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**CLINICAL INVESTIGATION** **Breast**

# HYPERBARIC OXYGEN THERAPY FOR LATE SEQUELAE IN WOMEN RECEIVING RADIATION AFTER BREAST-CONSERVING SURGERY

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**Purpose: Persisting symptomatology after breast-conserving surgery and radiation is frequently reported. In most cases, symptoms in the breast resolve without further treatment. In some instances, however, pain, erythema, and edema can persist for years and can impact the patient's quality of life. Hyperbaric oxygen therapy was shown to be effective as treatment for late radiation sequelae. The objective of this study was to assess the efficacy of hyperbaric oxygen therapy in symptomatic patients after breast cancer treatment.**

**Patients and Methods: Forty-four patients with persisting symptomatology after breast-conservation therapy were prospectively observed. Thirty-two women received hyperbaric oxygen therapy in a multiplace chamber for a median of 25 sessions (range, 7–60). One hundred percent oxygen was delivered at 240 kPa for 90-min sessions, 5 times per week. Twelve control patients received no further treatment. Changes throughout the irradiated breast tissue were scored prior to and after hyperbaric oxygen therapy using modified LENT-SOMA criteria.**

**Results: Hyperbaric oxygen therapy patients showed a significant reduction of pain, edema, and erythema scores as compared to untreated controls ($p < 0.001$). Fibrosis and telangiectasia, however, were not significantly affected by hyperbaric oxygen therapy. Seven of 32 women were free of symptoms after hyperbaric oxygen therapy, whereas all 12 patients in the control group had persisting complaints.**

**Conclusions: Hyperbaric oxygen therapy should be considered as a treatment option for patients with persisting symptomatology following breast-conserving therapy.** © **2001 Elsevier Science Inc.**

**Breast cancer, Breast injury, Radiation sequelae, Hyperbaric oxygen.**

## INTRODUCTION

Breast-conservation therapy consisting of breast-conserving surgery plus radiation is the standard treatment for the majority of women with Stage I and II breast carcinomas. Several randomized clinical trials have demonstrated that this treatment approach is safe with respect to local recurrence-free survival and overall survival (1). By 1995, 60% of women with Stage I and and 39% with Stage II breast carcinoma received breast conservation therapy in the United States (2). All long-term survivors, however, bear the risk of late treatment sequelae. With regard to quality of life, breast-conservation therapy is not satisfactory in all cases. Up to 42% of patients report pain throughout the treated breast tissue (3). Edema was noted in 11% and skin alterations in 40% of the cases. In a patient self-assessment study by McCormick *et al*., breast edema after breast-conserving therapy was the symptom that most often influenced daily activities (4). An evaluation from our institution indicates that approximately 10% of patients suffer from symptoms in their breasts related to the preceding radiation (5). Symptoms can be severe enough to reduce working ability and have a major impact on social activities. Assuming that inflammatory processes play a role, nonsteroidal antiinflammatory drugs are used in symptomatic patients; this treatment can relieve pain but has no significant effect on the breast edema itself.

Hyperbaric oxygen therapy was shown to be effective as a prophylaxis against and a treatment of late radiation sequelae (6, 7). It has been demonstrated in a case report that a longstanding breast edema after radiation can be succesfully treated with hyperbaric oxygen (8). In this study, the question has been addressed whether the positive effects of hyperbaric oxygen are reproducible.

## PATIENTS AND METHODS

The concept of breast-conserving therapy consists of limited surgery and radiation therapy. Patients were irradiated with tangential fields up to a total dose of 50 Gy, using a dose per fraction of 2 Gy. The boost was applied by direct

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Table 1. Modified LENT-SOMA criteria for scoring late sequelae in women receiving radiation therapy after breast conserving surgery (Pavy *et al.*)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Subjective | | | | |
| Pain | Occasional and minimal Hypersensation, pruritus | Intermittent and tolerable | Persistent and intense | Refractory and excruciating |
| Objective | | | | |
| Edema | Asymptomatic | Symptomatic | Secondary dysfunction | |
| Fibrosis*/fat necrosis | Barely papable increased density | Definite increased density and firmness | Very marked density, retraction and fixation | |
| Telangiectasia | $< 1/cm^2$ | $1–4/cm^2$ | $> 4/cm^2$ | |
| Erythema | On exertion | Part of the breast | Whole breast | |

electron portals. From July 1996 to March 1999, 635 patients in the Clinic for Radiation Oncology, University Duesseldorf were followed after breast-conserving therapy. In the case of late radiation effects, sequelae were recorded according to modified LENT-SOMA criteria (9, Table 1). All patients with pain higher than Grade III or with a total score of at least 8 points were candidates for hyperbaric oxygen therapy. Thus, a total of 44 patients with symptomatic breast edema fulfilling the inclusion criteria were identified. Thirty-two patients were enrolled in a treatment protocol with hyperbaric oxygen therapy. Twelve women received no further treatment and served as controls, because they refused to undergo hyperbaric oxygen therapy. The median interval after primary treatment was 13 months (range, 2–149 months).

Patients underwent physical examination, chest X-ray, and ENT check-up to identify risk factors for hyperbaric oxygen therapy. After informed consent, hyperbaric oxygen treatments were performed in a multiplace chamber. The median number of hyperbaric oxygen therapy sessions was 25 (range, 7–60) given 5 times per week. Treatment was continued until three consecutive hyperbaric oxygen therapy fractions did not show any further improvement. This explains the wide range of 7–60 hyperbaric oxygen therapy sessions. A pressure of 240 kPa was used with a total oxygen breathing time of 90 min. As described elsewhere (6, 10), treatment pressure is built up by compressed air within 10 min. Patients then breathe pure oxygen via face masks for 3 periods of 30 min each interrupted by 10-min air phases at the same pressure. Decompression takes 15 min and starts immediately after the third oxygen application. The total treatment time is 135 min.

