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Hyperbaric Oxygen Therapy and Late Local Toxic Effects in Patients With Irradiated Breast Cancer
A Randomized Clinical Trial

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IMPORTANCE Hyperbaric oxygen therapy (HBOT) is proposed as treatment for late local toxic effects after breast irradiation. Strong evidence of effectiveness is lacking.

OBJECTIVE To assess effectiveness of HBOT for late local toxic effects in women who received adjuvant radiotherapy for breast cancer.

DESIGN, SETTING, AND PARTICIPANTS This was a hospital-based, pragmatic, 2-arm, randomized clinical trial nested within the prospective UMBRELLA cohort following the trials within cohorts design in the Netherlands. Participants included 189 women with patient-reported moderate or severe breast, chest wall, and/or shoulder pain in combination with mild, moderate, or severe edema, fibrosis, or movement restriction 12 months or longer after breast irradiation. Data analysis was performed from May to September 2023.

INTERVENTION Receipt of 30 to 40 HBOT sessions over a period of 6 to 8 consecutive weeks.

MAIN OUTCOMES AND MEASURES Breast, chest wall, and/or shoulder pain 6 months postrandomization measured by the European Organization for Research and Treatment of Cancer QLQ-BR23 questionnaire. Secondary end points were patient-reported fibrosis, edema, movement restriction, and overall quality of life. Data were analyzed according to intention-to-treat (ITT) and complier average causal effect (CACE) principles.

RESULTS Between November 2019 and August 2022, 125 women (median [range] age at randomization, 56 [37-85] years) with late local toxic effects were offered to undergo HBOT (intervention arm), and 61 women (median [range] age at randomization, 60 [36-80] years) were randomized to the control arm. Of those offered HBOT, 31 (25%) accepted and completed treatment. The most common reason for not accepting HBOT was high treatment intensity. In ITT, moderate or severe pain at follow-up was reported by 58 of 115 women (50%) in the intervention arm and 32 of 52 women (62%) in the control arm (odds ratio [OR], 0.63; 95% CI, 0.32-1.23; $P = .18$). In CACE, the proportion of women reporting moderate or severe pain at follow-up was 32% (10 of 31) among those completing HBOT and 75% (9.7 of 12.9) among control participants expected to complete HBOT if offered (adjusted OR, 0.34; 95% CI, 0.15-0.80; $P = .01$). In ITT, moderate or severe fibrosis was reported by 35 of 107 (33%) in the intervention arm and 25 of 49 (51%) in the control arm (OR, 0.36; 95% CI, 0.15-0.81; $P = .02$). There were no significant differences in breast edema, movement restriction, and quality of life between groups in ITT and CACE.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, offering HBOT to women with late local toxic effects was not effective for reducing pain, but was effective for reducing fibrosis. In the subgroup of women who completed HBOT, a significant reduction in pain and fibrosis was observed. A smaller than anticipated proportion of women with late local toxic effects was prepared to undergo HBOT.

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Editorial

Supplemental content

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Approximately 70% of patients with breast cancer in the Netherlands receive adjuvant radiotherapy, as it reduces local recurrence rates and increases disease-free survival.[1-4] Radiotherapy is associated with an increased risk of late local toxic effects, including pain, fibrosis, edema, movement restriction, and impaired cosmetic outcome.[5,6] In a large Dutch breast cancer cohort, late toxic effects after radiotherapy were reported by 16% of patients, which was also associated with reduced quality of life (QOL).[6] Hyperbaric oxygen therapy (HBOT) has been proposed as treatment for reduction of late local toxic effects.[7] HBOT involves breathing 100% oxygen at 2.0 to 2.5 atmospheres absolute (ATA). The combination of high pressure and inhalation of 100% oxygen leads to elevated partial pressure of oxygen in blood and tissues, which induces angiogenesis and regeneration of the irradiated tissue.[8,9]

A limited number of studies, mostly small and single arm, have shown that HBOT is associated with a reduction of pain, fibrosis, or edema in patients with late toxic effects after breast irradiation.[7] It has proved to be challenging to conduct classic randomized clinical trials (RCTs) involving HBOT: late toxic effects may develop years after breast cancer treatment, when patients are no longer in active follow-up, which hampers recruitment.[10] Also, since HBOT is available as (reimbursed) routine care in many countries, including the Netherlands, participants may decide to undergo HBOT on their own initiative, when allocated to the control arm.[11] The trial within cohorts design (TWICS) approach attempts to overcome these issues.[12] The aim of the HONEY (The Effect of Hyperbaric Oxygen Therapy on Breast Cancer Patients With Late Radiation Toxicity) trial was to study whether HBOT reduces late local toxic effects in women who received adjuvant radiotherapy for breast cancer.

Key Points

Question What is the effectiveness of hyperbaric oxygen therapy (HBOT) for late local toxic effects in patients with irradiated breast cancer?

Findings In this cohort-based randomized clinical trial in the Netherlands including 189 women with late local toxic effects, 1 in 4 patients with late local toxic effects accepted to undergo HBOT when offered. In the intention-to-treat analysis, pain was not significantly reduced in women who were offered HBOT but fibrosis was; among women who completed HBOT, pain and fibrosis were significantly reduced.

Meaning HBOT seems effective for reducing pain and fibrosis in women with late local toxic effects after breast irradiation.

