ray,5,000cGy (200 cGy x 25 fractions) Brachytherapy, 3,200 cGy	15.5	Wall changes (edematous) other (telangiectasia)	2	Never	No	Yes	No
PROC 137B	M	9/1/1999	Prostate	AC	No	No	X-ray, 6,300 cGy (210 cGy x 30 fractions)	4.5	Diarrhea, cramping, pain	2, 5	Never	Yes	Yes	No
PROC 138A	M	12/15/2000	Prostate	AC	No	Hormonal therapy	X-ray, 6800 cGy (200 cGy x 34 fractions)	49.5	Cramping, pain, hemorrhage	4, 5	Past use	No	No	No
PROC 139B	F	3/30/2004	Uterine cervix	SCC/Ib2	No	Cisplatin/ 350 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,430 cGy	14	Hemorrhage	2	Never	No	No	Yes
PROC 140A	F	12/16/2003	Uterine cervix	AC	No	Cisplatin/50 mg	X-ray, 5,600 cGy (200 cGy x 28 fractions) Brachytherapy, 4,841 cGy	15.5	Hemorrhage, wall changes (edematous)	2	Never	Yes	No	No
PROC 141A	F	3/2/2004	Uterine cervix	SCC/IIb	No	Cisplatin/70 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,598 cGy	12.5	Hemorrhage, endarteritis, wall changes (edematous)	2	Never	No	No	No
PROC 142A	F	4/29/2002	Uterine cervix	Squamous transitional papilar cell carcinoma	No	Cisplatin/350 mg	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 2,625 cGy	19	Hemorrhage	2	Never	No	No	Yes
PROC 143B	F	12/8/2003	Uterine cervix	SCC/IIIb	No	Cisplatin/136 mg	X-ray, 6,750 cGy (250 cGy x 27 fractions)	17.5	Pain, hemorrhage	2, 3	Never	No	Yes	Yes

(Continued)

Table 3. Patient demographics (continued)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer treatments				Time to LENT diagnosis (mo)*	LENT presentation	Previous LENT treatment[y]	Toba use
				Cancer type/stage	Surgery (type)	Chemotherapy (type/dose)	RT/dosage				
PROC 144B	M	10/14/2003	Prostate	AC	TURP	No	X-ray, 7,000 cGy (200 cGy x 35 fractions)	11.5	Diarrhea, pain, hemorrhage, Hypocellularity, hypovascularity, wall changes (pale)	1, 2	Ne
PROC 145A	F	5/6/2004	Uterine cervix	SCC/IIb	No	Cisplatin/300 mg + gemcetabine/ 1000 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, check dosage	8.5	Hemorrhage	2	Ne
PROC 146A	M	10/17/2003	Prostate	AC	No	No	X-ray, 4,500 cGy (180 cGy x 25 fractions)	9	Diarrhea, cramping, pain, hemorrhage, wall changes (edematous)	2	Past
PROC 147B	F	3/10/2003	Rectum	AC	Low anterior resection	5-FU/15 g	X-ray, 5,040 cGy (180 cGy x 28 fractions)	9.5	Diarrhea, constipation, pain, hemorrhage, ulceration	NA	Ne
PROC 148B	F	3/26/2004	Uterine corpus	Mix mesodermal tumor (carcinosarcoma)	TAH	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,510 cGy	13.5	Diarrhea, hemorrhage	2	Ne
PROC 149A	F	10/20/2003	Uterine cervix	SCC/IIb	No	Cisplatin/300 mg	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,562 cGy	23.5	Hemorrhage, endarteritis, wall changes (edematous)	2	Ne
PROC 150B	M	12/19/2000	Prostate	AC	No	Hormonal therapy	X-ray, 6,600 cGy (200 cGy x 33 fractions)	-	Diarrhea, cramping, hemorrhage, wall changes (pale, fibrotic, mucosal thickening)	3, 11	Ne

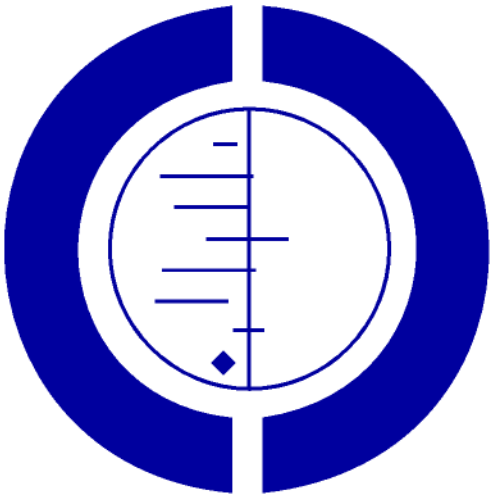
Abbreviations: RT = radiotherapy; LENT = late effects normal tissue; SCC = squamous cell carcinoma; AC = adenocarcinoma; BSO = bilateral salpingo-oophorectomy; TAH = total abdominal hysterectomy; ASCC = Adenosquamous cell carcinoma; FU = Fluorouracil; FA = Folinic acid; PVC = portal vein chemotherapy; TURP = transurethral resection of prostate.

* Rounded to nearest month.

y Previous LENT treatment: 1 = antibiotics; 2 = anti-inflammatory agent; 3 = antispasmodic agents; 4 = anticholinergic agents; 5 = antidiarrheal agents; 6 = intestinal bypass; 7 = intestinal resection; 8 = fistula repair; 9 = colostomy; 10 = ileostomy; 11 = fulguration; 12 = other.

Hyperbaric oxygen therapy for late radiation tissue injury (Review)

Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C



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Hyperbaric oxygen therapy for late radiation tissue injury (Review)

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A B S T R A C T

Background

Cancer is a significant global health problem. Radiotherapy is a treatment for many cancers and about 50% of patients having radiotherapy with be long-term survivors. Some will experience LRTI developing months or years later. HBOT has been suggested for LRTI based upon the ability to improve the blood supply to these tissues. It is postulated that HBOT may result in both healing of tissues and the prevention ofproblems following surgery.

Objectives

To assess the benefits and harms ofHBOT for treating or preventing LRTI.

Search strategy

We searched The Cochrane Central Register ofControlled Trials (CENTRAL) Issue 3, 2004, MEDLINE, EMBASE, CINAHL and DORCTHIM (hyperbaric RCT register) in September 2004.

Selection criteria

Randomised controlled trials (RCTs) comparing the effect of HBOT versus no HBOT on LRTI prevention or healing.

Data collection and analysis

Three reviewers independently evaluated the quality of the relevant trials using the guidelines ofthe Cochrane Handbook Clarke 2003) and extracted the data from the included trials.

Main results

Six trials contributed to this review (447 participants). For pooled analyses, investigation ofheterogeneity suggested important variability between trials. From single studies there was a significantly improved chance ofhealing following HBOT for radiation proctitis (relative risk (RR) 2.7, 95% confidence Interval (CI) 1.2 to 6.0, P = 0.02, numbers needed to treat (NNT) = 3), and following both surgical flaps (RR 8.7, 95% CI 2.7 to 27.5, P = 0.0002, NNT = 4) and hemimandibulectomy (RR 1.4, 95% CI 1.1 to 1.8, P = 0.001, NNT = 5). There was also a significantly improved probability ofhealing irradiated tooth sockets following dental extraction (RR 1.4, 95% CI 1.1 to 1.7,P=0.009,NNT=4).

There was no evidence ofbenefit in clinical outcomes with established radiation injury to neural tissue, and no data reported on the use ofHBOT to treat other manifestations of LRTI. These trials did not report adverse effects.

Authors' conclusions

These small trials suggest that for people with LRTI affecting tissues of the head, neck, anus and rectum, HBOT is associated with improved outcome. HBOT also appears to reduce the chance of osteoradionecrosis following tooth extraction in an irradiated field. There was no such evidence ofany important clinical effect on neurological tissues. The application ofHBOT to selected patients and tissues may be justified. Further research is required to estabish the optimum patient selection and timing ofany therapy. An economic evaluation should be also be undertaken. There is no useful information from this review regarding the efficacy or effectiveness of HBOT for other tissues.

PLAIN LANGUAGE SUMMARY

Hyperbaric oxygen (HBO) may improve radiation injuries of the head, neck and bowel. It also appears to reduce the chance of bone death following tooth extraction.

There is a risk of serious complications developing after radiation treatment for cancer (late radiation tissue injury (LRTI). Hyperbaric oxygen therapy (HBOT) involves breathing oxygen in a specially designed chamber. It is used as a treatment to improve oxygen supply to damaged tissue and stimulate healing. We found some evidence that LRTI affecting the head, neck and lower end ofthe bowel can be improved with HBOT. There is little evidence for or against benefit in other tissues affected by LRTI. Our conclusions are based on six randomised trials with a limited number ofpatients. Further research is needed.

BACKGROUND

Cancer is a significant global health problem. According to World Health Organization statistics, more than 10 million people are diagnosed with cancer every year, and it is estimated there will be 15 million new cases every year by 2020. Cancer causes 6 million deaths everyyear or 12% ofdeaths worldwide (WHO 2004). Radiotherapy is a well-established treatment ofsuitable malignancies in a wide variety of anatomical areas. Of the approximately 1.2 million new cases of invasive cancer diagnosed annually in the USA, for example, about 50% will receive radiation therapy (Jemal 2002), and ofthese, about 50% will be long-term survivors. While radiation therapy may acutely injure any normal tissue in the path ofthe radiation, this acute injury generally resolves following completion of the treatment course. Serious, radiation-related complications developing months or years after radiation treatment, collectivelyknown as late radiation tissue injury (LRTI), are relatively rare and will significantly affect between 5% and 15% of those long-term survivors who received radiation therapy, althought the incidence varies widelywith dose, age and site (Rubin 1968; Stone 2003; Thompson 1999; Waddell 1999). Although any tissue may be affected, LRTI is in practice most common in the head and neck, chest wall, breast and pelvis - reflecting the anatomical areas most commonly irradiated and the likelihood of survival for patients treated for cancer at these anatomical sites.

When late radiation injuries occur, tissues undergo a progressive deterioration characterised by a reduction in the density of small blood vessels (reduced vascularity) and the replacement of normal tissue cells with dense fibrous tissue (fibrosis), until there is insufficient oxygen supplied to sustain normal function. This situation is frequently exacerbated by secondary damage due to infection or surgery in the affected area (Rubin 1984). This progressive and delayed radiation damage may reach a critical point where the tissue breaks down to form an ulcer or area of cell death (radiation necrosis, or radionecrosis). LRTI can affect any organ system, although some tissues are more sensitive to radiation effects than others (Thompson 1999; Trott 1984; Waddell 1999).

Historically, the management of these injuries has been unsatisfactory. LRTI may be life threatening and may significantly reduce quality of life. Conservative treatment is usually restricted to symptom management, while definitive treatment traditionally entails surgery to remove the affected part and extensive repair (Stone 2003). Surgical intervention in an irradiated field is often disfiguring and associated with an increased incidence of delayed healing, breakdown ofa surgical wound or infection.

HBOT has been proposed to improve tissue quality, promote healing and prevent breakdown of irradiated tissue fields. It may be defined as the therapeutic administration of 100% oxygen at environmental pressures greater than one atmosphere absolute (ATA). Administration involves placing the patient in an airtight vessel, increasing the pressure within that vessel, and giving 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased pressure ofoxygen to the lungs, blood and tissues. Typically, treatments involve pressurisation to between 2.0 and 2.5 ATA for periods between 60 and 120 minutes once or twice daily to a total of 30 to 60 sessions of treatment.

The intermittent application of HBO is the only intervention that has been shown to increase the number of blood vessels in irradiated tissue. This has been demonstrated by Marx in a rabbit mandibular (jaw bone) model and further confirmed by serial tissue oxygen level measurements using electrodes placed on the overlying skin (transcutaneous oximetry) in humans undergoing a course of therapy for radiation necrosis of the mandible (Marx 1988; Marx 1990). In the rabbit study, the jaw and surrounding soft tissues were heavily irradiated and one group 'rescued' with HBO six months later. The 2 control groups showed no improvement while a series of 20 sessions at 2.4 atmospheres absolute (ATA) on 100% oxygen returned the density of blood vessels to 80% of normal. In the human study, a progressive recovery of low transcutaneous oximetry readings into the normal range was achieved in a group of patients receiving therapy for underlying osteoradionecrosis (radiation necrosis ofbone).

HBOT seems most likely to achieve such improvements through a complex series of changes in affected tissues. Tissue swelling is probably improved through an osmotic effect of oxygen, while the establishment of a steep oxygen gradient across an irradiated tissue margin is a powerful stimulus to the growth of new blood vessels(Davis 1988; Hills 1999). In addition, improving oxygen

levels will improve white cell and fibroblast function, further enhancing wound healing (Mandell 1974). Improved tissue quality has been demonstrated in a model ofradiation small bowel injury (Feldmeier 1995; Feldmeier 1998).

While HBOT has been used for LRTI since at least 1975 (Mainous 1975), most clinical studies have been limited to relatively small case series or individual case reports. There have been relatively few comparative studies published, and no previous quantitative systematic reviews ofwhich we are aware. In a recent semi-quantitative review, Feldmeier and Hampson located 71 such reports involving a total of 1193 patients across 8 different tissues (Feldmeier 2002). In these patients, for whom conservative treatment had failed to improve symptoms, there were clinically significant improvements in the majority ofpatients. Results varied between tissue types, with neurological tissue appearing the most resistant to improvement. Only 7 of 71 reports indicated a generally poor response to HBOT. The present review will complement Feldmeier 2002 by using explicit Cochrane methodology to locate, quantitatively appraise and summarise the comparative data, while not discussing in any detail the non-comparative series summarised in that review.

HBOT is associated with some risk of adverse effects including damage to the ears, sinuses and lungs from the effects of pressure, temporary worsening of short sightedness (myopia), claustrophobia and oxygen poisoning. Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention. It has further been suggested that HBOT may increase the incidence and rate, or both of growth of tumours in patients with a history ofmalignancy. A recent comprehensive review fails to support these concerns (Feldmeier 2003).

O B J E C T I V E S

The objectives of this review were to determine the efficacy and safety of HBOT in the treatment of patients with late radiation tissue injury.

Specifically we addressed the following questions:

- Is a course ofHBOT more efficacious than placebo or no treatment in improving symptoms, signs and disability for patients with LRTI?
- Is a course of HBOT more efficacious than placebo or no treatment in preventing further deterioration for patients with LRTI?
- Is HBOT administration safe?

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types ofstudies

Randomised and pseudo-RCTs that compared the effect ofa regimen including HBOT on any form oflate radiation tissue injury, with any treatment regimen not including HBOT.

Types ofparticipants

Any person with late radiation tissue injury (including necrosis) of whatever tissue. We also accepted patients treated with large dose radiation therapylikely to induce relatively early necrosis (e.g. radiosurgery to a brain lesion).

Types ofintervention

We accepted trials comparing regimens which included HBOT with similar regimens that excluded HBOT. Where co-interventions differed significantly between studies this was clearly stated and the implications discussed.

The intervention under examination was HBOT administered in a compression chamber between pressures of 1.5 ATA and 4.0 ATA and treatment times between 30 minsand 120 mins daily or twice daily. These parameters exclude trivial treatments on the one hand, and highly toxic exposures on the other. The comparator group was diverse, and we accepted any standard treatment regimen designed to promote tissue healing or prevent further deterioration.