Control and hyperbaric oxygen therapy patients were followed for a median of 7 and 11 months, respectively. Changes in the treated breast tissue were scored by the physician in charge using modified LENT-SOMA criteria (Table 1). For each individual patient, the scores of the evaluated items were summed up. A Mann–Whitney test was carried out to compare the posttreatment scores for patients receiving hyperbaric oxygen therapy or no further treatment using standard computer software (SPSS 8.0.0, SPSS© Inc., 1989–1997).

## RESULTS

Pre- and posttreatment scores for observation and hyperbaric oxygen therapy groups are summarized in Table 2. The comparison of pre-treatment scores for both groups revealed no significant differences. Group assignment was not randomized, and it is possible though not obvious that a bias in selection or symptom grading was experienced. Patients treated with hyperbaric oxygen showed a significant reduction of pain, edema, and erythema scores compared to untreated controls ($p < 0.001$). Fibrosis and telangiectasia were not significantly affected by hyperbaric oxygen therapy. Seven of 32 patients were completely free of symptoms after hyperbaric oxygen therapy, whereas all 12 patients reported persisting complains after observation alone. No toxicities related to hyperbaric oxygen therapy were observed.

Table 2. Pre- and posttreatment scores for women with symptomatic breast edema treated with hyperbaric oxygen or followed without further treatment; all values are given as median, minimum, maximum

| | Observation | Hyperbaric oxygen | *p* value |
|---|---|---|---|
| Follow-up (months) | 7 (2–38) | 11 (1–32) | |
| Pain score | | | |
| Pretreatment | 3 (1–3) | 3 (1–4) | |
| Posttreatment | 3 (1–4) | 0 (0–2) | <0.001 |
| Edema score | | | |
| Pretreatment | 2 (0–3) | 3 (1–3) | |
| Posttreatment | 2 (0–3) | 1 (0–2) | <0.001 |
| Fibrosis score | | | |
| Pretreatment | 0 (0–3) | 0 (0–3) | |
| Posttreatment | 0 (0–3) | 0 (0–3) | NS |
| Telangiectasia score | | | |
| Pretreatment | 0 (0–2) | 0 (0–3) | |
| Posttreatment | 0 (0–2) | 0 (0–3) | NS |
| Erythema score | | | |
| Pretreatment | 3 (0–3) | 2 (0–3) | |
| Posttreatment | 2 (0–2) | 0 (0–2) | <0.001 |
| Score sum | | | |
| Pretreatment | 8 (3–12) | 9 (6–14) | |
| Posttreatment | 7 (3–12) | 2 (0–6) | <0.001 |

## DISCUSSION

The presented data show a significant reduction of pain, erythema, and edema for women receiving hyperbaric oxygen therapy after breast-conserving surgery and radiation. However, hyperbaric oxygen therapy had no significant effect on fibrosis and telangiectasia in the irradiated breast. The pathophysiology of radiation sequelae is not yet clear. Most acute reactions are primarily due to the disturbance of parenchymal cell turn over. The first visible reaction usually occurs in the coreacting vascular-connective tissue as an inflammatory process (11). Early radiation effects on the vasculature, such as swelling, thrombosis, vasoconstriction, and perivascular compression, are well documented (12–14). Similarly, vessel depletion plays a major role for late radiation damage, i.e., mandibula and spinal cord (15, 16). Using an infrared diode laser Doppler flowmeter, Doll *et al*. demonstrated that blood flow after a heat stress is significantly reduced in irradiated breasts compared to the untreated side, suggesting that persisting changes of the vascular-connective tissue contribute to radiation effects in the breast (17). An additional damage can be caused by surgery and radiation therapy to the lymph vessels, which can even worsen the situation. Generally, edematous tissues are at risk for inflammation, which in some cases presents with superficial infections like erysipelas. As to the frequency of associated pain, it remains speculative whether it is caused by suffocation after breakdown of afferent vessels, compression due to edema, inflammation, or other reasons.

Effects of hyperbaric oxygen on irradiated tissues have been investigated in a rabbit model. It was demonstrated that hyperbaric oxygen promotes the formation of collagen matrix and angiogenesis in the irradiated mandible (15). But the cellular and biochemical mechanisms of how hyperbaric oxygen therapy affects edema, erythema, and pain in the irradiated breast are still to be resolved. Fibrosis and telangiectasia did not show measurable improvement as evaluated by modified LENT-SOMA criteria. From current knowledge, fibrosis is regarded as a disturbance of the well-balanced cell type ratio of the interstitial fibroblast-fibrocyte cell system (18). It appears that hyperbaric oxygen has no short-term influence on this radiation effect. Similarly, telangiectasia seems to be an irreversible endpoint that cannot be counteracted by hyperbaric oxygen.

During the course of hyperbaric oxygen therapy an improvement of the clinical state was noted in all patients. As a rule, treatment was continued until three consecutive hyperbaric oxygen therapy fractions did not show any further improvement. This explains the wide range of 7–60 hyperbaric oxygen therapy sessions. But it is our impression from this study that most patients need 25 hyperbaric oxygen therapy sessions to be free of symptoms.

From this study, it is concluded that hyperbaric oxygen is a valuable clinical tool for patients suffering from persisting pain, edema, and erythema following breast irradiation. A prospective randomized trial to test the efficacy of hyperbaric oxygenation is in preparation.

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