Non-randomised Phase II Trial of Hyperbaric Oxygen Therapy in Patients with Chronic Arm Lymphoedema and Tissue Fibrosis after Radiotherapy for Early Breast Cancer

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Summary

Background
Radiation-induced arm lymphoedema is a common and distressing complication of curative treatment for early breast cancer. Hyperbaric oxygen (HBO₂) therapy promotes healing in bone rendered ischemic by radiotherapy, and may help some soft-tissue injuries too, but is untested in arm lymphoedema.

Methods
Twenty-one eligible research volunteers with a minimum 30% increase in arm volume in the years after axillary/supraclavicular radiotherapy (axillary surgery in 18/21 cases) were treated with HBO₂. The volunteers breathed 100% oxygen at 2.4 ATA for 100 minutes in a multiplace hyperbaric chamber on 30 occasions over a period of 6 weeks. The volume of the ipsilateral limb, measured optoelectronically by a perometer and expressed as a percentage of contralateral limb volume, was selected as the primary endpoint. A secondary endpoint was local lymph drainage expressed as fractional removal rate of radioisotopic tracer, measured using lymphoscintigraphy.

Findings
Three out of 19 evaluable patients experienced >20% reduction in arm volume at 12 months. Six out of 13 evaluable patients experienced a >25% improvement in ⁹⁹Tc-nanocolloid clearance rate from the ipsilateral forearm measured by quantitative lymphoscintigraphy at 12 months. Overall, there was a statistically significant, but clinically modest, reduction in ipsilateral arm volume at 12 months follow up compared with baseline (p = 0.005). The mean percentage reduction in arm volume from baseline at 12 months was 7.51. Moderate or marked lessening of induration in the irradiated breast, pectoral fold &/or supraclavicular fossa was recorded clinically in 8/15 evaluable patients. Twelve out of 19 evaluable patients volunteered that their arms felt softer, and six reported improvements in shoulder
mobility at 12 months. No significant improvements were noted in patient self-assessments of quality of life.

**Interpretation**

Interpretation is limited by the absence of a control group. However, measurement of limb volume by perometry is reportedly reliable, and lymphoscintigraphy is assumed to be operator-independent. Taking all data into account, there is sufficient evidence to justify a double-blind randomised controlled trial of hyperbaric oxygen in this group of patients.

**Background**

Clinical syndromes associated with radiotherapy complications are variable, but all are progressive and irreversible [27]. The commonest indication for high dose radiotherapy in the UK is the management of women with early breast cancer. A proportion of this population develop arm lymphoedema, painful hardening and shrinkage of the breast, rib fracture, lung damage, cardiac injury and, rarely, nerve damage [1]. One of the commonest and most distressing of these consequences is lymphoedema of the upper limb when the axilla has been irradiated, especially following axillary surgery [6,26]. In severe cases, the volume of the limb is increased by 40% or more, causing disability by virtue of added weight and impeded joint movement [11]. In a population-based retrospective study in the South of England, 28% of 1,077 women remaining disease-free after treatment of breast cancer reported some degree of arm swelling [17]. No reliable data exist on NHS workload related to this group of patients, but the experience of patient advocate groups suggests that the need for rehabilitation services far exceed the resources available [12]. Conventional treatment consists of skin-care, exercises to maintain and promote shoulder movement, massage (either self- or professionally-applied) and compression garments to improve lymph drainage and soften the tissues. In many cases, the condition can be managed with appropriate advice and compression sleeves for life [16]. In a minority, compression bandaging and other measures fail to prevent progression to a grossly swollen limb. In response to the need for integrated management by a range of health professionals with appropriate expertise, clinical
oncologists, breast care nurses, pain specialists, physiotherapists, occupational therapists and complementary therapists have been identified in each NHS Region [12].