Methods

Study Design and Informed Consent

HONEY was a pragmatic, nonblinded, 2-arm RCT nested within the prospective UMBRELLA (Utrecht Cohort for Multiple Breast Cancer Intervention Studies and Long-Term Evaluation) cohort.[13,14] UMBRELLA is a multicenter hospital-based cohort study, initiated in 2013, including patients with histologically proven invasive breast cancer or ductal carcinoma in situ. Participants provide written informed consent for the collection and use of clinical data and patient-reported outcomes up to 10 years after cohort enrollment.[13] On cohort enrollment, patients are also asked to provide consent to be randomized for cohort-based trials and to be offered interventions when allocated to an intervention arm.[12,13]

In the HONEY trial, 189 eligible UMBRELLA cohort participants were randomly assigned to the intervention or control arm in a 2:1 ratio using a Microsoft Access (Microsoft Corporation) database running a blind computer-generated sequence with varying block sizes (n = 3-6), stratified for time since radiotherapy (12-29 months vs ≥30 months) (**Figure 1**). Participants randomized to the intervention arm were offered HBOT. Women who accepted HBOT and provided additional informed consent were referred for HBOT, whereas women who declined received standard care. Following the TWICS concept, participants randomized to the control arm were not informed about the trial, and their UMBRELLA cohort data were used comparatively.[12,13,15] For logistic reasons, participants were recruited and randomized in 4 batches between November 2019 and August 2022.[16]

The HONEY trial (protocol in Supplement 1) was approved by the Medical Ethics Research Committee of the University Medical Center (UMC) Utrecht (NL69081.041.19) and registered on ClinicalTrials.gov (NCT04193722).[13,14] HONEY followed the Consolidated Standards of Reporting Trials Extension (CONSORT-ROUTINE) reporting guideline for the reporting of RCTs conducted using cohorts and routinely collected data.[17,18] Demographic data and tumor and treatment characteristics were provided by the Netherlands Cancer Registry.[19]