Types of outcome measures

Appropriate outcome measure depended on the nature of the LRTI and the anatomical location. Studies were eligible for inclusion ifthey reported any ofthe following outcome measures:

A l anatomical areas

Primary outcome measures:

(1) Survival

(2) Complete resolution ofnecrosis or tissue damage

(3) Improvement in LENT-SOMA scale

[The LENT-SOMA scales (Late Effects Normal Tissues - Subjective, Objective, Management, Analytic) were developed jointly by the European Organization for Research and Treatment ofCancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) in 1995 in order to standardise assessment ofLRTI (Pavy 1995). Scales are location specific and have been summarised in a number of forms for each location. The implications for pooling are discussed as required. The scale dimensions are summarised in Table 01.]

Secondary outcome measures:

(4) Resolution ofpain

(5) Resolution ofswelling

(6) Improvement in quality oflife (QOL) and/or function

(7) Osteoradionecrosis (ORN)

Primary outcome measures:

(a0 Healing with complete soft tissue coverage over bone

(b) Resolution of sinus tract bewteen bone and skin or mucosa

(c) Resolution of fracture or re-establishment of bony continuity

(d) Development ofORN in tooth socket following extraction

Secondary outcome measures:

(e) Improvement in X-Ray appearance

(8) Head and neck soft tissues

Primary outcome measures:

(a) Wound dehiscience (breakdown of a surgical wound)

(b) Surgical removal oflarynx

(c) Major vessel bleeding

Secondary outcome measures:

(d) Speed ofwound healing

(e) Improvement in swelling or 'woodiness' of tissue

(f) Reversal of tracheostomy (surgical breathing hole in the trachea)

(9) Urinary bladder

Primary outcome measures:

(a) Resolution ofbleeding

(b) Removal ofbladder and urine diversion procedures

Secondary outcome measures:

(c) Improved cystoscopic appearance

(d) Frequency

(e) Dysuria (pain on passage ofurine)

(10) **Chest wal** Nil additional to those listed under 'All anatomical areas'.

(11) Bowel

Primary outcome measures:

(a) Resolution ofbleeding

(b) Operations on the bowel such as colostomy, ileostomy or bowel resection

Secondary outcome measures:

(c) Improvement in pain score

(12) Neurological tissue

Primary outcome measures:

(a) Improvement in objective motor function

(b) Improvement in visual acuity

Secondary outcome measures:

(c) Improvement in sensory function

(d) Improvement in functional ability or activities ofdaily living

(e) Improvement in neuropsychiatric testing

(f) Improvement in X-ray or scan appearance

(g) Reduction in steroid dose

Extremities

Nil additional to those listed under 'All anatomical areas'.

Adverse events ofHBOT

(a) Recurrence of tumour (locally or remote)

(b) Visual disturbance (short and long term)

(c) damage from pressure (aural, sinus or pulmonary barotrauma, in the short and long-term)

(d) Oxygen toxicity (short-term)

(e) Withdrawal from treatment for any reason

(f) Any other recorded adverse effect

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

It was our intention to capture both published and unpublished studies.

Electronic searches

We searched: CENTRAL (The Cochrane Library August 2004), MEDLINE (1966 to August 2004), EMBASE (1980 to August 2004), CINAHL (1982 to August 2004) and an additional database developed in our hyperbaric facility, The Database of Randomised Trials in Hyperbaric Medicine (Bennett 2004). The search strategy was broad and the keywords in the following strategies were adapted as appropriate. The EMBASE and MEDLINE (OVID) strategies are given in Table 02.

In addition we made a systematic search for relevant controlled trials in specific hyperbaric literature sources as follows.

- Experts in the field and leading hyperbaric therapy centres (as identified by personal communication and searching the Internet) were contacted and asked for additional relevant data in terms ofpublished or unpublished randomized trials.

- Handsearch of relevant hyperbaric textbooks (Kindwall, Jain, Marroni, Bakker, Bennett and Elliot), journals (Undersea and Hyperbaric Medicine, Hyperbaric Medicine Review, South Pacific Underwater Medicine Society (SPUMS) Journal, European Journal of Hyperbaric Medicine and Aviation, Space and Environmental Medicine Journal) and conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society, International Congress of Hyperbaric Medicine) published since 1980.

- Contacted of authors of relevant studies to request details of unpublished or ongoing investigations.

- Examination of the reference list of all trials for inclusion in this review.

All languages were considered. Authors were contacted if there was any ambiguity about the published data.

METHODS OF THE REVIEW

Data retrieval and management

One reviewer (MB) was responsible for handsearching and identification of appropriate studies for consideration and all possibly relevant studies were entered into a bibliographic software package (Review Manager). Three reviewers (MB, JF and NH) then examined the electronic search results and identified comparative studies that mayhave been relevant. Studies were retained when one or more reviewers identified them as appropriate. Retained studies were retrieved in full and reviewed independently by three reviewers, all with content expertise in HBOT, one with content expertise in radiation oncology (JF). In addition one of the reviewers (MB) has expertise in clinical epidemiology. Reviewers recorded data using the data extraction form developed for this review.

Data extraction

Each reviewer independently extracted the relevant data. Primary authors were contacted to provide information when missing data was encountered or ifnecessary data such as adverse events were not clearly stated. All differences were resolved by discussion among the reviewers and no disputed trials required referral to the Review Group contact editor for appraisal.

Quality assessment

Study quality was assessed using an adaptation of the method outlined in Schulz (Schulz 1995), and recommendations made for inclusion or exclusion from the review. Results from the study quality assessment are presented in a descriptive manner. The following characteristics were assessed:

Adequacy ofthe randomization process:
A - Adequate sequence generation is reported using random number tables, computer random number generator, coin tossing, or shuffling;

B - Did not specify one of the adequate reported methods in (A) but mentioned randomization method;

C - Other methods of allocation that appear to be unbiased.

Adequacy ofthe allocation concealment process:
A - Adequate measures to conceal allocations such as central randomization; serially numbered, opaque, sealed envelopes; or other description that contained convincing elements of concealment;

B- Unclearly concealed trials in which the author either did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the categories in (A);

C- Inadequately concealed trials in which method ofallocation is not concealed such as alternation methods or use of case record numbers.

Potential for selection bias after allocation:
A- Trials where an intention-to-treat analysis is possible and few losses to follow-up are noted;

B- Trials which reported exclusions (as listed in A but exclusions were less than 10%);

C- No reporting on exclusions or exclusions greater than 10% or wide differences in exclusions between groups.

Level of masking (treatment provider, patient, outcome assessor):
A- Double or triple-blind;

B- Single-blind;

C- Non-blind.

These four factors were considered for possible sensitivity analysis.

Analyses

It was our intention where possible to analyse the data from different anatomical sites together (see outcomes listed under 'all anatomical areas'). However, many outcomes are specific to a particular anatomical site, and these outcomes were analysed separately. All comparisons were made using an intention-totreat analysis where possible and reflect efficacy in the context of randomized trialling, rather than true effectiveness in any particular clinical context. While we planned to compare survival over time using the log Hazard Ratio and variance (Parmar 1998), no suitable data was available. For dichotomous outcomes RRwas used. For continuous data, the mean difference (MD) between treatment and control arms in each trial was calculated and aggregated using inverse variance weights to estimate an overall MD and its 95% CI. We used a fixed-effect model where there was no evidence of significant clinical heterogeneity between studies (see below), and employed a random effects model when such heterogeneitywas likely. All statistical analysis was performed using RevMan software.

Where co-interventions differed significantly between studies this was clearly stated and the implications discussed.

Overal primary outcomes (Al anatomic areas):

(1) Survival. For each trial, we calculated the RR for survival in the HBOT group compared to the control group. These RRs were pooled in a meta-analysis to estimate an overall RR and its 95% CI. A statistically significant difference between experimental intervention and control intervention was assumed if the 95% CI of the RR did not include the value 1.0. As an estimate of the clinical relevance of any difference between experimental intervention and control intervention, we calculated the number needed to treat (NNT) and number needed to harm (NNH) with 95% CI as appropriate, using the formulaNNT = 1/RD with 95% CI calculated from the 95% CI ofthe RR, following the method recommended in Altman 2001.

(2) Complete resolution ofnecrosis or tissue damage. The RR for complete resolution ofnecrosis or tissue damage with and without HBOT was calculated using the methods described in (1) above.

(3) Improvement in LENT-SOMA scales. For each trial, the mean difference (MD) in this score between HBOT and control groups was to be calculated and combined in a meta-analysis to estimate an overall MD and its 95% CI. No trials reported this outcome.

Overal secondary outcomes:

(4) Radiological improvement. Statistical analysis would depend on the nature of the data, but would have followed the methods outlined above. No trials reported this outcome.

The outcomes for each anatomical site will be approached in an analogous manner to that outlined above.

(5) Adverse events . For each trial, we planned to calculate the RR for each adverse event in the HBOT compared to the control group. These RRs were to be pooled in a meta-analysis to estimate an overall RR and its 95% CI. No trials reported this outcome.

Sensitivity analyses

We intended to perform sensitivity analyses for missing data and study quality where appropriate.

Missing data

We employed sensitivity analyses using different approaches to imputing missing data. The best-case scenario assumed that none of the originally enrolled patients missing from the primary analysis in the treatment group had the negative outcome of interest whilst all those missing from the control group did. The worst case scenario was the reverse.

Study quality

Ifappropriate, we had planned to conduct a sensitivity analysis by study quality based on the presence or absence ofa reliable random allocation method, concealment of allocation and blinding of participants or outcome assessors.

Heterogeneity

Heterogeneity was assessed using the I_2 statistic and consideration given to the appropriateness ofpooling and meta-analysis.

Subgroups

We considered subgroup analysis based on:

- Anatomical location
- Dose ofoxygen received (pressure, time and length oftreatment course)
- Nature of the comparative treatment modalities
- Severity ofinjury

DESCRIPTION OF STUDIES

We identified 103 publications apparently dealing with the use of HBOT for the treatment ofLRTI. Initial examination confirmed 62 were case reports or case series, 25 were reviews or letters without new data, one was a report of a planning workshop and one was a report of animal work. These reports were excluded, leaving 14 possible randomised comparative trials. After appraisal of the full reports we further excluded five reports with non-random controls (Carl 2001; Gal 2003; Granstrom 1999; Maier 2000; Niimi 1997), two systematic reviews (Coulthard 2002; Denton 2002) with no further randomised data and one randomised trial with no quantitative data (Tobey 1979). See table 'Characteristics of excluded studies'. The other six trials were accepted into the review (Clarke 2004; Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Pritchard 2001). Marx 1999a and Marx 1999b are trials reported for the first time in a textbook. The recruitment period for these studies is not known.

The included trials were published between 1985 and 2004, and the reviewers are aware that there is a large, multicentre trial underway into the effect ofHBOT on eight different manifestations of LRTI. Clarke 2004 is the first brief report of one arm of that trial. In total, these trials include data on 447 participants, 224 receiving HBOT and 223 control. The largest (Marx 1999b) accounts for 36% of cases. (See Table: 'Characteristics of included studies').

Where sex was specified, the trials enrolled more females than males (Pritchard 2001 enrolled 34 participants, all female; Hulshof 2002 six females and one male). With regard to age, Pritchard 2001 enrolled participants from age 40 to 79 years and in Hulshof 2002 the average age was 46 years. Two studies did not specify any such characteristics except prior exposure to 6400 cGy in the area under investigation (Marx 1999a; Marx 1999b). The other four studies specified exclusion of those unfit for compression or the presence of residual tumour, while Marx 1985 also excluded those with penicillin sensitivity, recent chemotherapy or concurrent disease known to effect wound healing. No details of prior therapy for the pathology under study were given, while Marx 1985 specified a minimum prior radiation dose of 6000 cGy at least six months prior to enrollment. Clarke 2004 entered participants with radiation proctitis, Hulshof 2002 those with cognitive deficits following brain irradiation with at least 30 Gy, Pritchard 2001 radiation-induced brachial plexus lesions, Marx 1999a candidates for hemimandibular jaw reconstruction, Marx 1 999b candidates requiring major soft tissue surgery or flaps, and Marx 1985 participants requiring tooth extraction.

Both the dose of oxygen per treatment session and for the total course of treatment varied between studies. The lowest pressure administered was 2.0 ATA (Clarke 2004) and the highest 3.0 ATA (Hulshof 2002), while all other trials utilised 2.4 ATA. Treatment periods for each session ranged from 90 minutes (Marx 1985; Marx 1999a; Marx 1999b) to 120 minutes (Clarke 2004). All trials administered a total of 30 treatments except Clarke 2004, where there was an option to continue to 40 treatments.

Marx 1985 involved a comparator treatment ofpenicillin for 10 days, while there were no active comparator regimens in the other trials. Two trials administered a blinded sham therapy (Clarke 2004; Pritchard 2001) Details are given in the table 'Characteristics ofincluded studies'.

The follow-up periods varied between three weeks following the treatment course (Marx 1999b), three months (Clarke 2004), six months (Hulshof 2002; Marx 1985) and one year (Pritchard 2001). Marx 1999a did not specify the time at which outcome was measured. All included studies reported at least one clinical outcome of interest. Of the outcomes identified above, these trials reported data on primary outcomes (resolution of problem, bony continuity established, wound dehiscience and LENTSOMA scale) and secondary outcomes (oedema resolution, pain scores, QOL, physical functioning, sensory function and neuropsychiatric testing).

Other outcomes (including non-clinical) reported included: self-rated memory and dexterity (Hulshof 2002), sensory action potentials (Pritchard 2001), post-surgical complication rate (Marx 1999a) and wound infection rate (Marx 1999b).

METHODOLOGICAL QUALITY

Details of the quality assessment are given in the table 'Characteristics ofincluded studies'. Study qualityvaried widely, however, because very few analyses could be pooled, study quality was not used as a basis for sensitivity analysis. Although Clarke 2004 is an abstract only, this trial is known to the reviewers and many details have been provided through personal communication.

Alocation concealment

Allocation concealment was adequately described in three studies (Clarke 2004; Hulshof 2002; Pritchard 2001), all three using a remotelylocated randomisation officer. For none ofthe remaining studies is there a clear indication that the investigators were unable to predict the prospective group to which a participant would be allocated.

Randomisation

Randomisation procedures were described in two studies (Clarke 2004; Pritchard 2001), both employing a computer generated random number table, but not in the other four.

Subject baseline characteristics

Given the variation in pathology outlined in 'Description of Studies' above, it is not surprising that there is considerable variation in patient baseline characteristics. Two studies did not specify any baseline characteristics except prior exposure to 6400 cGy in the area under investigation (Marx 1999a; Marx 1999b). The other four studies specified exclusion ofthose unfit for compression. No details ofprior therapy for the pathology under studywere given, while Marx 1985 specified a minimum prior radiation dose of 6000 cGy at least six months prior to enrollment.

Blinding

Two studies utilised a sham therapy in order to mask subjects and outcome assesors to HBOT (Clarke 2004; Pritchard 2001), while no sham was employed in the remaining four studies (Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b). Noauthorformally tested the success of their blinding strategy.

Patients lost tofolow-up

Five studies did not report any losses to follow-up or violation of the studyprotocol (Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Pritchard 2001). Clarke 2004 lost seven control subjects and four HBOT group subjects, and these subjects we excluded from the analysis reported in the abstract. Sensitivity analysis using best and worse case scenarios were performed where this study contributed data to the analysis.

Intention-to-treat analysis

OnlyPritchard 2001 specificallydetailed an intention to treat analysis (two subjects in the HBOT group did not complete therapy, but were included in analysis). Four of the remaining five studies reported full follow-up and did not report any protocol violation (see above).