Data from our own study testing HBO₂ in patients with radiation-induced brachial plexopathy (RIBP) [20] showed no reliable evidence to support the hypothesis that HBO₂ therapy slows or reverses RIBP in a substantial proportion of affected individuals, although improvements in warm sensory threshold offered some suggestion of therapeutic effect. However, 2/6 cases with marked chronic arm lymphoedema reported major and persistent improvements in arm volume for at least 12 months after treatment with HBO₂. This observation was not anticipated, and forms the basis of the current hypothesis under test, namely that hyperbaric oxygen therapy improves long-standing arm lymphoedema in a proportion of patients. The study was performed in collaboration with the patient lobby group Radiotherapy Action Group Exposure (R.A.G.E.) and was funded by the UK Medical Research Council. The protocol was approved by the Research Ethics Committees of the Royal Marsden NHS Trust and the Institute of Naval Medicine.

**Patients and Methods**

*Eligibility and pretreatment assessment*

Inclusion criteria included ipsilateral arm lymphoedema following treatment for breast cancer causing ≥30% increase in arm volume, freedom from cancer recurrence, physical and psychological fitness for HBO₂, availability for follow up and written informed consent. Pretreatment baseline assessments included magnetic resonance imaging (MRI) of the suprACLAVICULAR fossa, axilla and brachial plexus to exclude cancer recurrence, clinical assessment of subcutaneous induration within the radiotherapy volume, measurement of arm volume using a perometer, quantitative lymphoscintigraphy to assess local lymph drainage in the forearm, clinical photographs and patient self-assessments using the EORTC Quality of Life Questionnaires QLQ-C30 and BR23 [3].

*Clinical assessments*
Clinical examination was undertaken by an oncologist to confirm trial eligibility and grade induration of the breast boost site, pectoral fold and supraclavicular fossa. The latter was done by palpation using a scale 0-3 (0 = none, 1 = a little, 2 = quite a lot, 3 = very much) and was repeated at follow up assessments by the same clinician to ensure consistency. Response was defined as an improvement of at least 2 grades (e.g. 3→1, 3→0, 2→0) at 12 months, since this was regarded as a clinically worthwhile improvement that could not easily be attributed to measurement error. Clinical photographs were taken of the upper body (hands on hips and above head) and of both arms, but response (change in photographic appearance at 12 months) was not predefined.

**Measurement of arm volume**

Arm volumes were measured in an operator-independent manner using a perometer (Model 400T, Pero-System GmbH, Wuppertal, Germany [5,24]). The volume from wrist to axilla was determined by placing the arm vertically inside a square measuring frame containing rows of infrared light-emitting diodes on two adjacent sides. On moving the frame along the arm, volume was calculated from pairs of diameter measurements every 3 mm, assuming a circular or elliptical cross-section. The volume of the ipsilateral limb was expressed as a percentage of the contralateral (control) limb volume. Response was defined in the protocol as a >20% reduction in ipsilateral arm volume on the grounds that this was considered a clinically worthwhile improvement unlikely to be due to supportive measures or changes in lifestyle.

**Quantitative lymphoscintigraphy**

Lymphoscintigraphy was performed on as many volunteers as possible. Patients were acclimatised to their surroundings for at least 45 minutes before starting. The patient sat with both arms resting on a table with palms facing up and the gamma camera (Starcam GE 400ACT, General Electric Medical Systems, Milwaukee, WI, USA), wide-field-of-view, low energy, high resolution collimator) positioned above the arms for ventral viewing. A site on the ventral surface of the ipsilateral forearm particularly affected by swelling was selected for injection (typically one-third of the distance from the
antecubital crease to the wrist). The site was carefully marked and the distance to the outstretched fingertip and to the olecranon process was measured in cm to enable relocation to the same position for the repeat scan at 12 months. The corresponding site on the contralateral arm was also marked. 0.2 ml of $^{99m}$Tc-Nanocoll in saline, containing approximately 35 MBq, was injected subcutaneously in each forearm using a 1-ml syringe and a 23-gauge needle. The site was not massaged. The camera was immediately lowered to 2 cm above the injection site and a 60-second static acquisition was performed. Acquisitions were repeated at 30 min, 60 min, 90 min, 120 min and 180 min. In between acquisitions the patient sat in the waiting room and read. No exercise was performed. The number of counts recorded within a rectangular region of interest (area 54 cm$^2$), encompassing the depot, was obtained from the computer (GE acquisition computer). The removal rate constant for the radiotracer, $k$ (local lymph flow per unit volume of distribution of tracer, units: % min$^{-1}$), was determined from the regression slope of the plot of log$_e$ fraction of counts remaining at the depot against time [25]. No formal definition of response was agreed prior to the study.