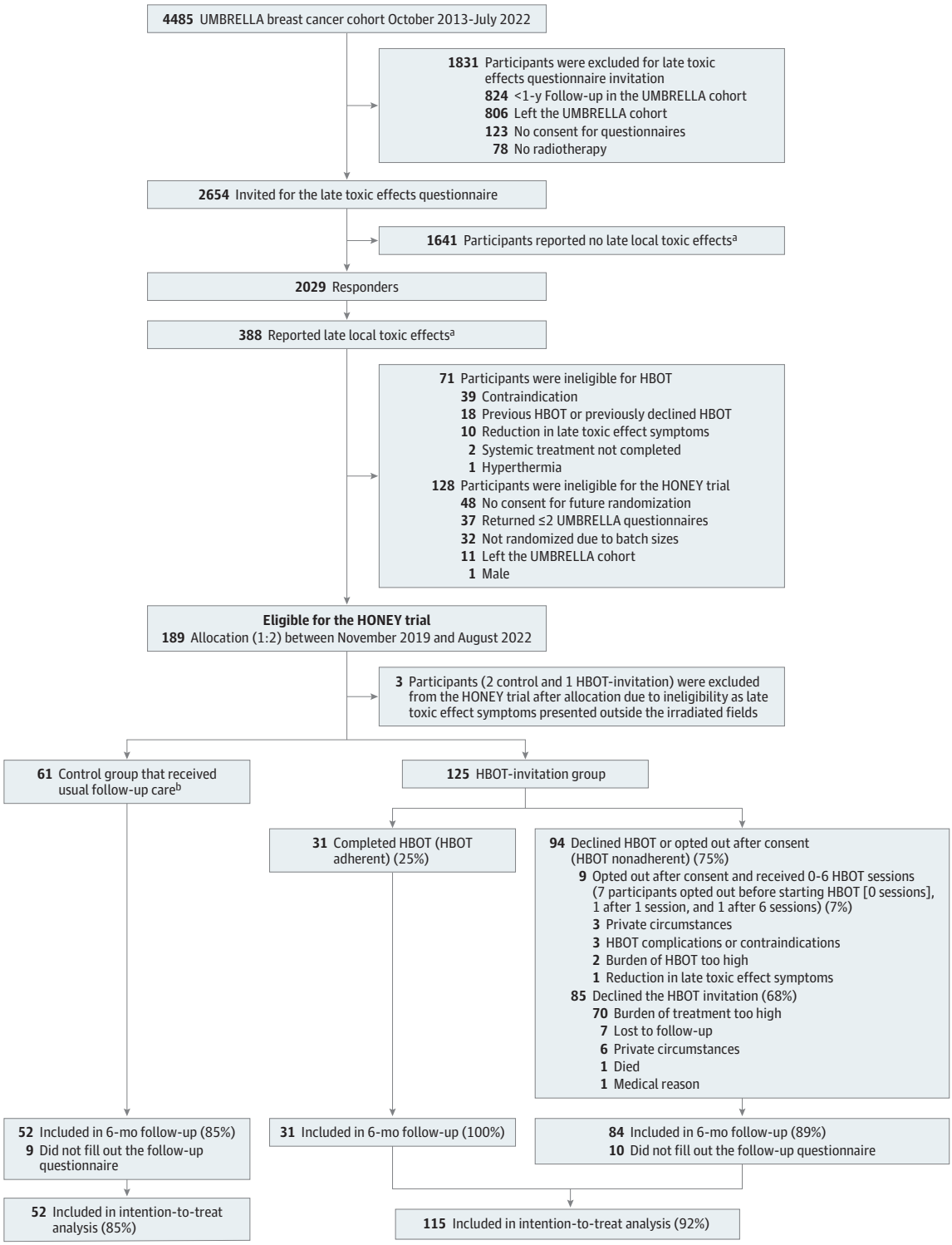
Patient Recruitment

To identify eligible participants, a late toxic effects questionnaire was developed and sent out to UMBRELLA cohort participants (eAppendix in Supplement 2).[6] Women were eligible for HONEY when meeting the following criteria: (1) provided consent for randomization to intervention studies within UMBRELLA, (2) finished primary breast cancer treatment with curative intent (except for hormonal therapy), and (3) had patient-reported late local toxic effects 12 months or longer after adjuvant radiotherapy. Late local toxic effects were defined as moderate or severe breast, chest wall, and/or shoulder pain in combination with at least 1 symptom of mild, moderate, or severe fibrosis, breast edema, and/or movement restriction. In case of shoulder pain, women were eligible when treated with locoregional radiotherapy. Exclusion criteria for HONEY were (1) poor response to patient-reported outcomes questionnaires (return of ≤2 UMBRELLA questionnaires), (2) previous HBOT, (3) contraindications for HBOT, and (4) metastatic disease or recurrent breast cancer.[20,21]

HBOT-Invitation Group and Control Group

Women who accepted the HBOT invitation were invited to the Department of Radiation Oncology in the UMC Utrecht. If late toxic effects within the irradiated fields were confirmed by a

Figure 1. Flowchart of Recruitment, Randomization, and Follow-Up in the HONEY Trial



HBOT indicates hyperbaric oxygen therapy; HONEY, The Effect of Hyperbaric Oxygen Therapy on Breast Cancer Patients With Late Radiation Toxicity; UMBRELLA, Utrecht Cohort for Multiple Breast Cancer Intervention Studies and Long-Term Evaluation.

[a] Late local toxic effects was defined as moderate or severe breast, chest wall, and/or shoulder pain in combination with at least 1 symptom of mild, moderate, or severe fibrosis, breast edema, and/or movement restriction.

[b] None of the participants in the control group had undergone HBOT between randomization and the 6-month-follow-up.

dedicated breast radiation oncologist (F.V.D.L.), women were referred for HBOT.[22] HBOT consisted of 30 to 40 treatment sessions over a period of 6 to 8 consecutive weeks. During HBOT, patients were seated in a hyperbaric chamber for 120 minutes per session. After pressure was increased to 2.5 ATA, patients breathed 100% oxygen through an oxygen mask during 4 intervals of 20 minutes. Thereafter, pressure was decreased to standard atmosphere. Women who underwent HBOT were advised to continue their standard follow-up care. Women who completed HBOT were classified as HBOT adherent and those who declined or attended fewer than 7 HBOT sessions as HBOT nonadherent. Women randomized to the control group were not offered HBOT, not informed about the trial, and received standard follow-up care.

Data Collection

Outcome measures were obtained via the late toxic effects questionnaire (eAppendix in Supplement 2).[13] The questionnaire contained items of the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0; toxic effects criteria of the Radiation Therapy Oncology Group; and the European Organization for Research and Treatment of Cancer QLQ-BR23 questionnaire.[23-25] Questions were scored on a 4-point Likert scale with answer options of not at all (none), a little (mild), quite a bit (moderate), and very much (severe). Participants were invited to complete the late toxic effects questionnaire prior to randomization and 6 months thereafter, ie, the anticipated duration of the intake period, HBOT treatment, and 3-month follow-up (eFigure 1 in Supplement 2). This follow-up period was chosen because the treatment effect may improve for up to 3 months after completion of HBOT.[26] When participants preferred to postpone the start of HBOT due to personal reasons, outcome assessment was performed at 5 months after the start of HBOT, ie, 3 months after completion of treatment (eFigure 1 in Supplement 2). When the late toxic effects questionnaire was not completed, outcomes from the next standard UMBRELLA cohort questionnaire (with a maximum of 2 years postrandomization) were used. Fibrosis and edema of the breast, chest wall, and/or axilla among HBOT-adherent patients were assessed by 1 radiation oncologist (F.V.D.L.) according to the CTCAE, version 5.0.[23] Blinding of outcome assessors was not feasible for the HBOT-invitation group and radiation oncologist.