RESULTS

Combined anatomical areas

Primary outcomes

(1) Death (comparison 01)

No trial reported any data on this outcome.

(2) Complete resolution oftissue damage or necrosis (comparison 02)

(a) Complete resolution ofclinical problem at three months (comparison 02, outcomes 01, 02, 03)

Three trials reported this outcome (Clarke 2004; Marx 1999a; Pritchard 2001), involving 172 participants (39% ofthe total participants in this review), with 86 randomised to both HBOT and control arms. Overall, 64 (74%) ofparticipants in the HBOT arm achieved resolution, versus 40 (47%) in the control group. Analysis for heterogeneity suggested a high proportion of variability between trials was not due to sampling variability (I^2= 65%), and so this comparison was made using a random effects model with stratification by tissue type involved (other subgroup analyses did not separate these studies). Further, one study (Pritchard 2001) did not report any participants with resolution, so could not contribute to the analysis.

There was a significantly improved probability ofresolution with the administration ofHBOT for both radiation proctitis (RR 2.7, 95% CI 1.2 to 6.0, P = 0.02) (Clarke 2004), and hemimandibulectomy (RR 1.4, 95% CI 1.1 to 1.8, P = 0.001, (Marx 1999a). The result for proctitis was however, sensitive to the allocation of dropouts (best case: RR 3.3, 95%CI 1.5 to 7.3, P = 0.002; worst case: RR 1.2, 95% CI 0.7 to 2.2, P = 0.4). For proctitis, 16 participants (47%) achieved resolution oftheir problem following HBOT versus six participants (18%) in the control group, suggesting the number needed to treat with HBOT to achieve one extra subject with a resolved problem was 3, (95% CI 2 to 11).

For participants requiring hemimandibulectomy, 48 participants (92%) achieved resolution following HBOT versus 34 (65%) in the control group, NNT 4, (95% CI 2 to 8).

(3) LENT-SOMA scores (comparison 03)

(a) Improvement in LENT-SOMA score at three months

Only one trial reported this outcome (Clarke 2004) involving 68 subjects (15% of the total), with 34 randomised to both HBOT and control. The mean improvement in LENT-SOMA score was greater in the HBOT group (4.7 versus 0.73), and this difference was statistically significant (WMD 4.0, 95% CI 1.7 to 6.3, P = 0.0007).

Secondary outcomes

(4) Pain scores (comparison 04)

(a) Change in pain score (0 to 100 scale) from baseline to six months after treatment (comparison 04, outcome 01)

Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% ofthe total) with 17 randomised to both HBOT and control. Pain scores increased over this time period in both groups, but more so with HBOT (5.3 points versus 1.2). Standard deviations were not reported around these means, precluding further analysis.

(b) Change in pain score (0 to 100 scale) from baseline to 12 months after treatment (comparison 04, outcome 02)

Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% ofthe total) with 17 randomised to both HBOT and control. Pain scores were reduced in both groups, but more so in the controls (-5.0 points versus -0.7). Standard deviations were not reported around these means, precluding further analysis.

5. Swelling (comparison 05)

(a) Resolution oflymphoedema in arm at six months (comparison 05, outcome 01)

Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% ofthe total) with 17 randomised to both HBOT and control. Two subjects (12%) in the HBOT arm achieved resolution, while none in the control group did so. This difference in favour ofHBOT was not statistically significant (RR ofresolution with HBOT 5.0, 95% CI 0.3 to 97.0, P = 0.29).

(6) Quality oflife or functional scores (comparison 06)

(a) SF-36 score for general health at 12 months (comparison 06, outcome 01)

Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% ofthe total) with 17 randomised to both HBOT and control. The mean score for general health self-rating was lower in the HBOT group (5 8.8 versus 61.1), but not significantly so (WMD -2.3, 95% CI -19.0 to 14.4, P = 0.79).

(b) 2 SF-36 score for physical functioning at 12 months (comparison 06, outcome 02)

Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% ofthe total) with 17 randomised to both HBOT and control. The mean score for self-rating of physical functioning was lower in the HBOT group (53.5 versus 57.5), but not significantly so (WMD -4.0, 95% CI -19.4 to 11.4, P = 0.61).

(7) Osteoradionecrosis

Primary outcomes

(a) Acheivement of complete mucosal cover (comparison 07, outcome 01)

Two trials reported this outcome (Marx 1985; Marx 1999a), involving 178 subjects (40% of the total), with 89 randomised to both HBOT and control arms. Eighty three (93%) ofsubjects in the HBOT arm achieved resolution, versus 60 (67%) in the control group. Heterogeneity did not appear tobe a problem with this analysis (I^2= 0%). There was a significantly improved probability ofattaining mucosal cover with the administration ofHBOT (RR 1.4, 95% CI 1.2 to 1.6, P < 0.001). The NNT to achieve one further case with mucosal cover with the application ofHBOT is 4, (95% CI2 to 8).

(b) Resolution ofsinus tract (comparison 07, outcome 03) No study reported data on this outcome

(c) Establishment of bony continuity (comparison 07, outcome 02)

Only one trial contributed results to this outcome (Marx 1995a) involving 104 subjects (23% ofthe total), 52 randomised to both HBOT and control. Forty eight (92%) ofsubjects in the HBOT arm achieved continuity, versus 60 (65%) in the control group. There was a significantly improved probability of attaining bony continuity with the administration of HBOT (RR 1.4, 95% CI 1.1 to 1.8, P = 0.001). The NNT to achieve one further casewith bony continuity with the application of HBOT is 4, (95% CI 2 to 8).

(d) Healing oftooth sockets following extraction in irradiated field at six months (comparison 07, outcome 03)

Only one trial contributed results to this outcome (Marx 1985) involving 74 subjects (17% of the total), 37 randomised to both HBOT and control. 35 (95%) of subjects in the HBOT arm achieved healing of all sockets, versus 26 (70%) in the control group. There was a significantly improved probability of healing with the administration ofHBOT (RR 1.4,95% CI 1.1 to 1.7, P = 0.009). The NNT with HBOT to achieve one further case with all tooth sockets healed is 4, (95% CI 2 to 13).

Secondary outcomes

(e) Improvement bin X-Ray appearance (comparison 07, outcome 05)

No study reported data on this outcome.

8. Head and neck tissues

Primary outcomes

(a) Wound dehiscience (comparison 08, outcome 01)

Two trials reported this outcome (Marx 1999a; Marx 1999b), involving 132 subjects (60% of the total subjects in this review), with 132 randomised to both HBOT and control arms. Overall,

8 (6%) subjects in the HBOT arm suffered wound breakdown, versus 37 (28%) in the control group. Analysis for heterogeneity suggested a high proportion ofvariability between trials was not due to samplingvariability (I2=70%), and so this comparison was made using a random effects model. There was a significantly improved chance ofwound breakdownwith control (RR4.2, 95% CI 1.1 to 16.8, P = 0.04). Stratification by tissue type involved confirmed the direction of effect was the same for both studies, but it remained significant only for soft tissue flaps and grafts (RR following hemimandibulectomy (Marx 1999a) 2.2,95% CI 0.8 to 5.9, P = 0.12; RR following soft tissue flap or graft (Marx 1999b) 8.7, 95% CI 2.7 to 27.5, P = 0.0002). The number needed to treat with HBOT to avoid one wound dehiscience overall was 5 (95% CI 1 to 59), and for soft tissue repairs alone was 4 (95% CI 3to6).

(b) Surgical removal of the larynx (comparison 08, outcome 02)
No study reported data on this outcome.

(c) Major bleeding (comparison 08, outcome 03)
No study reported data on this outcome.

Secondary outcomes

(d) Speed ofwound healing (comparison 08, outcome 04)
No study reported data on this outcome.

(e) Improvements in tissue quality (comparison 08, outcome 05)
No study reported data on this outcome.

(f) Reversal oftracheostomy (comparison 08, outcome 06)
No study reported data on this outcome.

(9) Urinary bladder (comparison 9)

No study reported data on outcomes for this tissue.

(10) Chest w a l (comparison 10)

No study reported data on outcomes for this tissue.

(11) Bowel (comparison 11)

No study reported data on outcomes for this tissue.

(12) Neurological tissue (comparison 12)

Primary outcomes

(a) Objective motor function (comparison 12, outcome 01)
No study reported data on this outcome.

(b) Visual acuity (comparison 12, outcome 02)
No study reported data on this outcome.

Secondary outcomes

(c) Warm sensory threshold at one week after therapy (comparison 12, outcome 03)

Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% ofthe total) with 17 randomised to both HBOT and control. The mean threshold temperature for reporting awarm sensation at one week after therapy (compared to pretreatment baseline) was reduced in the HBOT group, but not in the controls (-0.1 degree versus 1 degree). This difference was not statistically significant (WMD 1.1 degrees lower, 95% CI -1.9 to 4.1, P = 0.47).

(d) Warm sensory threshold at one year after therapy (comparison 12, outcome 04)

Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% ofthe total) with 17 randomised to both HBOT and control. The mean threshold for reporting a warm sensation was increased in both groups, but less so in controls (0.5 degrees versus 1.4). This difference was not statistically significant (WMD 0.9 degrees, 95% CI -2.3 to 4.0, P = 0.47).

(e) Functional ability scores and ADL (comparison 12, outcome 05)

No study reported data on this outcome.

(f) Net number of neuropsychological tests (maximum 25 tests) improved at three months (comparison 12, outcome 06) Only one trial reported this outcome (Hulshof 2002) involving seven patients (2% of the total) with four randomised to HBOT and three to control. The mean net number ofimproved tests was greater in the HBOT group (3.3 versus 1.3), but not significantly so (WMD 2, 95% CI -1.6 to 5.0, P = 0.28).

(g) Net number of neuropsychological tests (maximum 25 tests) improved at six months (comparison 12, outcome 06) Only one trial reported this outcome (Hulshof 2002) involving seven patients (2% of the total) with four randomised to HBOT and three to control. The mean net number ofimproved tests was greater in the HBOT group (3 versus 2), but not significantly so (WMD 1.1, 95% CI -3.6 to 5.6, P = 0.67).

(13) **Adverse events** No study reported data on these outcomes.

D I S C U S S I O N

This reviewhas included datafrom six trials investigating the use of HBOT for tissue suffering from late radiation damage, and we believe these represent all randomised human trials in this area, both published and unpublished, at the time ofsearching the databases. We found some evidence that HBOT improves the probability of healing in radiation proctitis and following hemimandibulectomy and reconstruction of the mandible; improves the probability of achieving mucosal coverage and the restoration ofbony continuity with ORN; prevents the development of ORN following tooth extraction from a radiation field; and reduces the risk ofwound dehiscience following grafts and flaps in the head and neck. Although there was some trend toward secondary favourable outcomes in neurological tissue, there was no evidence of benefit in important clinical outcomes with established radiation brachial plexus lesions or cerebral tissue injury. There was no data reported from any randomised trials involving the use of HBOT to treat other manifestations of radiation tissue damage.

Only six trials with 447 participants were available for evaluation using our planned comparisons, and meta-analysis was not appropriate or possible for most of these. Many of the trials enrolled modest numbers of patients, particularly the trial investigating cerebral radiation injury, where only seven subjects were reported (Hulshof 2002). Other problems for this review were the poor methodological quality of some of these trials (particularly Marx 1999a; Marx 1999b), variability in entry criteria and the nature and timing of outcomes, and poor reporting of both outcomes and methodology. In particular, there is a possibility ofbias in the combined tissue outcomes due to different anatomical locations and extent oftissue damage on entry to these trials, as well as from non-blinded management decisions in three of the trials (Marx 1985; Marx 1999a; Marx 1999b). Further, it is not clearwhen the subjects for Marx 1999a and Marx 1999b werer recruited - these trials may represent work from some years earlier.

These trials were published over a 19-year period up to 2004, and from a wide geographical area. We had planned to perform subgroup analyses with respect to anatomical location, dose ofoxygen received (pressure, time and length oftreatment course), nature of the comparative treatment modalities and the severity of injury. However, the paucity of eligible trials and poor reporting ofsome trials suggested that except for anatomical location, these analyses would not be informative. The oxygen dose used was reasonably standard over most trials. Patient inclusion criteria were not standard, and poorly reported in some trials. Specific comparator therapies were generally not employed.

Three trials reported on complete resolution of the clinical problem (Clarke 2004; Marx 1999a; Pritchard 2001). Results varied widely and could not be pooled. Clarke 2004 and Marx 1999a reported significant improvement in the chance of healing radiation proctitis (RR 2.7, P = 0.02, NNT 4), and following hemimandibulectomy and reconstruction (RR 1.4, P = 0.001, NNT 4) respectively. Pritchard 2001, in contrast, reported no such resolution in any subject treated for established radiation brachial plexopathy. This difference in outcome could reflect the unresponsiveness of neurological tissue in general (an assertion supported by a similar lack of response for brain radiation injury in Hulshof 2002, or the relatively long-standing nature of the injuries enrolled in that trial (mean period from radiotherapy to HBOT was 11 years). The Clarke 2004 analysis was also sensitive to the allocation of dropouts and we await further reporting of this trial in full. Although this trial has only been reported in abstract, the author has provided considerable methodological detail in private correspondence for this review.

Pooling data for clinical outcomes of interest could only be performed with respect to the the risk of wound dehiscience. This analysis suggested some benefit from HBOT administration (RR of dehiscience with control group was 4.2 [95% CI 1. 1 to 16.8], NNT 5 [95% CI 3 to 8]). This result was subject to a high proportion ofvariability being due to differences between trials rather than to sampling variability, and the two trials were of relatively low quality. It should be interpreted with great caution. This possible treatment effect is, however, ofgreat clinical importance and deserves further investigation.

The incidence of adverse effects was not assessed by the studies included in this review. There are a number of minor complications that may occur commonly. Visual disturbance, usually reduction in visual acuity secondary to conformational changes in the lens, is very commonly reported - perhaps as many as 50% ofthose having a course of 30 treatments (Khan 2003). While the great majority ofpatients recover spontaneously over a period of days to weeks, a small proportion of patients continue to require correction to restore sight to pre-treatment levels. None of the trials included in this review reported visual changes. The second most common adverse effect associated with HBOT is middle-ear barotrauma. Barotrauma can affect any air-filled cavity in the body (including the middle ear, lungs and respiratory sinuses) and occurs as a direct result ofcompression. Ear barotrauma is by far the most common as the middle ear air space is small, largely surrounded by bone and the sensitive tympanic membrane, and usually requires active effort by the patient in order to inflate the middle ear through the eustachian tube on each side. Barotrauma is thus not a consequence ofHBOT directly, but rather of the physical conditions required to administer it. Most episodes ofbarotrauma are mild, easily treated or recover spontaneously and do not require the therapy to be abandoned.

All of these findings are subject to a potential publication bias. While we have made every effort to locate further unpublished data, it remains possible that this review is subject to a positive publication bias, with generally favourable trials more likely to achieve reporting. With regard to long-term outcomes following HBOT and any effect on the QOL for these patients, we have located little relevant data.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence that HBOT improves outcome in late radiation tissue injury affecting bone and soft tissues ofthe head and neck, for radiation proctitis and to prevent the development ofosteoradionecrosis following tooth extraction in an irradiated field. There was no such evidence of any important clinical effect on neurological tissues, either peripheral or central. Thus, the application ofHBOT to selected patients and tissues may be justified. The small number ofstudies, the modest numbers ofpatients and the methodological and reporting inadequacies ofsome ofthe primary studies included in this review demand a cautious interpretation. Further research is required to estabish the optimum patient selection and timing ofany such therapy. An economic evaluation should also be undertaken. There is no evidence ofa benefit from

HBOT for the treatment of affected neurological tissue, and to date, no useful information regarding the efficacy or effectiveness of HBOT for other tissues can be provided.