**Quality of life**

The EORTC core questionnaire QLQ-C30 and breast module BR23 were chosen for the study. The core questionnaire QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dysphnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease. The breast module BR23 comprises 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy and hormonal treatment), body image, sexual functioning and future perspective [3]. Volunteers were asked to complete set of a baseline questionnaires before they started HBO$_2$ therapy.

*Hyperbaric oxygen therapy*
Research volunteers were registered on the first day of treatment by a telephone call to the Clinical Trials & Statistics Unit, Institute of Cancer Research. Volunteers were compressed to 2.4 ATA (243 kba) in a multiplace Category 1 hyperbaric chamber at the Royal Hospital Haslar. Patients breathed 100% oxygen at pressure via a transparent hood. The total time at 2.4 ATA was 100 minutes, including two 5-minute ‘air breaks’. Each participant received a total of 30 pressure exposures, treating five days a week for six weeks.

**Follow up**

Clinical assessment and perometer measurement of arm volumes were repeated within 1 week of completing six weeks of HBO\textsubscript{2} therapy and 6 and 12 months after start of treatment. Self-assessments of quality of life were completed at the same intervals plus 3 and 9 months after start of treatment. Lymphoscintigraphy and clinical photographs were repeated at 12 months only.

**Endpoints**

The primary endpoint was defined as an absolute change of >20% in the relative volume of the ipsilateral arm vs. contralateral arm at 12 months. In addition, the relative change in excess arm volume (arm swelling) between baseline and 12 months was analysed as an unplanned endpoint.

Planned secondary endpoints included i) lymphoscintigraphy, ii) patient self-assessments of arm swelling, tissue hardness and physical functioning, and iii) physician assessments of photographic appearance and palpable induration of the breast/chest wall, pectoral fold and/or supraclavicular fossa. In addition, comments on arm softening and shoulder mobility volunteered by patients at clinical assessment were incorporated as unplanned endpoints.
**Sample size**

The appropriate size of the study group was determined by the feasibility of testing a complex treatment as much as by statistical considerations. A sample size of 21 patients was judged to be large enough to provide some indication of whether HBO$_2$ has any effect on arm lymphoedema.

**Analysis**

Change in ipsilateral arm volume was analysed on a continuous scale as the percentage change in excess volume of the swollen arm as a percentage of the contralateral arm at baseline (bl) and after therapy. In the protocol definition of response was an absolute change of >20% in the relative volume of the ipsilateral arm vs. contralateral arm at 12 months (absdif = voldif12-voldifbl) e.g. for case 1 (see Table 1) voldif12-voldifbl = 131-137 = -6 (minus sign indicates a reduction in volume). Change from baseline at 12 months was examined using a paired t-test, since an inspection of the histogram and normal probability plot suggested that a t-test was appropriate. In addition, the relative change in excess arm volume (arm swelling) between baseline and 12 months was analysed using the formula reldif = ((voldif12/voldifbl) x 100)-100 (where reldif is the relative difference in excess volume at 12 months e.g. for case 1 ((31/37) x 100)-100 = -16% relative change (reduction)). Health status scales were derived from the questionnaires using standard methods [3]. Change in lymphoscintigraphy, breast induration (palpation), breast appearance (clinical photographs), arm softening and shoulder mobility were recorded for each individual volunteer. No formal statistical analyses were planned of the secondary endpoints, since the sample size was not large enough to provide reliable results on multiple endpoints. However, it was felt appropriate to analyse the lymphoscintigraphy data formally. Paired t-tests were used after confirming the normality of the data.