Primary and Secondary Outcomes

The primary end point was presence of patient-reported moderate or severe breast, chest wall, and/or shoulder pain at 6-month follow-up. At baseline, all women reported moderate or severe breast, chest wall, and/or shoulder pain. Effectiveness of HBOT was defined as reduction to no or mild breast, chest wall, and shoulder pain. Secondary end points included the presence of patient-reported moderate or severe fibrosis, breast edema, and movement restriction and overall QOL at 6-month follow-up. In the group of participants undergoing HBOT, toxic effects outcomes were evaluated by a dedicated breast radiation oncologist (F.V.D.L.) 3 months posttreatment and adverse effects by a hyperbaric oxygen physician up to completion of HBOT. Other secondary end points, as per the study protocol, ie, oxygenation of the skin, cosmetic outcome, and QOL on the different subdomains, will be reported in a subsequent publication.[14]

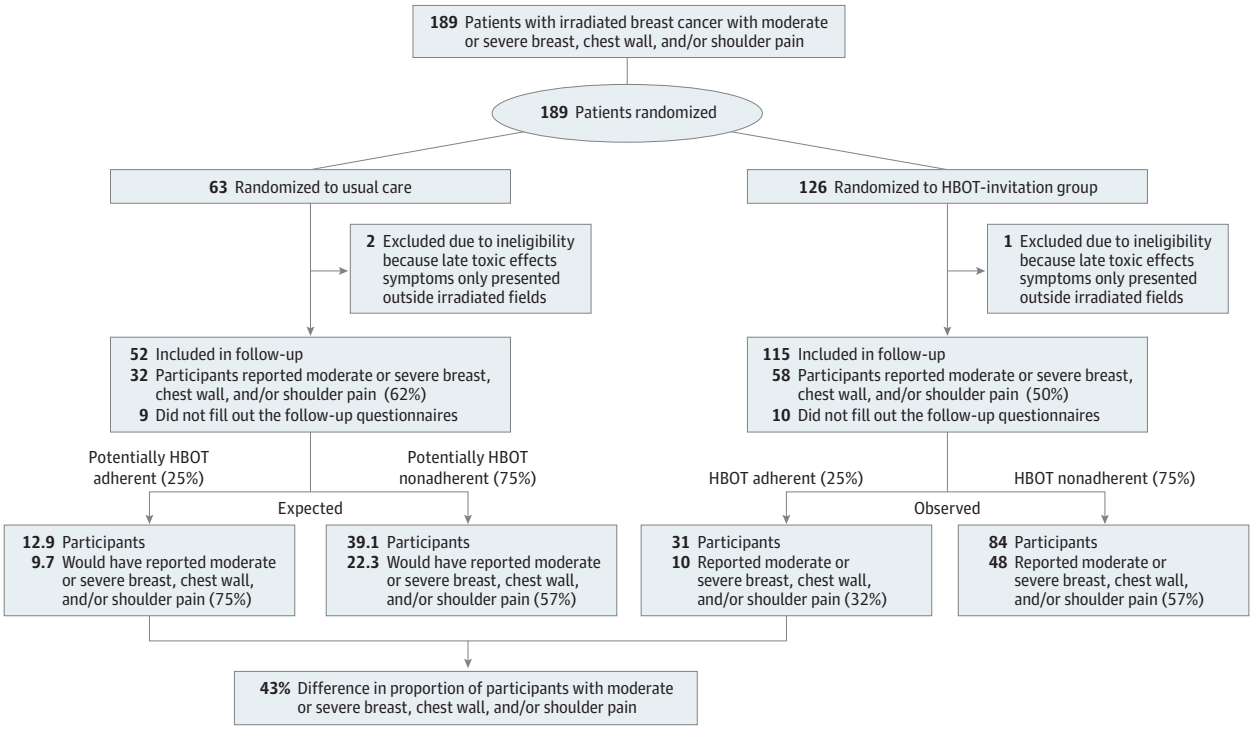
Statistical Analysis

The trial was designed to have power of 80% to detect an absolute between-group difference of 25% in the proportion of women reporting moderate or severe pain at follow-up in the intention-to-treat (ITT) population (55% in the intervention and 80% in the control arm).[14] For the sample size, we assumed that 50% of women offered HBOT would accept the intervention. A 1-sided type I error of 5% was assumed. Based on a 2:1 allocation ratio and adjustment for 10% withdrawal from the UMBRELLA cohort, 80 participants were required in the HBOT-invitation group and 40 in the control group. After recruitment of 119 women, acceptance rate in the HBOT-invitation group was lower than anticipated (ie, 33%), after which the sample size was adapted to a total of 240 women. No interim analyses were performed. Symptoms of late toxic effects were summarized using frequencies and proportions and QOL using mean with standard deviation. Logistic regression adjusted for stratification was performed on an ITT and per-protocol basis to assess between-group differences on the primary outcome. Secondary late toxic effects outcomes were further adjusted for the baseline value of the outcome. To account for the substantial proportion of women who declined the HBOT invitation and the resulting dilution of the HBOT effect in ITT, we additionally performed a complier average causal effect (CACE) analysis to estimate the effect of undergoing HBOT.[27] Here, we compared outcomes between women who underwent HBOT to those in the control group who would have completed HBOT if offered (**Figure 2**).[28-32] Odds ratios (ORs) were estimated via instrumental variable analysis using the 2-stage least squares method.[33,34] In the first stage, the relation between treatment assignment and adherence was estimated using logistic regression.[31] In the second stage, the effect of HBOT on the outcome was estimated using logistic regression adjusting for the predicted probabilities obtained in the first stage and imbalances in baseline characteristics, ie, age, smoking status, and (neo)adjuvant systemic treatment. Mean European Organization for Research and Treatment of Cancer QLQ-C30 scores between baseline and follow-up were compared with a paired-samples *t* test. ITT analyses were repeated after multiple imputation of missing outcomes. Analyses were performed using SPSS, version 26.0.0.1 (IBM Corporation) and RStudio, version 4.2.1 (R Foundation for Statistical Computing), using mice, ivtools, and tidymodels packages. Two-tailed *P* values, with significance set at $P < .05$; and 95% CIs are reported.