Implications for research

There is a strong case for further large randomised trials of high methodological rigour in order to define the true extent ofbenefit from the administration ofHBOT for patients with late radiation tissue injury. Specifically, more information is required on the subset ofdisease severity and tissue type affected that is most likely to benefit from this therapy, the time for which we can expect any benefits to persist, and the oxygen dose most appropriate. Any future trials would need to consider in particular:

Appropriate sample sizes with power to detect expected differences generated by this review

Careful definition and selection of target patients

Appropriate oxygen dose per treatment session (pressure and time)
Appropriate supportive therapy to which HBOT would be an adjunct

Use of an effective sham therapy

Effective and explicit blinding of outcome assessors

Appropriate outcome measures including all those listed in this review

Careful elucidation of any adverse effects
The cost-utility of the therapy

POTENTIAL CONFLICT OF INTEREST

None known.

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Ongoing study Starting date of trial not provided. Contact author for more information.

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-Indicates the majorpublicationfor the study

TABLES

Characteristics ofincluded studies

Study	Clarke 2004
Methods	Multicentre RCT with allocation concealment and patient/outcome assessor blinding.
Participants	68 patients with problematic radiation proctitis.
Interventions	Control: Air breathing at 1ATA for 120 minutes 30 times over 6 weeks. Sham compression to trivial pressure and return. HBOT: 100% oxygen at 2.0 ATA for 30 or 40 sessions over six to eaigth weeks
Outcomes	Healing or significant improvement. LENT-SOMA Scores
Notes	Preliminary abstract report of one arm of 8 armed study
Allocation concealment A – Adequate	

Study	Hulshof 2002

Methods	Randomised trial using random number table with allocation concealement but no blinding. Randomised in matched pairs.

Characteristics ofincluded studies *(Continued)*

Participants	7 patients with cognitive deficits present at least 1.5 years after irradiation of the brain with at least 3000 cGy.
Interventions	Control: Nil specific HBOT: 100% oxygen at 3 ATA for 115 minutes for 30 sessions over six weeks (five days out of seven each week).
Outcomes	Neuropsychiatric testing
Notes	Very low power study with many outcomes
Allocation concealment	A – Adequate

Study	**Marx 1985**
Methods	Multicentre randomised trial. No details of methodology for randomisation , allocation concealment or blinding.
Participants	74 patients requiring tooth extraction in a field irradiated with at least 6000 cGy more than 6 months and less than 15 years previously. Also excluded with penicillin or HBOT contrandications, active tumour present, recent chemotherapy or concurrent disease (e.g. diabetes) that might affect wound healing.
Interventions	Control: teeth extracted in standard way with 1 million units penicilling pre-extraction and 500mg four times each day for 10 days post-extraction. HBOT: 20 pre-operative treatment sessions at 2.4 ATA for 90 minutes daily five or six days each week, followed by 10 further sessions post-operatively.
Outcomes	Development of clinical osteoradionecrosis with non-healing at 6 months
Notes	
Allocation concealment	B – Unclear

Study	**Marx 1999a**
Methods	Described as randomised. No details concerning blinding or allocation concealment.
Participants	104 patients requiring hemimandibular jaw reconstruction in tissue beds exposed to at least 6400 cGy radiotherapy. No other specific exclusions.
Interventions	Control: Not stated HBOT: 20 pre-operative treatment sessions at 2.4 ATA for 90 minutes daily five days each week, followed by 10 further sessions post-operatively.
Outcomes	"Success" defined as achievement of continuity, restoration of alveolar bone height, restoration of osseous bulk, restoration ofarch form, maintenance ofbone form for 18 months and restoration offacial contours. Complication rate (infection or dehiscience).
Notes	Sketchy account within a textbook chapter written by the author.
Allocation concealment	B – Unclear

Study	**Marx 1999b**
Methods	Described as randomised. No details concerning blinding or allocation concealment.
Participants	160 patients requiring major soft tissue surgery or flaps into an irradiated area (>6,400 cGy). No other specific exclusions.
Interventions	Control: not stated HBOT: 20 pre-operative treatment sessions at 2.4 ATA for 90 minutes daily five days each week, followed by 10 further sessions post-operatively.
Outcomes	Wound infection, dehiscience, delayed healing

Notes	Sketchy account within a textbook chapter written by the author.

Allocation concealment B – Unclear

Study	Pritchard 2001
Meth ods	Randomised, allocation concealed with blinding ofoutcome assessors and patients.
Participants	34 patients with established radiation-related brachial plexopathy, median duration 3 years. Subjects with active tumour or contraindications to HBOT excluded.
Interventions	Control: 100 minutes at 2.4 ATA breathing 41% oxygen to simulate 100% oxygen at 1ATA, daily 5 days per week to a total of 30 sessions. HBOT: 100% oxygen breathing on the same schedule.
Outcomes	Sensory thresholds, quality oflife scores, McGill pain Score, lymphoedema resolution
Notes	Many other outcomes reported
Allocation concealment A – Adequate	

ATA: Atmospheres absolute

Brachial plexopathy: Poor fuctioning of the nerves going through the armpit to supply the arm adn resulting in loss of sensation, muscle power and function in the arm.

cGy: Centi-Grey

HBOT: Hyperbaric oxygen therapy

Characteristics ofexcluded studies

Study	Reason for exclusion
Carl 2001	Case series only, no randomised comparator
Coulthard 2002	Systematic review - no new data
Denton 2002	Systematic review - no new data
Gal 2003	Retrospective cohort study
Granstrom 1999	Case control study - not randomly allocated
Maier 2000	Retropective cohort study
Niimi 1997	Cohort study
Tobey 1979	RCT but no quantitative data given. Both arms received some HBOT (1.2 versus 2.0 ATA)

ADDITIONAL TABLES

Table 01. The LENT-SOMA Scales - Conceptual summary

(S)ubjective	(O)bjective	(M)edical management	(A)nalytic
The injury from the patient point ofview. May involve interview, diary or questionnaire depending on the system to be used.	Morbidity assessed objectively by clincian during physical examination.	The active steps that have been taken in order to ameliorate the symptoms.	Diagnostic and imaging tools used to further objectively define the level of injury.

Table 02. Search Strategies

EMBASE	MEDLINE (OVID)
1. exp radiation injury/	1. exp radiation injuries
2. (head or neck or cerebr$ or cervi$ or brain$ or pelvi$ or mandib$ or chest or uter$ or bladder or bowel or rect$).mp.	2. exp radiotherapy
3. (radiation$ or radiotherap$ or late$ or damag$ or wound$ or destruction$ or oedema$ or edema$ or fracture$).mp	3. head or neck or cervi* or pelvi* or mandib* or chest or uter* or or bladder or bowel or rect* or leg
4. 2 and 3	4. radiation* or radiation inj* or late or damage* or wound* or destruction* or oedema* edema* or fracture*
5. 1 or 4	5. 3 and 4
6. exp radiotherapy/	6. 1 or 2 or 5
7. 5 or 6	7. exp hyperbaric oxygenation
8. exp hyperbaric oxygen/	8. (high*) adj3 (pressure or tension*)
9. (high adj5 (pressur$ or oxygen$)).mp.	9. hyperbaric*
10. hyperbaric$.mp.	10. oxygen*
11. 8 or 9 or 10	11. 6 or 7 or 8
12. oxygen$.mp.	12. 9 and 10
13. 11 and 12	13. HBO or HBOT
14. (HBO or HBOT).mp.	14. multiplace chamber*
15. multiplace chamber$.mp.	15. monoplace chamber*
16. monoplace chamber$.mp.	16. 11 or 12 or 13 or 14 or 15
17. 13 or 14 or 15 or 16	17. 16 and 17
18. 7 and 17	
19. 18	

ANALYSES

Comparison 02. Complete resolution of problem

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Complete resolution ofclinical problem at three months	Relative Risk (Random) 95% CI			Subtotals only
02 Sensitivity analysis for missing data in proctitis (best case)	1	68	Relative Risk (Fixed) 95% CI	3.33 [1.53, 7.26]
03 Sensitrivity analysis for missing data in proctitis (worst case)	1	68	Relative Risk (Random) 95% CI	1.23 [0.71, 2.15]

Comparison 03. Improvement in mean LENT-SOMA score

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean LENT-SOMA score at three months	1	57	Weighted Mean Difference (Fixed) 95% CI	3.97 [1.69, 6.25]

Comparison 04. Resolution ofpain

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain score change at end of treatment	1	34	Weighted Mean Difference (Fixed) 95% CI	Not estimable
02 Pain score change at one year			Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 05. Resolution ofswelling

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Improvement oflymphoedema	1	34	Relative Risk (Fixed) 95% CI	5.00 [0.26, 97.00]

function

Comparison 06. Improvements in quality oflife or

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 SF-36 mean score at twelve months (general health)	1	34	Weighted Mean Difference (Fixed) 95% CI	-2.30 [-18.95, 14.35]
02 SF-36 mean score for physical function at 12 months	1	34	Weighted Mean Difference (Fixed) 95% CI	-4.00 [-19.40, 11.40]

Comparison 07. Osteoradionecrosis

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Complete mucosal cover	2	178	Relative Risk (Fixed) 95% CI	1.38 [1.19, 1.61]
02 Establishment of bony continuity	1	104	Relative Risk (Fixed) 95% CI	1.41 [1.14, 1.75]
03 Successful healing of tooth sockets after tooth extraction	1	74	Relative Risk (Fixed) 95% CI	1.35 [1.08, 1.68]

Comparison 11. Head and Neck

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Wound dehiscence	2	264	Relative Risk (Random) 95% CI	4.23 [1.06, 16.83]

Comparison 12. Neurological tissue

Outcome title	No. of	No. of
03 Warm sensory threshold one week after treatment (degrees Centigrade change from baseline)		
04 Warm sensory threshold at one year		
06 Net number of significantly improved neuropsychological tests at three months (25 tests total)		

studies	participants		Statistical method		Effect size	
1	34	Weighted Mean Difference (Fixed) 95% CI	1	34	Weighted Mean Difference (Fixed) 95% CI	-0.87 [-3.97, 2.23]
1	34	Weighted Mean Difference (Fixed) 95% CI	1	7	Weighted Mean Difference (Fixed) 95% CI	2.00 [-1.60, 5.60]
1	34	Weighted Mean Difference (Fixed) 95% CI	1	7	Weighted Mean Difference (Fixed) 95% CI	1.12 [-1.90, 4.14]

07 Net number of significantly improved neuropsychiatric tests at six months	1	7	Weighted Mean Difference (Fixed) 95% CI	1.00 [-3.55, 5.55]

INDEX TERMS

Medical Subject Headings (MeSH)

-Hyperbaric Oxygenation; Neoplasms [radiotherapy]; Osteoradionecrosis [prevention & control]; Radiation Injuries [prevention & control; -therapy]; Randomized Controlled Trials

MeSH check words

Humans

COVER SHEET

Title
Hyperbaric oxygen therapy for late radiation tissue injury

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Contribution of author(s)
Micheal Bennett: Principal author, conception, search strategy and execution, data extraction and critical appraisal, hyperbaric medicine content expert, statistical analysis.
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Date authors' conclusions section amended Information not supplied by author

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Editorial group code HM-GYNAECA

GRAPHS AND OTHER TABLES

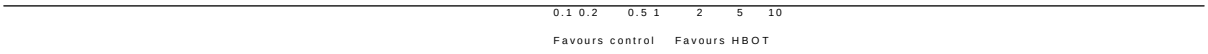
Analysis 02.01. Comparison 02 Complete resolution of problem, Outcome 01 Complete resolution of clinical problem at three months

Review: Hyperbaric oxygen therapy for late radiation tissue injury Comparison: 02 Complete resolution of problem

Outcome: 01 Complete resolution ofclinical problem atthree months

01 Proctitis

Study	HBOT n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Clarke 2004	16/34	6/34			
Subtotal (95% CI)	34	34	Total events:	100.0	2.67 [1.19,5.99]
16 (HBOT), 6 (Control) Test for heterogeneity: not applicable			Test for overall	100.0	2.67[1.19,5.99]
effect z=2.38 p=0.02					
02 Hemi-mandibular reconstruction					
Marx 1999a	48/52	34/52			
Subtotal (95% CI)	52	52		100.0	1.41 [1.14, 1.75]
				100.0	1.41 [1.14, 1.75]
Total events: 48 (HBOT), 34 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=3. 18 p=0.001					
03 Brachial plexus radiation neuropathy					
x Pritchard 2001	0/17	0/17		0.0	Not estimable
Subtotal (95% CI)	17	17		0.0	Not estimable
Total events: 0 (HBOT), 0 (Control) Test for heterogeneity: not applicable Test for overall effect: not applicable					

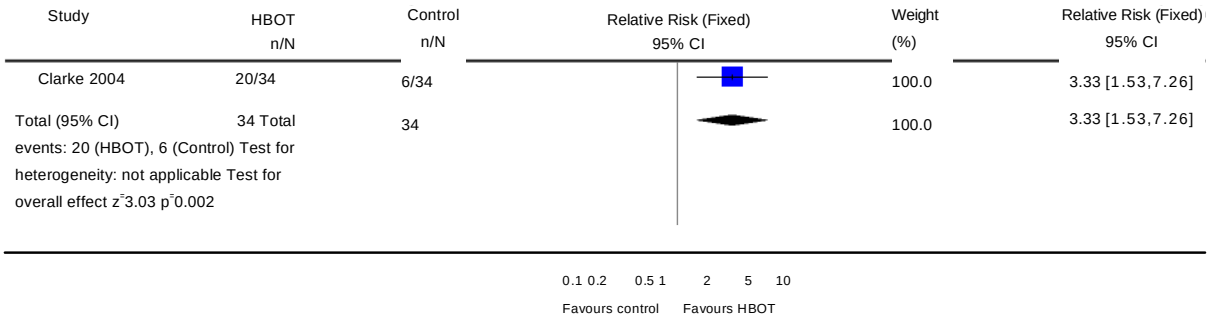


Analysis 02.02. Comparison 02 Complete resolution of problem, Outcome 02 Sensitivity analysis for missing data in proctitis (best case)

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 02 Complete resolution of problem

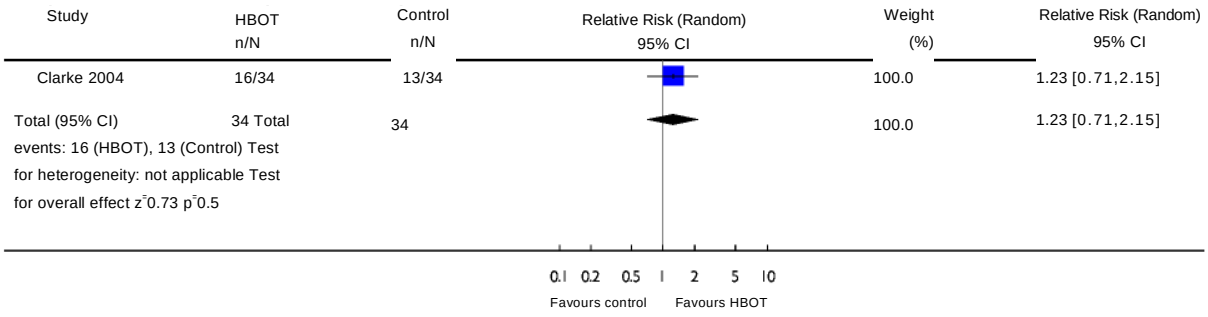
Outcome: 02 Sensitivity analysis for missing data in proctitis (best case)