**Results**

**Patient demographics**

The median age of the 21 volunteers (20 female and 1 male) at the start of HBO$_2$ was 64 years (range 53-76). The median time from primary therapy for breast cancer and onset of lymphoedema was 2
years (range 1 month-34 years). The median time from radiotherapy treatment to HBO₂ was 14 years (range 7-35). 10/21 volunteers had wide local excision as part of their primary treatment for breast cancer, and 8 of these patients had some form of axillary surgery as well. Eleven out of 21 volunteers underwent mastectomy, and 10 of these volunteers had some form of axillary surgery as well. The level of axillary surgery performed was described in various terms, including “level I” and “axillary clearance”, but the exact description was rarely available in the patients’ operation notes. All volunteers had radiotherapy to the breast/chest wall and axilla +/- supraclavicular fossa.

Compliance
Compliance with the treatment protocol was 100%. All planned 126 patient self-assessment questionnaires were completed and returned on time, and only two individuals missed follow up assessments (one moved away and declined her 12-month assessment; and another was hospitalised with septicaemia and was advised by her medical practitioners not to travel). Hence, 81/84 (96%) of perimeter measurements and clinical assessments were completed as planned. Due to logistical problems, only 15/21 (71%) patients entered the lymphoscintigraphy protocol. We found ourselves in a situation where we were ready to start HBO₂ therapy, but unable to fit in a sufficient number of pretreatment lymphoscintigraphy scans. It was therefore decided to enter as many volunteers as possible within the timeframe given, and the selection of individuals was entirely random. Fourteen out of 15 (93%) completed the lymphoscintigraphy protocol (one volunteer did not attend for her 12-month scan). Unfortunately, one follow up scan was accidentally erased from the computer system, and this volunteer was therefore not evaluable for the study.

Lymphoedema
Results of arm volume measurements before HBO₂, one week post-HBO₂, at 6 months and 12 months from study entry are listed in Table 1. Twenty-one out of 21 volunteers were assessed one week after the end of therapy (7 weeks after start of HBO₂), 20/21 at 6 months after start of HBO₂ and 19/21 at 12 months. For the purpose of the analysis only the 19 patients assessed at 12 months were included. The
median volume of the ipsilateral limb expressed as a percentage of contralateral limb volume at baseline was 154% (range 131-213%). One week after the end of HBO\textsubscript{2} therapy the median volume was 159% (range 128-205%). 6 months after start of therapy this was reduced to 150% (range 114-202%), and at 12 months the median volume of the ipsilateral limb expressed as a percentage of contralateral limb volume was 144% (range 115-199%). The mean difference calculated at the same time points changed from 157% at baseline to 149% 12 months after start of therapy.

In the trial protocol, a 'response' was defined as >20% reduction in arm volume at 12 months. This level of improvement was considered to be both clinically significant and unlikely to be attributable to supportive measures or change in lifestyle. 3 patients (volunteers 3, 14 and 15) were responders according to this classification (range 21-29%), 16 patients were non-responders and 2 patients (volunteers 7 and 21) could not be assessed, as they did not complete their 12-month clinical assessments. Examining the relative reduction in arm swelling (excess arm volume rather than total arm volume) as an unplanned secondary endpoint, 5/19 patients (volunteers 3, 6, 8, 14 and 15) experienced >20% (range 25-66%) reduction in arm swelling at 12 months.

There was a statistically significant reduction in arm volume from baseline at 12 months (p = 0.005). The mean percentage reduction in arm volume from baseline at 12 months was 7.68 (95% CI 2.65-12.72).