Results

Of all 4485 cohort participants, 2654 were invited to complete the late toxic effects questionnaire (Figure 1; eAppendix in Supplement 2). Of the 2029 responders (76%), 388 (19%) experienced late local toxic effects, ie, moderate or severe breast, chest wall, and/or shoulder pain in combination with

Figure 2. Flowchart of the Complier Average Causal Effect (CACE) Analysis According to the Cuzick Model Showing the Effect of Hyperbaric Oxygen Therapy (HBOT) on Moderate or Severe Breast, Chest Wall, and/or Shoulder Pain Adjusted for Nonparticipation



CACE analysis was performed with the use of an instrumental-variables method in which the instrumental variable was the randomization to the HBOT-invitation group. For this analysis, the primary outcome in the HBOT-adherent patients, ie, those who completed HBOT, was compared with that in patients in the control group who would have accepted HBOT if offered. A detailed flowchart with stepwise explanation of the CACE analysis can be found in eFigure 2 in Supplement 2. HONEY indicates The Effect of Hyperbaric Oxygen Therapy on Breast Cancer Patients With Late Radiation Toxicity.

at least 1 symptom of mild, moderate, or severe fibrosis, breast edema, and/or movement restriction. Of those, 71 cohort participants were ineligible to undergo HBOT, and 128 were ineligible for the HONEY trial. In total, 126 women were randomly assigned to the intervention arm. After exclusion of 1 patient due to ineligibility, 125 women were invited for HBOT (median [range] age at randomization, 56 [37-85] years). Sixty-three women were randomized to the control arm; 2 were excluded after randomization due to ineligibility, with a final control sample of 61 women (median [range] age at randomization, 60 [36-80] years). Trial inclusion was halted after cohort exhaustion, as all eligible cohort participants had been screened and enrolled in HONEY.

Adherence

Thirty-one women (25%) accepted and completed HBOT (Figure 1). The HBOT invitation was declined by 85 women (68%), mostly due to the high burden of undergoing HBOT (n = 70). Nine women (7%) opted out after consent, of whom 7 did not start HBOT (Figure 1). Follow-up questionnaires were completed by 92% (n = 115) of the HBOT-invitation group and 85% (n = 52) of the control group. Median (IQR) time between randomization and completing follow-up questionnaire was 8 (7-11) months for the HBOT-invitation group, 8 (6-9) months for the control group, and 10 (8-12) months for the HBOT-adherent patients (**Table 1**).[35] For most characteristics, trial arms were well balanced (Table 1). When compared to the control group, the HBOT-invitation group was younger and more often received hormonal therapy. Within the intervention arm, HBOT-adherent patients were younger, more often treated with (neo)adjuvant systemic treatment, and more often received follow-up care for their late toxic effects symptoms compared to HBOT-nonadherent patients.

Primary Outcome

In ITT analysis, moderate or severe breast, chest wall, and/or shoulder pain at follow-up was reported by 58 of 115 women (50%) in the HBOT-invitation group and 32 of 52 (62%) in the control group (12% difference; OR, 0.63; 95% CI, 0.32-1.23; P = .18, **Table 2**; eTable in Supplement 2). In CACE analysis, we compared women in the intervention arm, who completed HBOT, with women in the control arm who would have completed HBOT if offered. Here, 10 of 31 women (32%) who completed HBOT reported moderate or severe breast, chest wall, and/or shoulder pain; this proportion was estimated to be 75% (9.7 of 12.9) among control participants who would have completed HBOT if offered (43% difference; adjusted OR, 0.34; 95% CI, 0.15-0.80; P = .01; Table 2, Figure 2; eFigure 2 in Supplement 2). In per-protocol analysis, 10 of 31 women (32%) undergoing HBOT reported moderate or severe breast,