Analysis 02.03. Comparison 02 Complete resolution of problem, Outcome 03 Sensitrivity analysis for missing data in proctitis (worst case)

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 02 Complete resolution of problem



Outcome: 03 Sensitrivity analysis for missing data in proctitis (worst case)

Analysis 03.01. Comparison 03 Improvement in mean LENT-SOMA score, Outcome 01 Mean LENT-SOMA score at three months

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 03 Improvement in mean LENT-SOMA score Outcome:

01 Mean LENT-SOMA score at three months

Study	HBOT		Control		Weighted Mean Difference (Fixed)	Weight	Weighted
	N	Mean(SD)	N	Mean(SD)	95% CI	Mean Difference (Fixed)	
Clarke 2004	30	4.70 (4.70)	27	0.73 (4.10)		(%)	95% CI
						100.0	3.97 [1.69,
Total (95% CI)	30		27			6.25]	
Test for heterogeneity: not applicable							
Test for overall effect z=3.4 1 p=0.0007					100.0	3.97 [1.69, 6.25]	

Analysis 04.01. Comparison 04 Resolution of pain, Outcome 01 Pain score change at end of treatment

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 04 Resolution of pain

Outcome: 01 Pain score change at end oftreatment

Study	HBOT		Control		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
x Pritchard 2001	17	5.30 (0.00)	17	1.20 (0.00)		0.0	Not estimable
Total (95% CI)	17		17			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

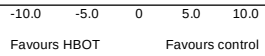
Analysis 04.02. Comparison 04 Resolution of pain, Outcome 02 Pain score change at one year

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 04 Resolution of pain

Outcome: 02 Pain score change at one year

Study	HBOT		Control		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
x Pritchard 2001	17	-0.70 (0.00)	17	-5.00 (0.00)		0.0	Not estimable
Total (95% CI)	17		17			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

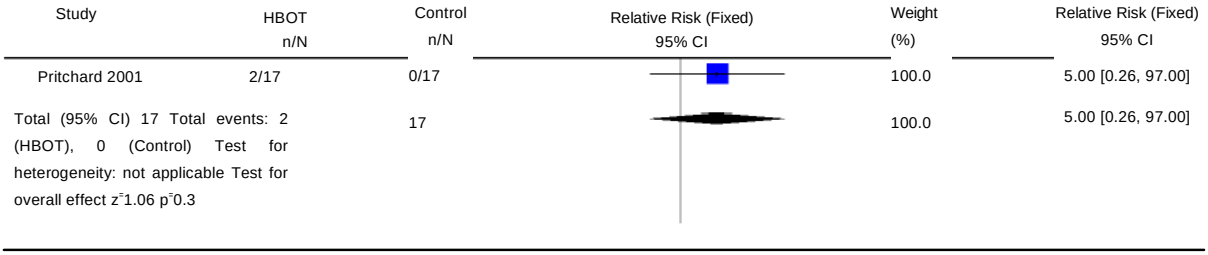


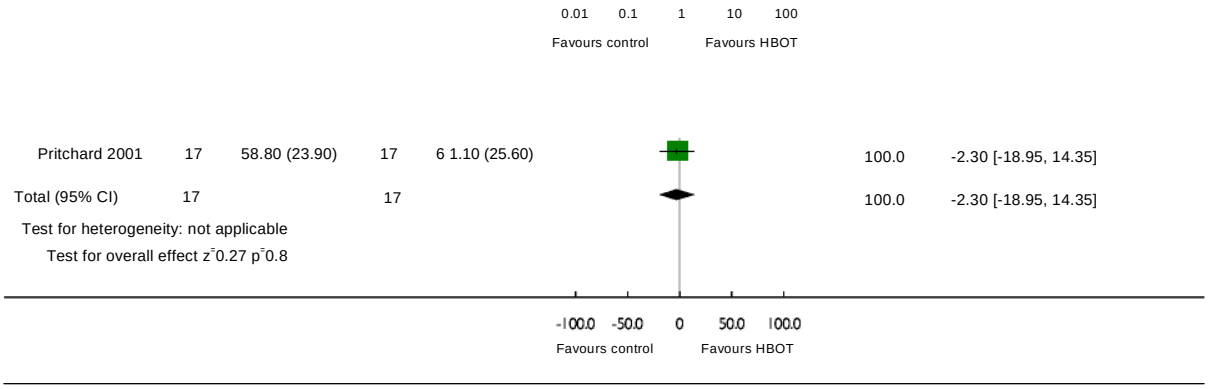
Analysis 05.01. Comparison 05 Resolution of swelling, Outcome 01 Improvement of lymphoedema

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 05 Resolution ofswelling

Outcome: 01 Improvement of lymphoedema





Analysis 06.01. Comparison 06 Improvements in quality of life or function, Outcome 01 SF-36 mean score at twelve months (general health)

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 06 Improvements in quality of life or function Outcome: 01

SF-36 mean score at twelve months (general health)

Study	HBOT N	HBOT Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI

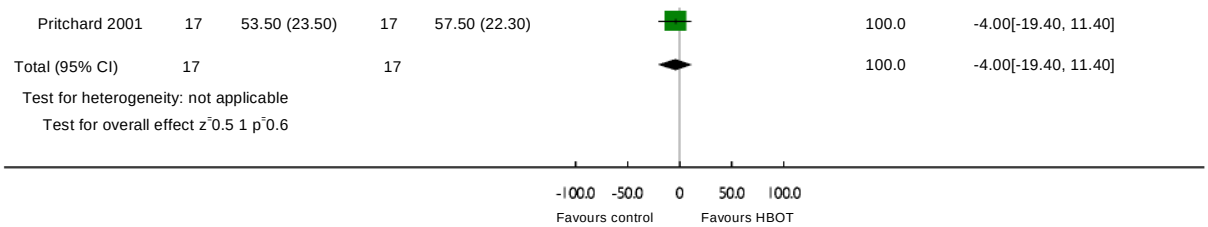
Analysis 06.02. Comparison 06 Improvements in quality of life or function, Outcome 02 SF-36 mean score for physical function at 12 months

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 06 Improvements in quality of life or function Outcome: 02

SF-36 mean score for physical function at 12 months

Study	HBOT N	HBOT Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI

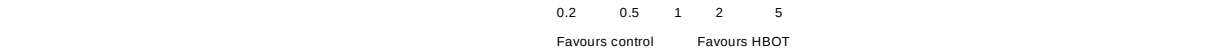


Analysis 07.01. Comparison 07 Osteoradionecrosis, Outcome 01 Complete mucosal cover

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 07 Osteoradionecrosis
Outcome: 01 Complete mucosal cover

Study	HBOT n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Marx 1985	35/37	26/37		43.3	1.35 [1.08, 1.68]
Marx 1999a	48/52	34/52		56.7	1.41 [1.14, 1.75]
Total (95% CI)	89	89		100.0	1.38 [1.19, 1.61]

Total events: 83 (HBOT), 60 (Control)
Test for heterogeneity chi-square=0.09 df=1 p=0.76 I² =0.0%
Test for overall effect z=4. 1 1 p=0.00004

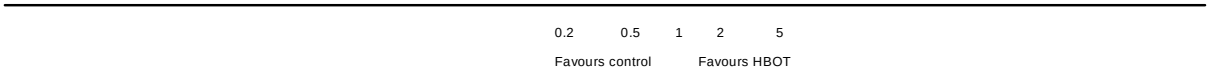


Analysis 07.02. Comparison 07 Osteoradionecrosis, Outcome 02 Establishment of bony continuity

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 07 Osteoradionecrosis
Outcome: 02 Establishment of bony continuity

Study	HBOT n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Marx 1999a	48/52	34/52		100.0	1.41 [1.14, 1.75]
Total (95% CI)	52 Total	52		100.0	1.41 [1.14, 1.75]

events: 48 (HBOT), 34 (Control) Test for heterogeneity: not applicable Test for overall effect z=3. 18 p=0.001

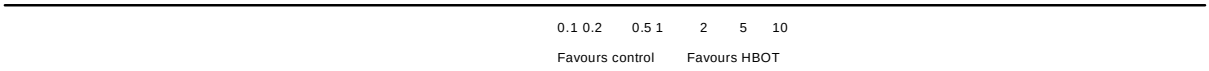


Analysis 07.03. Comparison 07 Osteoradionecrosis, Outcome 03 Successful healing oftooth sockets after tooth extraction

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 07 Osteoradionecrosis

Outcome: 03 Successful healing of tooth sockets aftertooth extraction

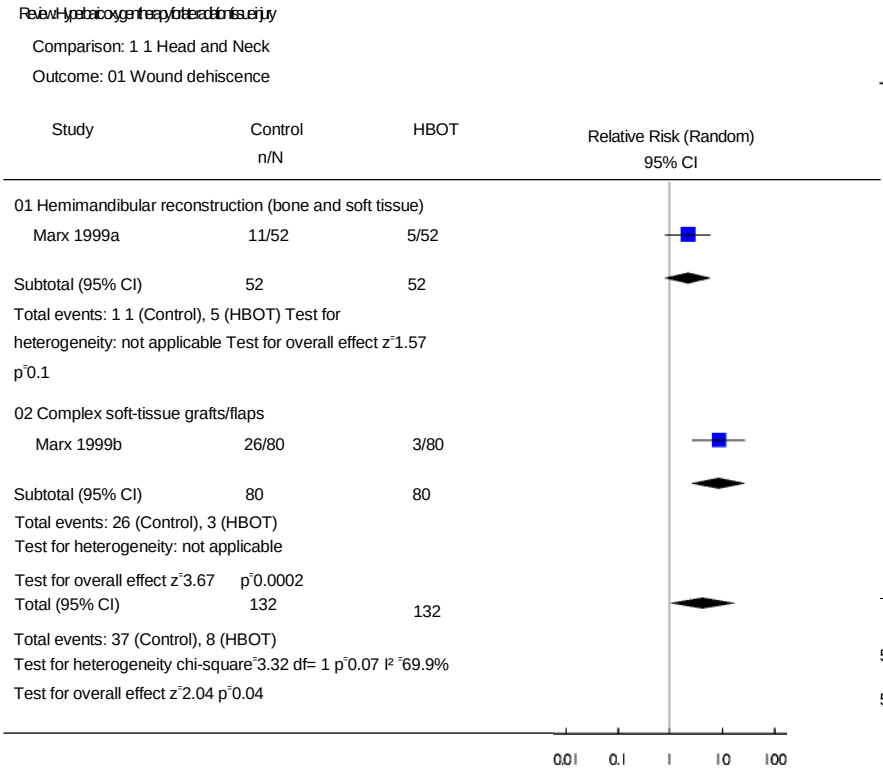


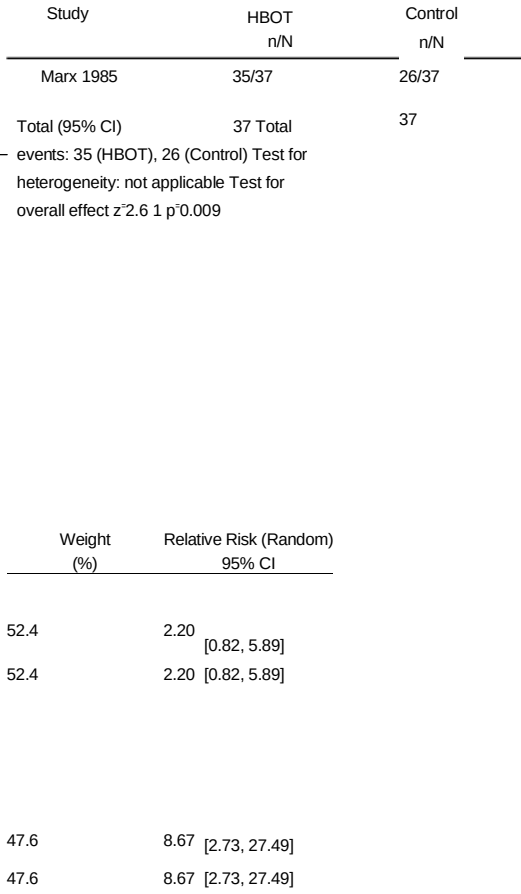
Analysis 11.01. Comparison 11 Head and Neck, Outcome 01 Wound dehiscence

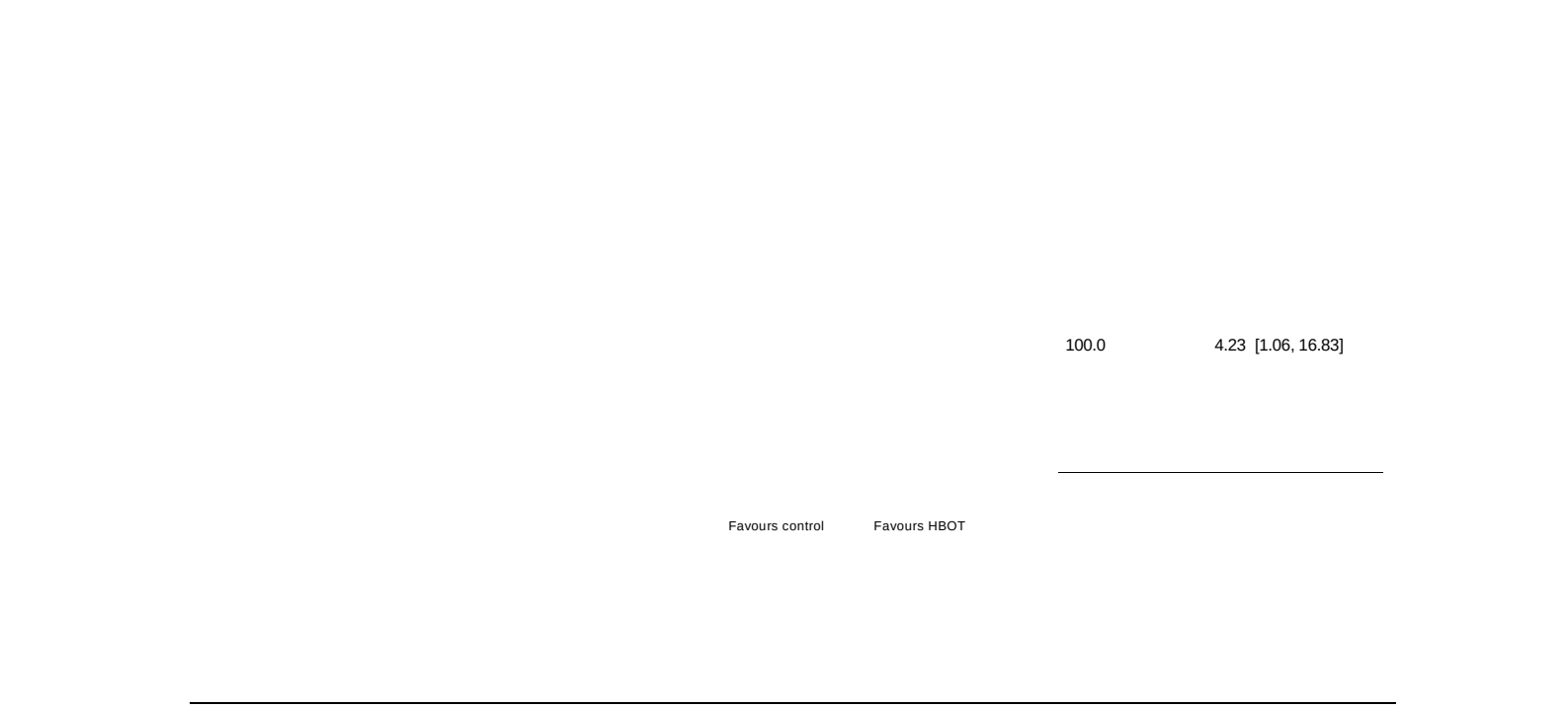
Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 1 1 Head and Neck