**Lymphoscintigraphy**

The lymphoscintigraphy outcome is shown graphically in Fig 1. Lymphoscintigraphy was performed before HBO\textsubscript{2} and 12 months after start of therapy as a planned secondary endpoint. This was not a condition for participation in the study, but 13/21 volunteers consented and were evaluable. The mean ratio between the lymphatic clearance rate in the arm affected by lymphoedema and the contralateral arm ($k_{\text{ipsilat}}/k_{\text{contralat}}$) at baseline was 0.76, i.e a reduction of 24% in the ipsilateral arm (constant with published findings [25]). At 12 months after the start of HBO\textsubscript{2} the mean value for $k_{\text{ipsilat}}$ had increased
from 0.0244 to 0.0334 min⁻¹ (59%), whereas the mean value for $k_{\text{contralat}}$ had increased from 0.0366 to 0.0386 min⁻¹ (19%). As a result, the mean ratio $k_{\text{ipsilat}}/k_{\text{contralat}}$ was increased to 0.92, i.e. an improvement of 16% at 12 months post start of HBO₂.

There was a statistically significant difference between $k_{\text{ipsilat}}$ and $k_{\text{contralat}}$ at baseline ($p = 0.05$), but not at 12 months after start of therapy ($p = 0.20$). Comparing $k_{\text{ipsilat}}$ at baseline and $k_{\text{ipsilat}}$ at 12 months there was a statistically significant improvement ($p = 0.03$), whereas there was no significant difference between $k_{\text{contralat}}$ at baseline and $k_{\text{contralat}}$ at 12 months ($p = 0.71$). Finally, when comparing the ratio ipsilateral/contralateral baseline versus 12 months there was a significant difference ($p = 0.02$).

**Clinical assessments including tissue hardness and clinical photographs**

The results of the serial clinical assessments of tissue hardness are summarised in Table 2. At baseline 17/19 patients had some degree of tissue hardness in irradiated areas of the breast/chest wall (n = 8), pectoral fold (n = 16) and/or supraclavicular fossa (n = 12). Softening of a substantial number of these sites was noted at the first post-therapy assessment one week after end of HBO₂, and further softening was recorded in some cases at 12 months post-therapy. The total improvement at 12 months were 1/8 (13%) sites on the breast/chest wall, 8/16 (50%) sites in the pectoral fold and 4/12 (33%) sites at the supraclavicular fossa (total 13/36 (36%) sites in 8/17 (47%) patients). Clinical photographs were taken of the volunteers at baseline and 12 months post start of HBO₂, but these were not found to be informative, recording no changes in appearance that were not recorded by perometry.

**QLQ-C30 & BR23 and patient self-reports**

The data were analysed but recorded no significant changes for better or worse over the study period (data not shown). However, a proportion (12/19, 63%) of volunteers reported a definite softening in the tissues of their affected arms. Six volunteers reported improvement in shoulder mobility and, in
cases of marked volume reduction, improved posture and less pain and feeling of heaviness, see Table 2. In Table 2, it is clear that there are no obvious associations between any of the endpoints reported.

**Discussion**

Fibrosis is believed to contribute to the development of lymphoedema. The pathophysiology of lymphoedema after radiotherapy and/or surgery involves obstruction of lymphatic flow causing an imbalance between capillary filtration and lymph drainage [16,23]. Although physical removal of lymphatic vessels at surgery offers a partial explanation, the variable onset, progression rate and ultimate severity indicate that this is not the only mechanism. Radiotherapy to the axilla is a potent cause of arm lymphoedema in its own right, more so after any kind of surgical disturbance of the axilla [9]. The continuous accumulation and contraction of scar tissue over many years is considered to be a cause of progressive lymphatic obstruction in response to radiotherapy. The most vivid accounts of fibrosis come from the surgical records of affected patients describing scar tissue infiltrating and compressing axillary structures, especially the neurovascular sheath.

The traditional view regards radiation fibrosis as a passive phenomenon, representing the residual extracellular matrix of a tissue depleted of cells. As such, fibrosis is regarded as an end-state beyond effective therapeutic intervention. An alternative model considers radiation fibrosis in terms of deregulated collagen metabolism with fibroblasts playing a central role [4,21]. The active model shares features with other fibrotic states characterised by chronic imbalances between collagen deposition and resorption [7]. The significance of the active model is that it raises possibilities for reversing established fibrosis.