Table 1. Patient, Tumor, and Treatment Characteristics at Baseline

Characteristic	No. (%)[a]			
	HBOT-invitation group, total (n = 125)[b]	HBOT-invitation group[b]		Control group (n = 61)
		Adherent (n = 31)	Nonadherent (n = 94)	
Patient characteristics				
Age at randomization, median (range), y	56 (37-85)	54 (42-81)	59 (37-85)	60 (36-80)
BMI, mean (SD)	26.7 (4.0)	27.8 (3.4)	26.4 (4.2)	26.7 (3.6)
Highest educational level				
Primary or postsecondary school	64 (51)	16 (52)	48 (51)	25 (41)
College, graduate, or professional degree	61 (49)	15 (48)	46 (49)	36 (59)
Smoking				
Active smoker	9 (7)	1 (3)	8 (9)	1 (2)
Former smoker	63 (50)	19 (61)	44 (47)	36 (59)
Nonsmoker	53 (42)	11 (36)	42 (45)	24 (39)
Tumor characteristics				
Tumor size, median (IQR), mm	18 (12-25)	15 (7-20)	21 (13-30)	15 (9-23)
Unknown	2 (2)	0	2 (2)	3 (5)
Pathologic N stadium				
0	64 (51)	18 (58)	46 (49)	37 (61)
I	50 (40)	11 (36)	39 (42)	19 (31)
II + III	3 (2)	1 (3)	2 (2)	2 (3)
X	8 (6)	1 (3)	7 (7)	3 (5)
Multifocality				
Yes	24 (19)	5 (16)	19 (20)	11 (18)
None	101 (81)	26 (84)	76 (80)	52 (82)
Differentiation grade				
1 (Well differentiated)	28 (22)	2 (7)	26 (28)	12 (20)
2 (Moderately differentiated)	51 (41)	15 (48)	36 (38)	24 (39)
3 (Poorly differentiated)	37 (30)	8 (26)	29 (31)	24 (39)
Unknown	9 (7)	6 (19)	3 (3)	1 (2)
Treatment characteristics				
Type of surgery				
Lumpectomy	92 (74)	22 (71)	70 (75)	48 (79)
Mastectomy without reconstruction	20 (16)	5 (16)	15 (16)	8 (13)
Mastectomy with direct reconstruction	13 (10)	4 (13)	9 (9)	5 (8)
Delayed breast reconstruction	12 (10)	4 (13)	8 (9)	8 (13)
Axillary treatment				
Sentinel node procedure[c]	107 (86)	27 (87)	81 (85)	56 (92)
Axillary lymph node dissection	10 (8)	2 (6)	8 (8)	2 (3)
None	8 (6)	2 (7)	6 (6)	3 (5)
(Neo)adjuvant systemic treatment				
Chemotherapy	70 (56)	20 (65)	50 (53)	35 (57)
Hormonal therapy	72 (58)	22 (71)	50 (53)	25 (41)
ERBB2-targeted therapy	21 (17)	8 (26)	13 (14)	6 (10)
None	30 (24)	3 (10)	27 (29)	16 (26)
Radiotherapy treatment				
Local radiotherapy without boost[d]	32 (26)	8 (26)	24 (26)	15 (25)
Local radiotherapy with boost[e]	41 (33)	10 (32)	31 (33)	23 (38)
Locoregional radiotherapy without boost[f]	28 (22)	11 (36)	17 (18)	15 (25)
Locoregional radiotherapy with boost[g]	24 (19)	2 (7)	22 (23)	8 (13)
Bilateral radiotherapy	13 (10)	3 (10)	10 (11)	2 (3)

(continued)

Table 1. Patient, Tumor, and Treatment Characteristics at Baseline (continued)

Characteristic	No. (%)[a]			
	HBOT-invitation group, total (n = 125)[b]	HBOT-invitation group[b]		Control group (n = 61)
		Adherent (n = 31)	Nonadherent (n = 94)	
Time between radiotherapy and randomization, median (IQR), mo	34 (21-52)	35 (17-64)	34 (21-52)	34 (21-53)
Late toxic effects care				
Physiotherapy	43 (33)	9 (29)	34 (36)	19 (31)
Edema therapy	73 (58)	21 (68)	52 (55)	33 (54)
Psychotherapy	31 (25)	10 (32)	21 (22)	13 (21)
Analgesics	15 (12)	3 (10)	12 (13)	9 (15)
None	37 (30)	6 (19)	31 (33)	22 (36)
Time between randomization and completion of the follow-up questionnaire, median (IQR), mo	8 (7-11)	10 (8-12)[h]	8 (6-11)	8 (6-9)
Overall quality of life at baseline, mean (SD)[h]	71.4 (18.7)	66.1 (20.3)	73.2 (18.0)	69.3 (17.0)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; HBOT, hyperbaric oxygen therapy.

[a] Categories may not total 100% because of rounding.

[b] In the group that was invited for HBOT, those who completed HBOT were classified as HBOT adherent, and those who declined or attended fewer than 10 HBOT sessions were classified as HBOT nonadherent.

[c] Including MARI (marking axillary lymph nodes with radioactive iodine seeds) procedure.

[d] 40 Gy in 15 fractions or 42.5 Gy in 16 fractions. One patient received 20 Gy in 1 fraction in the ABLATIVE trial.[35]

[e] Simultaneous integrated boost with a total dose to the tumor bed of 53.4 Gy in 20 fractions or 55.9 Gy in 21 fractions (standard boost dose) or a total boost dose of 58.75 Gy in 22 fractions or 61.2 Gy in 23 fractions (high boost dose). Two patients received a sequential boost.

[f] Radiation therapy on periclavicular and/or axillary lymph nodes; 40 Gy in 15 fractions or 42.5 Gy in 16 fractions.

[g] Radiation therapy on periclavicular and/or axillary lymph nodes; Simultaneous integrated boost with a total dose to the tumor bed of 53.4 Gy in 20 fractions or 55.9 Gy in 21 fractions (standard boost dose) or a total boost dose of 58.75 Gy in 22 fractions or 61.2 Gy in 23 fractions (high boost dose).

[h] Overall quality of life was measured via the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire. Quality of life ranges in score from 0 to 100. Higher score for overall quality of life denotes a better level of functioning. Number of responders was 121 for the HBOT-invitation group, 30 for the HBOT-adherent patients, 91 for the HBOT-nonadherent patients, and 54 for the control group.

chest wall, and/or shoulder pain vs 32 of 52 control participants (62%) (30% difference; adjusted OR, 0.31; 95% CI, 0.12-0.78; *P* = .01; Table 2).