Outcome: 01 Wound dehiscence







Analysis 12.03. Comparison 12 Neurological tissue, Outcome 03 Warm sensory threshold one week after treatment (degrees Centigrade change from baseline)

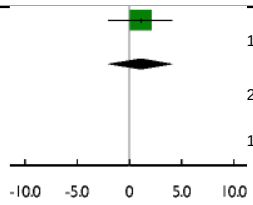
Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 12 Neurological tissue

Outcome: 03 Warm sensory threshold one week after treatment (degrees Centigrade change from baseline)

Study	Control		HBOT		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Pritchard 2001	17	1.00 (3.92)	17	-0.12 (5.01)		100.0	1.12[-1.90,4.14]
Total (95% CI)	17		17			100.0	1.12[-1.90,4.14]

Test for heterogeneity: not applicable Test for overall effect z=0.73 p=0.5



Favours control

Favours HBO

Analysis 12.04. Comparison 12 Neurological tissue, Outcome 04 Warm sensory threshold at one year

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 12 Neurological tissue

Outcome: 04 Warm sensorythreshold at one year

Study	Control		HBOT		95% CI Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)		(%)	95% CI
Pritchard 2001	17	0.53 (3.43)	17	1.40 (5.54)		100.0	-0.87 [-3.97, 2.23]
Total (95% CI)	17		17			100.0	-0.87 [-3.97, 2.23]

Test for heterogeneity: not applicable Test for overall effect z=0.55 p=0.6

Favours control

Favours HBOT

Analysis 12.06. Comparison 12 Neurological tissue, Outcome 06 Net number of significantly improved neuropsychological tests at three months (25 tests total)

Study	HBOT		Control		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	
Hulshof 2002	4	3.30 (3.40)	3	1.30 (1.20)		100.0	

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 12 Neurological tissue

Outcome: 06 Net number of significantly improved neuropsychological tests at three months (25 tests total)

Total (95% CI)	4		3			100.0	2.00 [-1.60, 5.60]

Test for heterogeneity: not applicable Test for overall effect z=1.09 p=0.3

Favours control

Favours HBOT

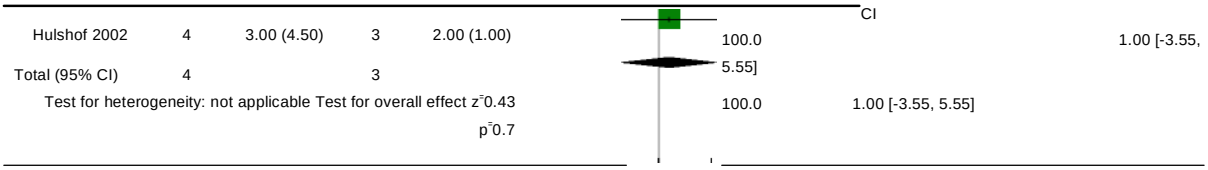
Analysis 12.07. Comparison 12 Neurological tissue, Outcome 07 Net number of significantly improved neuropsychiatric tests at six months

Review: Hyperbaric oxygen therapy for late radiation tissue injury

Comparison: 12 Neurological tissue

Outcome: 07 Net number of significantly improved neuropsychiatric tests at six months

Study	HBOT		Control		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)		95% CI	(%)	95% CI
Hulshof 2002	4	3.00 (4.50)	3	2.00 (1.00)		100.0		1.00 [-3.55, 5.55]
Total (95% CI)	4		3			100.0		1.00 [-3.55, 5.55]
Test for heterogeneity: not applicable Test for overall effect z=0.43 p=0.7								



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" 'lie JOURNAL OF UROLOGYVol. 159, 1630-4632, May 1998

HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF RADIO-INDUCED LESIONS IN NORMAL TISSUES

CONSENSUS CONFERENCE
Long Version
Jointly held by:
EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY - ESTRO
AND
EUROPEAN COMMITTEE FOR HYPERBARIC MEDICINE - ECHM
October 19-20th, 2001
Lisbon – Portugal

Pasquier et. al. Radiotherapy and Oncology 72 (2004) 1-13

Introduction

Surgery, radiation therapy and cytotoxic chemotherapy are the principal methods employed in the treatment of cancer. Although all have achieved considerable advances in the attainment of cure all are associated with a risk of morbidity and mortality. Radiation therapy differs from the other two modes of treatment in that its most serious associated morbidity tends to occur months and commonly years after treatment when management is often difficult and unsatisfactory.

It has been estimated that within the European Union there are five million people alive at five years or more after having received radiation therapy as the principal or as an adjuvant method of treatment. Although the large majority are fit and well with little or nothing to relate to the treatment given, troublesome symptoms may be present in up to 5% due to late radiation changes. Perhaps as many as 1%, that is, 50,000 people, may have serious problems, which are resistant to simple methods of treatment. Major surgery may be required as well as prolonged hospital care. Personal and social problems may be very distressing and commonly those affected are unable to pursue gainful employment.

Because a dominant feature of post-radiation change is the obliteration of small blood vessels leading to hypoxia, hyperbaric oxygen has been employed in the care of these patients. In the past forty years there have been many publications reporting benefit in studies, which have included some thousands of patients. Because the literature is dominated by case series containing modest numbers and by case reports and because there have been few randomised trials, there is considerable uncertainty as to the place of hyperbaric oxygen in the management of radiation morbidity. The importance of the problem led the European Society of Therapeutic Radiology and Oncology and the European Committee for Hyperbaric Medicine to jointly organise a Consensus Conference, so that the evidence could be reviewed and guidance drawn up as to clinical practice.

Format of the Conference

After listening to evidence, a jury drawn from authorities in the areas of medicine concerned, were asked to answer six questions covering the field of concern.
The jury and those attending the conference were informed by two highly detailed literature reviews:

(i) Radio-Induced Lesions in Normal Tissues: Incidence, Risk Factor and Conventional Treatment. Dr David Pasquier, Centre Oscar Lambret, Lille, France

(ii) Hyperbaric Oxygen Therapy in Radionecrosis (A review of the literature). Dr Jorg Schmutz, Hyperbaric Center, Basel, Switzerland

Nine experts prepared written reviews often with the assistance of colleagues and gave presentations which extended through the whole of the first day of the conference:

(iii) Professor Michael Baumann
Carl Gustav Carus, Dresden, Germany
Incidence, risk factors and cost of radio-induced lesions in normal tissues.
Written review by: Baumann, M. Holscher, T.

(iv) Professor Bernard Dubray
Centre Henri Becquerel, Rouen, France
Pathophysiological basis of radiation-induced lesions in normal tissues.
Written review by: Dubray, B. Lefaix, J-L. Martin, M. Delanian, S.

(v) Professor Gosta Granstrom
Goteborg Universitat, Goteborg, Sweden
Pathophysiological basis for HBO in the treatment of healing disorders in radio-injured normal tissues. Written review by: Granstrom, G.

(vi) Professor Johannes Van Merkesteyn
Leiden University Medical Center, The Netherlands
Hyperbaric oxygen therapy in the treatment of osteo-radionecrosis.
Written review by: Van Merkesteyn, J

(vii) Professor A J Van der Kleij
Academic Medical Center, Amsterdam, The Netherlands
Hyperbaric oxygen therapy in soft tissue radionecrosis. Radio-induced cystitis. Written review by: Van der Kleij, A J. De Rijke, T. Hulshof, M.

(viii) Dr F Roque
Hospital da Marinha, Lisboa, Portugal
Hyperbaric oxygen therapy for late radio-induced intestinal lesions.
Written review by: Roque, F. Saraiva, A. Simao, G. Sousa, A. Torres, P. Sampaio, J.

(ix) Professor J Yarnold
Institute of Cancer Research, Sutton, Surrey, UK
Hyperbaric oxygen therapy in soft tissue radionecrosis: Radiation-induced myelitis and plexopathy. Written review by: Yarnold, JR. Gothard, L.

(x) Professor John Feldmeier
Medical College of Ohio, USA
Hyperbaric oxygen: Does it have a cancer causing or growth enhancing effect? Written review by: Feldmeier, J.

(xi) Dr A Marroni
Centro Iperbarico Ravenna, Italy
A cost-benefit evaluation of hyperbaric oxygen use in tissue radio-induced lesions. Written review by: Marroni, A. Longobardi, P. Cali Corleo, R.

After each presentation there was a vigorous discussion amongst the 150 attendees who were physicians and surgeons with an interest in hyperbaric oxygen or radiation oncologists.

On the second morning there was a three-hour session of the jury. The members were:

Stanley Dische, President
Professor in Oncology – Centre for Cancer Treatment – Mount Vernon Hospital – UK
Dirk Bakker
Professor of Surgery – Academic Medical Center – Amsterdam – The Netherlands
Karl Hartmann
Department of Radiation Oncology – University of Dusseldorf – Germany
Ferran Guedea
Head of the department of Radiation Oncology – Institut Catala d'Oncologia – Barcelona – Spain
Joaquim Gouveia
Director Hospital Cuf-Descobertas/Former Director Instituto Portugues de Oncologia – Lisboa - Portugal
Eric Lartigau, ESTRO General Secretary
Professor in Radiation Oncology – Centre Oscar Lambret – Lille – France
Daniel Mathieu, ECHM General Secretary
Professor in Critical Care Medicine – Centre Hospitalier Universitaire – Lille – France
Advising the jury were –
David Pasquier
Centre Oscar Lambert – Lille – France
Jorg Schmutz
Hyberbaric Center – Basel – Switzerland

After the meeting of the jury there was an immediate report to the conference by the President of the Jury. A written report was drafted by the President and circulated to all members of the jury for comment, addition and deletion before presentation for publication.

Conference Report

The jury discussed all the evidence put before it and came to recommendations for clinical practice. In assessing the quality of the evidence, the scale:

1 (strong)
2 (convincing evidence)
3 (existing but weak evidence) and
4 (anecdotal evidence) was employed

The jury were grateful to the eleven reviewers who worked so hard to collect and analyse the evidence, which they had considered. These valuable reviews, which were at a high standard of scholarship, will be published on the web of ESTRO (www.estro.be), so as to be generally available. In this report the reviews will be referred to by the Roman numbers as noted above.

Question 1:

What are the incidence and the cost of the radio-induced lesions in normal tissues?

The jury was grateful to Professor Michael Baumann for his review of the subject. It was the modification of the late effects by use of hyperbaric oxygen that was the concern of the meeting and the incidence was much influenced by the definition and grading of the late changes. There was unfortunately no internationally agreed grading system but the

greatest experience was with the RTOG/EORTC system available for over thirty years and the LENT-SOMA, which was developed from it and published in 1995. Other systems such as the Franco Italian glossary and the dictionary approach had been proven of value in randomised clinical trials. International agreement as to the definition of morbidity would advance knowledge in the field. The Mitre Meeting held in Brussels in December 2000 effectively reviewed systems, which might be employed in routine practice. There was to be a meeting in Florida in April 2002 to try to make further advance in this field. The Conference gave its encouragement towards the pursuit of agreement in this area.

The hardest evidence as to the incidence of morbidity is contained in reports of randomised controlled clinical trials but some can be gained from reports of consecutive series. These have been reviewed by Dr Pasquier [i] and the incidence figures varied very widely according to definition and site. Even with one site a common range was from less than 1% to over 30%. There was no doubt that the incidence of late damage using the older techniques of radiotherapy, particularly the use of ortho-voltage apparatus, was considerable and has reduced with the employment of high energy equipment, with improvements in patient immobilisation, the introduction of precise planning using simulators and with greater precision in dose definition and delivery. Further improvements, such as advanced planning so that treatment is "conformal" to the tumour target volume and the use of intensity modulated radiotherapy, should spare normal tissue damage.

There were, on the other hand, developments in oncology, which might reverse this trend. "Conformal" radiotherapy has encouraged the attainment of higher tumour doses and inevitably some normal tissues will be included. The concomitant administration of cytotoxics where an adjuvant effect is likely to increase the incidence of late damage and the quantitative importance of these drug radiation interactions are difficult to predict. An increasing use of major surgery for restoration of function or for salvage of advanced recurrent disease is also associated with a high risk of morbidity when a heavily irradiated area is operated upon.

The maximum tolerable radiation dose is often set as that which produces an incidence of 5% of moderate or severe late damage. The number of patients with severe damage that is resistant to simple measures is likely in actual fact to be much smaller. However, a prevalence of 1% does represent a very large number of patients in need of care.

The risk factors are similar over all sites and include the total radiation dose, the overall time, the biological effective dose which takes into account fraction size and the overall time, the volume irradiated, the use of a combination of external beam with an implantation or intracavitary procedure, a high dose rate with brachytherapy, tumours adjacent to or involving bone, the presence of infection, the use of surgery and the occurrence of trauma.

Although we need better data concerning the incidence of late damage due to radiotherapy in routine practice the level of evidence to support the observations about incidence which we have made is extensive and certainly can be regarded as being at level 1/2.

Professor Baumann could find very little useful evidence to answer the question concerning the cost of morbidity. Dr Marroni, in his contribution [xi] concerned with cost effectiveness, has reviewed two papers from the United States concerned with mandibular radionecrosis where the average yearly costs of care reached $140,000 Much of the cost was due to hospitalisation and drugs and these figures did not include costs due to loss of work and care at home. Dr Marroni presented data from Italian hospitals suggesting that over 3000 patients in the year 2000 were discharged with a diagnosis of “radio-lesions of

the mandible and soft tissues» and these did seem to represent a high cost to the Italian Health Service. Dr Marroni also gave some evidence suggesting that hyperbaric oxygen treatment would considerably reduce the cost. The jury had some uncertainty about the reliability of this data but it did give some support to the view that the costs of care for radionecrosis were extremely high and that these might be reduced with the use of hyperbaric oxygen. Overall the current evidence was regarded to be at level 3, that is, weak.

Question 2:

What tissue changes induced by radiotherapy lead to impaired healing in radioinjured normal tissues?

When heavily irradiated tissues are examined at an interval of months or years after treatment the characteristic findings are a cellular depletion, fibrosis and a reduction in vascular density with marked narrowing of the small blood vessels. There is therefore hypoxia due to the vascular changes. Professor Granstrom [v] described the changes, which may be observed in irradiated tissue.

Professor Bernard Dubray reviewed the subject and stressed the inter-relationship between these three types of change. The exact mechanism of production of these changes is undoubtedly complex and incompletely understood. Molecular biology has shown that hypoxia could trigger altered gene expression leading to a whole range of effects. Use of hyperbaric oxygen in these circumstances may also lead to complex changes, which may not all be favourable.

There is laboratory and clinical evidence that interstitial fibrosis and necrosis can, at least in part, be reversed by drugs such as exogenous SOD or a combination of Pentoxifylline and vitamin E. The mechanism whereby the benefit is gained remains obscure and Professor Dubray expressed the need for better knowledge of radiation induced late damage in normal tissues

Question 3:

What is the rationale for Hyperbaric Oxygen Therapy in the treatment of radioinduced lesions in normal tissues?