Hyperbaric oxygen (HBO₂) therapy currently provides the strongest proof of principle in support of an active model for normal tissue responses to radiotherapy, with two comparative studies reported in patients with heavily damaged tissues. The first study tested preoperative hyperbaric oxygen against conventional penicillin cover in a randomised study of 74 patients requiring dental extraction.
following radical mandibular irradiation [15]. Only 5.4% of the patients in the hyperbaric oxygen
group compared to 30% of the patients in the penicillin-treated group experienced failure of wound
healing 6 months after surgery (p<0.05). In 160 patients treated by hyperbaric oxygen or standard
postoperative care following major soft tissue surgery for radiotherapy injury, four-fold reductions in
wound dehiscence, infection and delayed wound healing were seen in the hyperbaric oxygen treated
group (p<0.01) [13]. The pathological correlates of the response to hyperbaric oxygen in irradiated
tissues have been studied in animals, and include neovascularisation, organisation and marked
reductions in fibrous tissue [14]. However, it is not currently clear how these relate to the clinical
effects reported in humans.

There are several reports of HBO$_2$ in the treatment of patients with haemorrhagic cystitis following
pelvic radiation and refractory to conventional measures. Bevers et al. describe 40 patients treated for
20 sessions of HBO$_2$ for severe haematuria [2]. Thirty-seven of the 40 patients showed improvement in
symptoms and no adverse effects were reported. Lee et al. treated 20 similar patients from 1989-1992
and again showed improvement of haematuria in 90% [10]. Schoenrock and Cianci reported a patient
with severe haemorrhagic cystitis and a vesicocutaneous fistula which healed with HBO$_2$ [22]. Nakada
et al. gave 6 patients with radiation cystitis HBO$_2$ and also found improvement in all but one patient
[18]. Similar reports on small patient numbers are given by Kindwall, Weiss and Norkool [8,19,28].
No adverse effects of HBO$_2$ were reported in any of these studies.

Turning to the current data, the evidence is highly suggestive of a therapeutic effect, but falls short of
providing reliable evidence for clinical benefit. Assuming HBO$_2$ has reduced lymphoedema, it is not
possible to say if this relates to the changes induced by surgery, radiotherapy or both. Where
experimental design is concerned, the important decision to conduct a non-randomised study was
determined by the assumptions i) that perometry offers an operator-independent measure of arm
volume and ii) that a sustained reduction of >20% in arm volume could not occur spontaneously, or in
response to other interventions such as more intensive arm care by lymphoedema clinics. The average
reduction in arm volume reported was just below 10%, with only 3/19 patients recording >20% reductions in arm volume (5/19 with >20% reductions in arm swelling) at 12 months. Although this reproduces our previous observations, the modest level of effect makes it difficult to be certain that responses were HBO₂-induced, rather than seasonal fluctuation (this appears to be ruled out by reviewing the calendar months of measurements), changes in life-style and/or more intense interest shown by lymphoedema clinics responsible for routine management (we have no evidence for either of these effects).

Despite these uncertainties, quantitative lymphoscintigraphy offers strong supportive evidence for a durable effect attributable to HBO₂. The robustness of the technique is indicated by the similarity of the pre-HBO₂ difference (24%) with published data [25]. The baseline clearance rate of radioactive tracer was <0.9 (ratio of k_{ipsilat} to k_{contralat}) in the ipsilateral arm compared to the contralateral limb in 9/13 patients before treatment and in only 4/13 patients 12 months later, a statistically significant, and highly clinically significant, improvement. It is difficult to ignore the softening of the ipsilateral arm reported by so many (12/19) evaluable patients, not considered as a planned endpoint, but mentioned by so many patients without prompting. Assuming the recorded changes in arm volume, ⁹⁹Tc-Nanocoll clearance rate and arm hardness to be consequences of HBO₂, it is possible to speculate that limb tissues can be insufficiently elastic to respond to restoration of normal clearance rates by volume shrinkage.