Secondary Outcomes

At baseline, moderate or severe fibrosis was reported by 58% (n = 73) of the HBOT-invitation group and 64% (n = 39) of the control group (Table 2). At follow-up, 35 of 107 women (33%) in the HBOT-invitation group and 25 of 49 women (51%) in the control group reported moderate or severe fibrosis (18% difference; OR, 0.36; 95% CI, 0.15-0.81; *P* = .02). Of women who completed HBOT, 5 of 30 (17%) reported moderate or severe fibrosis compared to 10.6 of 12.3 control participants (86%) who would have completed HBOT if offered (69% difference; adjusted OR, 0.14; 95% CI, 0.04-0.48; *P* = .001). No significant effect of HBOT was observed for breast edema and movement restriction in ITT or CACE analysis.

At follow-up, mean (SD) scores for overall QOL were 72.1 (19.1) for the HBOT-invitation group (n = 91), 67.6 (20.2) for the HBOT-adherent patients (n = 26), 73.8 (18.5) for the HBOT-nonadherent patients (n = 65), and 72.9 (16.9) for the control group (n = 39). Overall QOL did not improve significantly between baseline and follow-up in all groups (Table 1).

For the HBOT-adherent patients, physician-reported fibrosis and breast edema of grade 1 or higher was less often reported at follow-up when compared to baseline (**Table 3**). Of all HBOT-adherent patients, 27 (87%) experienced transient myopia, 30 (97%) experienced fatigue, and 4 (13%) experienced ear barotrauma.

Sensitivity Analyses

Repeating ITT analyses with multiple imputation for missing toxic effects outcomes yielded comparable results (Table 2). When analyzing data without HBOT-adherent patients who started treatment more than 6 months postrandomization, comparable results were observed on the primary end point.

Discussion

In this cohort-based RCT, only 1 in 4 women with late local toxic effects after breast irradiation was prepared to undergo HBOT when offered. In ITT, offering HBOT was not significantly associated with a reduction in patient-reported pain, but patient-reported fibrosis was significantly reduced. This ITT analysis estimates the overall clinical effect, when the intervention would be available, with some people taking advantage of it while others would not. In CACE, completing HBOT was associated with a significant reduction in both pain and fibrosis until at least 3 months posttreatment. This CACE analysis estimates the causal effect of HBOT in those who would complete treatment when offered. No significant effect of HBOT on breast edema, movement restriction, and overall QOL was observed, neither in ITT nor CACE analysis.

Our results are in line with previous studies. In a prospective study involving 67 patients with irradiated breast cancer, Spruijt et al[26] observed a significant reduction in median pain score measured by visual analogue scale from 6 points prior to HBOT to 2 points at 3 months post-HBOT. In a

Table 2. Proportion of Patients With Moderate or Severe Breast, Chest Wall, and/or Shoulder Pain, Fibrosis, Breast Edema, and Movement Restriction at Follow-Up and Differences in Proportions Between Groups

Outcome	Breast, chest wall, and/or shoulder pain[a]		Fibrosis[a]		Breast edema[a]		Movement restriction[a]	
	HBOT-invitation group	Control group	HBOT-invitation group	Control group	HBOT-invitation group	Control group	HBOT-invitation group	Control group
Baseline								
No./total No. (%)	125/125 (100)	61/61 (100)	73/125 (58)	39/61 (64)	27/125 (22)	17/61 (28)	31/125 (25)	14/61 (23)
ITT analysis								
No./total No. (%)	58/115 (50)	32/52 (62)	35/107 (33)	25/49 (51)	13/114 (11)	11/52 (21)	15/114 (13)	9/52 (17)
OR (95% CI)	0.63 (0.32-1.23)	1 [Reference]	0.36 (0.15-0.81)	1 [Reference]	0.50 (0.19-1.29)	1 [Reference]	0.63 (0.23-1.80)	1 [Reference]
P value	.18	NA	.02	NA	.14	NA	.38	NA
OR after multiple imputation (95% CI)[b]	0.60 (0.31-1.18)	1 [Reference]	0.38 (0.16-0.87)	1 [Reference]	0.49 (0.18-1.30)	1 [Reference]	0.59 (0.22-1.60)	1 [Reference]
P value	.16	NA	.02	NA	.12	NA	.30	NA
CACE analysis								
HBOT-adherent patients in the invitation group								
No./total No. (%)	10/31 (32)	NA	5/30 (17)	NA	3/31 (10)	NA	1/31 (3)	NA
HBOT-nonadherent patients in the invitation group								
No./total No. (%)	48/84 (57)	NA	30/77 (39)	NA	10/83 (12)	NA	14/83 (17)	NA
Potential adherent patients in the control group (who would have completed HBOT if offered)[c]								
Expected No./total No. (%)	NA	9.7/12.9 (75)	NA	10.6/12.3 (86)	NA	6.3/13.0 (48)	NA	2.4/13.0 (18)
Potential nonadherent patients in the control group (who would have declined or not completed HBOT if offered)[c]								
Expected No./total No. (%)	NA	22.3/39.1 (57)	NA	14.4/36.8 (39)	NA	4.7/39.0 (12)	NA	6.6/39.0 (17)
Adjusted OR (95% CI)[d]	0.34 (0.15-0.80)	1 [Reference]	0.14 (0.04-0.48)	1 [Reference]	0.51 (0.16-1.67)	1 [Reference]	0.18 (0.02-1.61)	1 [Reference]
P value	.01	NA	.001	NA	.27	NA	.12	NA
Per-protocol analysis								
No./total No. (%)	10/31 (32)	32/52 (62)	5/30 (17)	25/49 (51)	3/31 (10)	11/52 (21)	1/31 (3)	9/52 (17)
Adjusted OR (95% CI)	0.31 (0.12-0.78)	1 [Reference]	0.14 (0.04-0.43)	1 [Reference]	0.32 (0.06-1.26)	1 [Reference]	0.17 (0.01-1.15)	1 [Reference]
P value	.01	NA	.002	NA	.13	NA	.12	NA