This subject was fully reviewed by Professor Granstrom (v). He considered papers, which gave evidence that there could be an increase in vascular density in irradiated skn and soft tissues after treatment with hyperbaric oxygen. There was further evidence using bone densitometry that new bone formation capacity could be increased. In a controlled study in rabbits where implants had been performed there was evidence of a significant increase in the force necessary to unscrew implants. In another animal study hyperbaric oxygen increased the capacity for osseo-integration. Further it has been found that hyperbaric oxygen could stimulate bone maturation.

Experimental studies of animals with myocutaneous flaps showed significantly increased vascularity with hyperbaric oxygen. It was found that steep oxygen gradients stimulated macrophage angiogenesis factor and macrophage derived growth factor. Bone healing in mice was enhanced.

There was evidence at a similar level which suggested that in patients, hypoxia was a major component of delayed wound healing because a reduced fibroblast activity and less efficient production of collagen. Hyperbaric oxygen inducing a temporary increase in the oxygen supply stimulated angiogenesis and modified fibrosis.

The jury considered there was a real rationale for hyperbaric oxygen to be used in radiation-induced morbidity as gained from these studies. The evidence was at level 1 and level 2.

Question 4:

What are the locations of radio-induced lesions where hyperbaric oxygen therapy has shown efficacy?

Mandibular osteo-radionecrosis:
Here there was a large body of evidence [i,ii & vi]. The conservative management combines the use of antiseptic solutions, analgesics, oral hygiene, systemic antibiotics and simple sequestrectomy. Lesions less than 1cm in maximum diameter commonly heal but larger lesions tend to be refractory, however very varied healing rates are reported in the literature [i].

When conservative measures fail then surgery, often mandibulectomy with complex reconstructive work becomes indicated. These procedures tend to be followed by post-operative complications, which tend to be great when a large area of heavily irradiated bone must be incised.

Hyperbaric oxygen has been used in the management of osteo-radionecrosis for forty years and it has often been employed with radical surgery, benefit rates of 30-100% have been reported but the situation is complex because surgery is also mployed in a number of the published series.

There is no randomised controlled trial of the use of hyperbaric oxygen in this area. However, impressive gains in healing have been reported when comparison has been made with previously treated cases. There were seven studies recorded since 1993 with improvements noted in 70-92% of the cases included in each series (ii).

In this situation where conservative treatment for gross mandibular radionecrosis can achieve at best a minimal healing and where commonly there may be progression of the process the results achieved in the management of consecutive cases can be given considerable importance. The proportion of cases showing improvement in many of the series was impressive. The jury felt that there was a considerable body of evidence to support a view that hyperbaric oxygen was effective in improving osteo-radionecrosis of the mandible and that it should be considered as part of management when conservative measures fail to allow healing to take place (**level 2 evidence**).

There was a wide variety of clinical presentation of osteo-radionecrosis of the mandible and the use of hyperbaric oxygen alone or in combination with surgery would need to be decided according to the features of a particular case.

Osteo-radionecrosis at other sites:
There was a body of literature concerned with the treatment of bone necrosis at other sites and these included the maxilla, spine and pelvic bones. Many of the contributions to the literature were anecdotal and the tendency for publication to be of positive results and lack of interest in publishing negative results must lead to some reservation. However, with the evidence for benefit in osteo-radionecrosis of the mandible, hyperbaric oxygen therapy could be considered as a possible method to employ in refractory cases of osteo-radionecrosis at other sites than the mandible (**level 3**).

Radionecrosis of the larynx:

Here there was some evidence of benefit. Five papers reporting a total of 45 cases with publication dates between 1976 and 2000 were available (ii). In general the majority of the patients appeared to benefit, however, the evidence must be regarded as insufficient and at **level 4**. Hyperbaric oxygen could be employed in this situation.

Radiation cystitis:
Here there was a considerable literature and fifteen papers reporting a total of 256 cases have been published since 1989 (ii). Haematuria was a dominant symptom, one which was relieved in many cases. Frequency and incontinence was also reported as improved in some cases. Professor Van der Kleij gave us a full review of the subject. Radiation cystitis occurred after radiotherapy for pelvic tumours, with incidence figures varying from less than 1 to over 30%. However, much depended on the radiotherapy given and the criteria for reporting the complications.

Conservative treatment included antibiotic therapy, corticosteroids, blood transfusion, bladder irrigation and Tocopherol.

Intervention included irrigation of the bladder with alum and installation of formalin solution. These measures can be effective but the use of formalin may be associated with major complications. Limited cysto-diathermy and laser photocoagulation may also be employed in the management of small areas of bladder where the sites of bleeding can be demonstrated.

Surgery in the form of a urinary diversion, an ileo-cystoplasty or a cystectomy with diversion may be employed. Operations performed in the heavily irradiated pelvis are associated with a high risk of further morbidities.

A recent literature review from Oxford identified 309 references where many different forms of treatment were employed. They concluded in the absence of randomised studies that it is impossible to set definite rules for treatment.
The jury were however impressed that in patients resistant to conservative treatment and where the only measure to be considered was cystectomy, there was a high rate of response to hyperbaric oxygen; while recurrence of bleeding did occur in some, there were a considerable number where the improvement was maintained long term. The jury therefore considered that there was convincing evidence (**level 2**) tha in this situation hyperbaric oxygen should be employed in management.

There was possibly a place for hyperbaric oxygen at an earlier stage when the simplest methods of treatment had failed to gain a response. Further this was a logical development but its adoption must depend upon the result of a randomised controlled clinical trial.

Radiation-induced proctitis and enteritis:
Here there was a considerable literature which had been gathered [I, ii & vi] for review by the conference and the jury. Fifteen papers reporting 256 cases treated with hyperbaric oxygen were found and there were 10 papers reporting 116 cases from 1993 to 2000 (i,ii). The majority of the cases were reported as either cured or improved with regard to the symptoms and/or clinical findings. In their review Dr Roque and his colleagues found 13 papers reporting 107 cases between 1990 and 2000, and gained an even greater impression of improvement (viii). The symptom and findings in these cases were obviously complex, making assessment difficult.

The jury concluded that hyperbaric oxygen could be employed in the management of radiation poctitis and enteritis, however the evidence must be regarded as at **level 3**.

Radiation plexopathy:
The review by Dr Yarnold assisted by Mrs Gothard reviewed radiation induced myelitis and plexopathy. A randomised controlled trial involving 31 patients with brachial plexopathy performed by Dr Yarnold and his colleagues had yielded no evidence for benefit but the study, though performed with great care, was considerably underpowered. There were, in addition, a number of anecdotal reports concerning the use of hyperbaric oxygen for brain necrosis and radiation myelitis, however the evidence was unconvincing. There was therefore considerable uncertainty as to the place of hyperbaric oxygen in the treatment of radio necrosis in central nervous system and we could therefore come to no recommendation as regards its place in management.

Other sites
Evidence was presented concerning the use of hyperbaric oxygen at other sites, which included skin, the subcutaneous tissues, the eye and breast. The largest body of evidence was with regard to the **breast** where there may be a place for hyperbaric oxygen however the evidence must be regarded as weak (**level 3**)

Question 5:
May hyperbaric oxygen therapy play any role in the prevention of radio-induced tissue lesions?

a) Tooth extraction in irradiated tissues
Here there was considerable evidence gathered by our reviewers [eye,ii,v & vi]. Included was a randomised controlled trial performed by Marks [v, p.87] and the result was supported by other studies reporting consecutive cases where a comparison was made with cases managed without hyperbaric oxygen. The jury felt that there was convincing evidence (**levels 1 and 2**) that in a situation where teeth extraction was planned in an area of mandible or maxilla which had received high dose radiotherapy, hyperbaric oxygen importantly reduced the risk of osteo-radionecrosis. However some evidence was presented that the risk of tooth extraction in irradiated tissue was normally so low that hyperbaric oxygen was unnecessary as a preventative measure. It was however felt by the jury that in this report case selection may have played a role in that the radiation doses may have been moderate and so the risk may have been so low as to make hyperbaric oxygen unnecessary. This was obviously an area where radiation oncologist and surgeon must collaborate together to assess the site, volume and radiation dose so as to determine the indication. It was also obviously an area for further randomised studies.

b) Surgery in irradiated tissue
Considerable evidence was brought before the jury that post operative complications could be reduced by the use of hyperbaric oxygen when major surgery was planned in previously irradiated patients. Wound infections and dehiscence were significantly reduced as well as delayed wound healing reported as serious. No randomised controlled study has however taken place. The jury felt it was an area where hyperbaric oxygen may well have a place but the evidence remained weak (**level 3**) in the absence of a randomised controlled trial published in peer-reviewed journals, which is always necessary when a measure for prevention is being assessed.

c) Implants in irradiated tissues
There is an increasing use of implantation of metal prostheses into heavily irradiated tissue as restorative surgery is increasingly used in patients who have extensive resections and radiotherapy for advanced tumours. There was suggestive evidence that hyperbaric oxygen could have a role but it must be regarded as still insufficient to be

regarded as convincing evidence and so, remaining at **level 3** and again a need for a randomised controlled clinical trial was clear.

Question 6

Is hyperbaric oxygen therapy cost effective in these indications?

An important consideration in a patient with malignant disease was the possibility that there could be a harmful effect of hyperbaric treatment. Professor Feldmeier gave us a most interesting review of this subject. The question first arose over forty years ago when patients were being treated by radiotherapy in hyperbaric oxygen chambers. Dr Feldmeier effectively reviewed the subject and showed that the evidence that hyperbaric oxygen disseminated tumour and led clinically to a higher incidence of distant metastasis was extremely weak and the jury were convinced that this was not a problem. In patients who suffered post-radiation phenomenon the large majority were, of course, free of tumour so this was not a problem to even consider.

The evidence produced in reviews (iii) and (xi) has already been considered. The jury felt that there was so little hard evidence in this field that it was not possible to reach a conclusion. Costs of hyperbaric therapy could be measured but even here it was necessary to consider the personal and social costs as well as that of the actual treatment. The cost of radiation morbidity itself is obviously high but until real data was available it was not possible to determine whether hyperbaric oxygen would truly have a cost-saving effect. Their impression was that this would be the case but presently this could not be substantiated by hard evidence.

Future Research

The Consensus Conference did reveal many areas where research was required in order to advance knowledge and to lead to evidence-based decisions as to the place of hyperbaric oxygen in the management of late radiation morbidity.

The jury felt that data should be gathered concerning:

1. The incidence of post-radiation morbidity in routine practice. An internationally agreed simple system for recording such morbidity would be an essential prerequisite
2. Cost of radiation morbidity.

The jury felt that randomised controlled clinical trials were indicated in the clinical situations:

1. Where tooth extraction is planned in areas, which have received radiotherapy, but where the post-radiation change is not gross so as not to be included in the group where the jury felt that hyperbaric oxygen was already indicated.

2. In patients who are planned for extensive restorative surgery and/or prosthetic implantation after large volume radiotherapy to tumourcidal dosage.

3. Patients with irradiation cystitis after simple methods of management had failed but before the stage at which cystectomy/urinary diversion had become indicated.

The jury felt that these were all areas where, on a European basis, in a close collaboration between physicians and surgeons concerned with hyperbaric oxygen and radiation oncologists, together with surgeons called on to operate in postradiation situations, trials could be established, performed at a high standard and recruit sufficient numbers of patients.

Table I : Scale used to assess the evidence presented

Level
Grade
Definition

Strong evidence of beneficial action. At least 2 concordant, large, doubleblind, controlled randomised studies with no or only weak methodological bias.

Level 2
Convincing evidence of beneficial action. Existence of double-blind controlled, randomised studies but with methodological bias, or concerning only small sample, or only a single double-blinded, controlled, randomised study.

Level 3
Evidence of beneficial action but weakly supported. Only uncontrolled studies : historic control group, cohort study, …

Level 4
Anecdotal evidence of beneficial action Case report only or methodological or interpretation bias preclude any conclusion.

Table II :
Indications of HBO in the treatment of radio-induced lesions in normal tissues

Recommendation grade
Indication

Level 2 – convincing evidence
Radionecrosis of the mandible
Radiation Cystitis of the bladder resistant to conservative measures
Tooth extraction in irradiated tissues (preventive action)

Level 3 - Evidence of beneficial action but weakly supported.
Radionecrosis of other bones
Radiation-induced proctitis and enteritis
Radiation-induced lesions of soft tissues
Surgery and implants in heavily irradiated tissues (preventive action)

Level 4 – anecdoctal evidence
Radiation-induced lesions of the larynx
Radiation-induced lesions of the central nervous system.

No evidence to support
Radiation-induced plexopathy

Jones K, Evans AW, Levin W: RADIATION PROCTITIS TREATEMENT WITH HYPERBARIC OXYGEN . Proc. UHMS ASM 2004

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INTRODUCTION: Therapeutic radiation for malignant cancers in the pelvic region can result radiation proctitis in 2-20 % patients. About 70 % are mild and undergo remission in 2 years. There is no definite treatment available. Current modalities of treatment are medical therapies, which include oral and rectal steroids, 5-amino salicylates, sucralfate, short chain fatty acid, metranidazole, vitamin E and C, endoscopic therapies and surgical intervention. Of late, hyperbaric Oxygen therapy has gained acceptance as an option for the treatment of radiation proctitis. The aim of this study is to review the characteristics of these patients, treatment details, side effects and outcome of treatment.

METHODS: 16 patients with radiation proctitis were referred to the radiation late effect clinic in Princess Margaret Hospital during the period 2000 to 2004. Ten patients were treated with hyperbaric oxygen. Patients were retrospectively graded based on the LENT-SOMA classification. Upon initial assessment of these ten patients, three were ranked as grade 3 and seven were ranked as grade 2.

RESULTS: Outcome was clinically assessed. HBOT was well tolerated.

No. of Patients	Symptoms/Function	Response to		
		CR	PR	
9	Bleeding	4	3	
5	Pain/Discomfort	3	1	
5	Diarrheoa	1	3	

CR = completely resolved; PR = partially resolved; NR = not responsive.

Furthermore, a tool has been developed that will permit patients to self report their proctitis morbidity. This reporting is compatible with the recommended LENT-SOMA grading scale. Our experience with this tool will be discussed.

CONCLUSIONS: Hyperbaric treatment is an efficient treatment modality for patients with radiation proctitis. Education of peers regarding this form of treatment as a useful option should be a priority issue for treating institutions.

Mayer,-R; Klemen,-H; Quehenberger,-F; Sankin,-O; Mayer,-E; Hackl,-A; Smolle-Juettner,-F-M : Hyperbaric oxygen--an effective tool to treat radiation morbidity in prostate cancer. Radiother-Oncol. 2001 Nov; 61(2): 151-6

PURPOSE: We report the results of hyperbaric oxygen therapy (HBO) used in the treatment of radiation cystitis and proctitis following irradiation of prostate cancer.

MATERIALS AND METHODS: Between June 1995 and March 2000, 18 men (median age 71 years) with radiation proctitis (n=7), cystitis (n=8), and combined **proctitis/cystitis** (n=3) underwent HBO therapy in a multiplace chamber for a median of 26 sessions (range 2-60). The treatment schedule (2.2-2.4 atmospheres absolute, 60 min bottom time, once-a-day, 7 days a week) was set at a lower limit of 20 sessions; the upper limit was left open to symptom-related adjustment. Prior to HBO treatment, RTOG/EORTC late genitourinal (GU) morbidity was Grade 2 (n=3), Grade 3 (n=6) or Grade 4 (n=2); modified RTOG/EORTC late gastrointestinal (GI) morbidity was either Grade 2 (n=4) or Grade 3 (n=6).