The physician assessments of tissue softening recorded in Table 2 were planned secondary endpoints. Whilst these are highly subjective, it is considered unlikely that improvements of 2 grades represent measurement errors or spontaneous change. The pathological changes underlying induration are not clear, although tissue fibrosis and oedema are likely to be important. The same pathological features may be relevant to the pathogenesis of arm lymphoedema after lymphatic surgery and radiotherapy to HBO₂. If so, the response at one site might be expected to be associated with a response at another. Possibly due to the very small sample size, these associations are not apparent.
The improvements noticed in patient self-assessments of quality of life were not statistically significant. Patients commented that the choice of questionnaires was inappropriate. They felt that the questions would have been relevant to them in the first few years after their treatment for breast cancer/onset of lymphoedema, but not several years later when they had adjusted to their situation and body image.

In summary, it is perhaps unsurprising that firmer conclusions cannot be drawn from a sample size of 19 evaluable patients lacking a randomised control group. Nevertheless, even if the volume changes are difficult to attribute, the lymphoscintigraphy results are highly suggestive of a real effect in a group of patients receiving primary treatment a median of 14 years ago (range 7-35). We think further work is certainly justified in the context of a double-blind, randomised controlled clinical trial, and this is under development.

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References


Table legends

Table 1 Perometer measurements in 21 patients taken before hyperbaric oxygen therapy (HBO₂) and 12 months after therapy.

Table 2 Summary of results of study including change in arm volume and arm swelling, tissue softening, lymphoscintigraphy and patient self-reports in 19 patients evaluable at 12 months post HBO₂.

Figure legends

Figure 1 Removal rate constant, k, pre-HBO₂ and 12 months after hyperbaric oxygen therapy (HBO₂). p-values represent between-arms comparisons using the paired-t test.
Table 1
Perometer measurements in 21 patients taken before hyperbaric oxygen therapy (HBO\textsubscript{2}) and 12 months after therapy

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<td>+4</td>
<td>+6</td>
</tr>
<tr>
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<td>3849 / 2287 168</td>
<td>4193 / 2408 174</td>
<td>+6</td>
<td>+9</td>
</tr>
<tr>
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<td>5954 / 3202 186</td>
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<tr>
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<tr>
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<td>4622 / 1621 285</td>
<td>n/k n/k</td>
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* - = decrease; + = increase
n/k = not known
Table 2
Summary of results of study including change in arm volume and arm swelling, tissue softening, lymphoscintigraphy and patient self-reports in 19 patients evaluable at 12 months post HBO2

<table>
<thead>
<tr>
<th>Trial No</th>
<th>Years post RT</th>
<th>Change in volume 12 months after start of HBO₂</th>
<th>Tissue softening 12 months after start of HBO₂</th>
<th>Lymphoscintigraphy Improvement in clearance rate 12 months after start of HBO₂</th>
<th>Softening of arm tissue 12 months after start of HBO₂</th>
<th>Improvement in shoulder mobility 12 months after start of HBO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Arm volume (%)</td>
<td>Arm swelling (%)</td>
<td>Breast/chest wall</td>
<td>Pectoral fold</td>
<td>Supra clavicular fossa</td>
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</tbody>
</table>

nil Unevaluable: no change or no measurement at baseline.

yes Evaluable: Improvement at 12 months post HBO₂ from baseline.

no Evaluable: No improvement at 12 months post HBO₂ from baseline.
Fig 1

Removal rate constant, $k$ (% min$^{-1}$)

- Contralateral Pre-HBO$_2$
- Ipsilateral Pre-HBO$_2$
- Contralateral 12 months post-HBO$_2$
- Ipsilateral 12 months post-HBO$_2$

$p = 0.05$

$p = 0.20$