RESULTS: Sixteen patients underwent an adequate number of sessions. RTOG/EORTC late GU as well as modified GI morbidity scores showed a significant improvement after HBO (GI, P=0.004; GU, P=0.004; exact Wilcoxon signed rank test); bleeding ceased in five out of five patients with proctitis and in six out of eight patients with cystitis; one of those two patients, in whom an ineffective treatment outcome was obtained, went on to have a cystectomy.

CONCLUSIONS: HBO treatment seems to be an effective tool to treat those patients with late GI and GU morbidity when conventional treatment has led to unsatisfactory results. Particularly in patients with radiation cystitis, HBO should not be delayed too long, as in the case of extensive bladder shrinkage improvement is hard to achieve.

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PREOPERATIVE HYPERBARIC OXYGEN THERAPY FOR RADIATION INDUCED INJURIES

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ABSTRACT

Purpose: We present our experience with preoperatively administered hyperbaric oxygen therapy to patients who have sustained **significant** therapeutic radiation induced soft tissue injuries and subsequently undergo planned abdominal intervention/surgery.

Materials and Methods: From February 1993 to May 1997, 5 patients with a history of complications following therapeutic radiation were prospectively treated with hyperbaric oxygen before a planned abdominal operation.

Results: All patients had uneventful hospital courses. An additional procedure was eventually necessary in 2 patients but with fewer radiation related problems following hyperbaric oxygenation.

Conclusions: Hyperbaric oxygenation may improve postoperative outcomes when given before planned open operations in patients with previous therapeutic pelvic irradiation and a history of radiation related complications.

KEY WORDS: enteritis, hyperbaric oxygenation, radiation injuries, pelvic neoplasms

Damage to normal tissue and impaired tissue healing are well recognized sequelae of therapeutic radiation. In urological surgery these injuries often manifest as radiation cystitis, radiation enteritis and impaired healing with resultant fistulas, strictures and delayed wound healing. They are often insidious and progressive processes with a low likelihood of spontaneous healing. Hyperbaric oxygen therapy has known value in the treatment of radiation related injuries in head and neck surgery. It has also been shown in several series to be effective in treating radiation cystitis refractory to conventional therapy.[1-8] However, to our knowledge there are no reports concerning use of hyperbaric oxygen to treat other radiation injuries encountered by urological surgeons, especially when used preoperatively.

MATERIALS AND METHODS

During the last 4 years 5 patients with histories of radiaem'on induced injuries, poor wound healing and/or complications following prior operations were treated with hyperbaric oxygen before an additional planned abdominal procedure. Patient age ranged from 34 to 55 years (mean 44). Hyperbaric oxygen therapy was administered in a monoplace chamber. Smoking cessation was encouraged in all active smokers. We delivered 100% oxygen at 2.0 atmospheres absolute for 90 minutes at a time. After the first patient the protocol was to treat 5 or 6 days a weck for a total of 30 treatments preoperatively and 10 treatments postoperatively. Most of the sessions were delivered in an outpatient setting. The only complication of hyperbaric oxygen was serous otitis requiring myringotomy tubes in 1 case.

CASE HISTORIES

Case I. A 53-year-old white man was diagnosed with stage T3b grade 111/111 transitional cell carcinoma of the bladder in June 1991. He was treated with combination chemotherapy and external beam radiation. A total of 6,800 cGy. was delivered to the pelvis, and another 5,040 cGy. to the pelvic lymph nodes. The tumor recurred and in August 1992 salvage cystoprostatectomy was performed with an Indiana pouch continent urinary diversion. Severe radiation changes were evident in the pelvis and throughout the gastrointestinal tract. Reexploration 2 months later for feculent drainage per urethra revealed a necrotic sigmoid colon, which was resected, and a colostomy was created. A pouch lenk developed, which was controlled with bilateral nephrostoiny tubes. By March 1993 it was apparent that another laparotomy was needed to repair the nonhealing pouch.

In preparation the patient received 25 sessions of hyperbaric oxygen in 6 weeks. The following month the previous diversion was removed and a colon conduit was created. Subjectively, a surgeon present at each of the procedures (R. J. T.) believed that the bowel appeared much healthier and that it bled normally, unlike during previous explorations. The patient received a total of 84 treatments of postoperative hyperbaric oxygen. A small enterocutaneous fistula developed at a site distant from the anastomosis requiring open repair 6 months later. Subsequently, there were no further problems with the gastrointestinal and genitourinary tracts and no further open operations were performed. The patient died in September 1996 of complications related to peripheral vascular disease.

Case 2. A 46-year-old white woman was diagnosed in March 1991 with a mixed endometrioid and grade 111/111, stage IIc clear cell ovarian epithelial carcinoma. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, tumor debulking and omentectomy. I'ostoperatively 6 cycles of chemotherapy were given, consisting of cyclophosphamide. Following chemotherapy she underwent a second exploratory laparotomy due to increasing CA-125 levels and a suspicious pelvic lesion identified on positron emission tomography. The recurrent tumor was resected and ^{125}iodine seeds were placed around the tumor bed. The total activity of the brachytherapy implant was 20.6 mCi. Following recovery the patient received 6,000 cGy. external beam radiation, a third of which was delivered strictly to the pelvis.

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guring 1992, 3 more laparotomies were performed for bowel adhesions and a rectal stricture, with creation of a colostomy and resection of a significant portion of the small bowel. Due to the short length of remaining bowel and to radiation enteritis nutrition was maintained with daily hyperalimentation. Subsequently retroperitoneal fibrosis, bilateral ureteral obstruction and radiation cystitis developed.

At the time of referral in July 1995 she had bilateral percutaneous nephrostomy tubes in place for urine drainage. A total of 30 treatments of hyperbaric oxygen were given 2 months before a planned abdominal operation. In November the colostomy was revised and the remaining small bowel was incorporated into continuity. Bladder augmentation was performed using a portion of the left colon. Although small and scarred, the bladder wall bled well when opened. Ten postoperative hyperbaric oxygen treatments were given. The wounds and anastomoses healed well, and at 18-month followup she is tube-free, voiding normally with minimal incontinence and has stable renal function. Although the fecal transit time is still relatively short, with some dietary modifications weaning from hyperalimentation was accomplished. No further operative procedures have been necessary and she remains without evidence of tumor recurrence.

Case 3. A 41-year-old white woman diagnosed with bulky stage IB adenosquamous carcinoma of the cervix in Novem-60$^{0'}$993 was treated with external beam radiation and bic...aytherapy implants for 3 months and received 8,196 cGy. to the pelvis. Although clinically free of tumor, she began having intermittent gross hematuria in addition to incapacitating urinary frequency and nocturia. Cystoscopy with biopsy and urodynamics ruled out recurrent tumor, revealing a bladder with a 95 ml. capacity and severe radiation changes.

In February 1996 the patient received 30 treatments of hyperbaric oxygen before a planned urinary diversion. Following hyperbaric oxygen hematuria resolved but bladder capacity remained small, significantly affecting quality of life. At laparotomy in May the bladder was too hypovascular to support an enterocystoplasty, and so an Indiana pouch was formed. The wounds and pouch healed well, and the patient was satisfied with the catheterizable pouch. Postoperative hyperbaric oxygen treatments were refused. The defunctionalized bladder has been asymptomatic. A colovaginal fistula 15 months later developed for which a sigmoid colostomy was created. Convalescence was uneventful.

Case 4. A 34-year-old Hispanic woman underwent radical hysterectomy. for stage IB cervical carcinoma, which was Toll d by 5,025 cGy. external beam radiation. A right ureterginal fistula developed 8 months postoperatively, which was treated conservatively with a nephrostomy tube but it recurred and transureteroureterostomy was performed. Subsequently the patient continued to void urine per vagina and a vesicovaginal fistula was diagnosed and repaired in October 1995 by an abdominal approach with °mental interposition. Left ureteral obstruction developed 7 months later secondary to retroperitoneal fibrosis. In addition she was incontinent due to a noncompliant, relatively small capacity bladder.

With a history of poor postoperative healing and radiation damaged tissues, 30 treatments of preoperative hyperbaric oxygen were given. In October 1996 bilateral ureterolysis was performed with take down of the ureteroureterostomy and creation of a cecocystoplasty. Postoperatively, 10 treatments of hyperbaric oxygen were given. Recovery was uneventful, and the patient was continent on intermittent catheterization with stable renal function at last followup.

Case 5. A 47-year-old white man was diagnosed with a sacral chordoma in 1994, which was resected as was a pelvic recurrence later that year. Subsequently he received 6,300 cGy. pelvic irradiation. Although followed carefully a large pelvic recurrence was diagnosed January 1997. Before exploration, he received 30 treatments of hyperbaric oxygen. At operation in April the tumor was too extensive and invasive to remove entirely but muck of it was removed for palliation. Ten postoperative hyperbaric oxygen treatments were given. The bladder, prostate and rectum were left intact. The surrounding tissues appeared healthy with little of the radiation changes expected. He recovered well from the procedure and is currently being followed as an outpatient.

D ISC USS I ON

Therapeutic radiation is commonly used to treat pelvic malignancies. Not uncommonly, damage to nearby normal tissues occurs and occasionally causes significant complications. Radiation cystitis can manifest as hemorrhage and/or a small capacity bladder associated with frequency and urgency. Other processes of importance to the urological surgeon include poor surgical wound healing, retroperitoneal fibrosis, urinary fistula and radiation enteritis. The incidence of urological complications after pelvic radiation was 2.5% of 964 patients with 5 to 10-year followup reported by Dean and Lytton.[9] They found an increasing incidence of complications with doses of more than 6,000 cGy. More recently, Maier et al found a 1.24% rate of severe late urological complications in 10,709 patients who underwent primary radiotherapy for gynecological tumors.[10] These patients had difficult complications, including an anastomotic dehiscence, multiple fistulas and 3 deaths directly related to the radiation effects. Any form of treatment that could lessen the severity of these types of complications would be welcomed.

Marx and Johnson, as oral maxillofacial surgeons, focused their interest on radiation injury as it relates to the oral cavity, mandible and larynx.[11] They observed that the vascular endothelium is exquisitely sensitive to radiation injury. A progressive obliterative endarteritis occurs in tissues exposed to radiation in gradually lessening degrees as one progresses from the epicenter of radiation. The destruction of the microvasculature results in the 3 H's associated with radiation soft tissue injury, that is hypoxia, hypocellularity and hypovascularity. These deleterious effects are commonly unrecognized or underappreciated by most clinicians. Unfortunately these effects tend to progress with time, and clinical tissue injury is accelerated when the affected area is impacted by trauma, surgery and infection. With limited microvasculature available in areas of previous radiation, wound healing is commonly impaired as the delivery of nutrients, oxygen and antibiotics is compromised. Marx and Johnson observed that hyperbaric oxygen is the treatment capable of inducing angiogenesis in previously irradiated zones, thereby reversing radiation injury in the microvasculature, and routinely recommend preoperative hyperbaric oxygen to their patients with osteoradionecrosis.

In a review of hyperbaric oxygen Zel described the 5 major mechanisms of action as tissue hyperoxygenation, leukocyte activation, edema reduction, capillary angiogenesis and increased intracellular transport of antibiotics across cell membranes.[12] With hyperbaric oxygen tissue and arterial oxygen levels are elevated 10 to 15 times greater than normal, theoretically enabling an individual to survive on 100% oxygen at 3.0 atmospheres absolute on physically dissolved oxygen alone with no circulating hemoglobin for a limited period. Under hyperbaric condi tions, an increased pressure gradient is created from the elevated intravascular oxygen tensions in the normal surrouncling tissues to the more hypoxic conditions in radiation injured tissues, thereby resulting in an increased distance of oxygen diffusion from the intact vascular bed into the injured tissues. This combination of hypoxia and pulsed hyperoxia results in growth factor release by macrophages and stimulates angiogenesis.[13] With hyperbaric oxygen delivered in time, partial pressures of oxygen in radiation injured tissues can be restored to a near normal

range. The phagocytic action of leukocytes has been shown to be activated by hyperbaric oxygen. In a rabbit model it was demonstrated that hyperbaric oxygen was as effective as cephalothin in treating staphylococcal osteomyelitis due to the markedly improved phagocytic killing at elevated oxygen tensions." Tissue edema interferes with healing and it is decreased by 20% during hyperbaric oxygen.'[5] Lastly, Zel states that the modality has been shown to improve the transport of aminoglycosides across cell membranes.[12]

There have been a number of series in the literature showing the benefits of hyperbaric oxygen in the treatment of radiation induced hemorrhagic cystitis.[1-8] Weiss et al reported that 12 of 13 patients had durable cessation of hematuria.[8] All were difficult cases requiring hospital admission for intractable hematuria with radiation etiology. Norkool et al had a similar population of 14 patients, of whom 10 had a good outcome following hyperbaric oxygen.[4] They found the modality to be comparable in price and more effective than other forms of management. Of note, 2 of their patients had associated symptoms of radiation proctitis which resolved 1 to 2 weeks after treatment. The treatment protocol varies with the institution. Most centers use 2.0 atmospheres absolute for 60 to 90 minutes, although some deliver 2.4[2,4] or even 3.0.[1] Likewise, number of treatments delivered varies from 10 to 60. With relatively small numbers of patients and generally good results in all series, no conclusions can be made as to an ideal protocol.

Treatment of radiation proctitis with hyperbaric oxygen has not generally been as effective as that of osteoradionecrosis or radiation cystitis. Warren reported outcomes of 14 patients, of whom 8 had complete symptom resolution and 1 had significant improvement.[18] Only those with documented improvement on sigmoidoscopy had resolution of symptoms. The 65% improvement rate in this study provides some hope for this subgroup of patients.

The use of hyperbaric oxygen for treatment of radiation enteritis and proctitis was mentioned in the review by Ze1[12] but we were unable to find any mention in the world urological literature of using it to aid in postoperative healing of these and other radiation induced injuries. Our small series of patients with severely injured tissues and histories of radiation related complications did well following preoperative hyperbaric oxygen. The treatment was believed to enhance the vascular bed before surgical trauma, thus reducing the risk of postoperative complications, which is the same concept used in the treatment of osteoradionecrosis.

Our series has a number of shortcomings, the first of which is the small number of patients. Accumulating appropriüte patients at high risk of postoperative radiation related complications takes time even at a referral center. In addition, it is not possible to present objective findings to substantiate these observations further. Subjectively, the primary surgeon on all of these cases (R. J. T.), who is familiar with the hypovascular appearance of radiated bowel and other soft tissues, observed that the intraoperative appearance was much improved following hyperbaric oxygen in the 2 cases on which he had previously operated. The other 3 cases likewise had subjectively healthier appearing tissues compared to previous descriptions. All of the patients with severe radiation injuries seen during this time were treated with hyperbaric oxygen, providing no contemporary control group. Similarly, due to the small number and difficult nature of the complications in these patients, it is not possible to compare outcomes with historical patients. Subjectively, the treated patients had healthier appearing tissues and healed better than expected.

CONCLUSIONS

Hyperbaric oxygen therapy is effective in stimulating angiogenesis and subsequent healing in radiation injured tissues. It has been shown to have a place in the treatment of radiation cystitis and when given before surgical wounding in head and neck surgery. Our preliminary experience with hyperbaric oxygen given before abdominal and pelvic surgery to patients at risk of radiation related complications indicates that it is well tolerated and may aid in postoperative healing. Additional patients, objective findings and experience at other institutions are needed to confirm these observations.

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