Abbreviations: CACE, complier average causal effect; HBOT, hyperbaric oxygen therapy; ITT, intention-to-treat; NA, not applicable; OR, odds ratio.

[a] Categories may not total 100% because of rounding.

[b] ITT analysis was repeated with multiple imputation of missing values on the outcome as sensitivity analysis. All covariates, ie, baseline values of the outcome, randomization, stratification, and outcomes, were used as predictors. The imputed data were checked with convergence plots. Imputation was successful if the streams intermingled and were free of any trend. In total, 20 imputed datasets were produced with 10 iterations.

[c] These values in CACE analysis were not observed but were estimated on the assumption that the fraction of nonadherent patients in the HBOT-invitation group and the proportion reporting moderate or severe toxic effects among nonadherent patients were representative for potential nonadherent patients in the control group.

[d] Adjusted for stratification variable, baseline values of the outcome, age at randomization, (neo)adjuvant systemic treatment, and smoking status. CACE analysis was performed with the use of an instrumental-variables method in which the instrumental variable was the randomization to the HBOT-invitation group. For this analysis, the primary outcome in the HBOT-adherent patients, ie, those who completed HBOT, was compared with that in patients in the control group who would have accepted HBOT if offered. CACE analyses were performed for participants with available outcome measures.

Table 3. Adverse Effects, Number of Sessions, and Chemotherapy-Induced Peripheral Neuropathy Among Participants Who Completed Hyperbaric Oxygen Therapy (HBOT)

Treatment/adverse effect characteristic	HBOT-adherent patients, No. (%)[a] (n = 31)	
	Prior to HBOT	Follow-up
Physician-reported late toxic effects		
CTCAE grade of fibrosis of breast, chest wall, and/or axilla		
0	9 (29)	12 (40)
1	13 (42)	15 (48)
2	7 (23)	3 (10)
3	2 (7)	1 (3)
CTCAE grade of edema of breast, chest wall, and/or axilla		
0	17 (55)	23 (74)
1	12 (39)	7 (23)
2	2 (7)	1 (3)
3	0	0
HBOT sessions		
30	1 (3)	NA
35	1 (3)	NA
40	28 (90)	NA
41	1 (3)	NA
Adverse effects	**Yes**	**No**
Adverse effects of HBOT[b]		
Transient myopia	27 (87)	4 (13)
Fatigue	30 (97)	1 (3)
Hypoglycemia	1 (3)	30 (97)
Barotrauma to ear[c]	4 (13)	27 (87)
Oxygen toxicity	0	31 (100)
Chemotherapy-induced peripheral neuropathy		
Prior to HBOT	13 (42)	18 (58)
Improvement up to 3 mo post-HBOT	8 (62)	5 (39)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable.

[a] Categories may not total 100% because of rounding.

[b] Worst reported adverse effect by hyperbaric oxygen physicians or participants.

[c] MacFie grade 1 was reported for 1 participant, MacFie grade 2 for 1 participant, and MacFie grade 3 for 2 participants.

retrospective cohort study by Batenburg et al,[36] 271 of 460 patients with breast cancer (58.8%) with moderate or severe breast pain before the start of treatment reported no or mild pain at the end of HBOT. Teguh et al[10] observed that of 56 patients, 66.7% reported moderate or severe breast pain prior to HBOT and 14.5% at the end of HBOT ($P < .05$). In our study, 21 of 31 women (68%) with moderate or severe pain prior to HBOT reported no or mild pain at 3-month follow-up. A direct comparison of results is difficult, because most studies were nonrandomized and conducted without a control group, had limited sample sizes, or included patients who received HBOT within 1 year after breast cancer treatment, as result of which the effect might also be associated with a natural reduction of (acute) toxic effects over time.[37] In line with our findings, fibrosis improved significantly between baseline and 3 months post-HBOT in the study by Spruijt et al.[26]

HONEY followed the TWICS design, which allowed for efficient selection and recruitment of representative patients. In total, 189 of 317 cohort participants (59.6%) with late toxic effects were eligible for this trial and randomized into HONEY. This proportion is much higher than the proportion of eligible patients usually randomized into classic RCTs, particularly RCTs involving HBOT.[11,38] As observed in previous trials, the TWICS approach proved to be rather efficient, as 189 participants were enrolled in a single institution within 22 months, despite interruption of study recruitment due to COVID-19 lockdowns.[39-41]

This trial provided important information regarding the willingness of women with late toxic effects to undergo HBOT. The majority (68%) of women who were offered HBOT declined the invitation, despite experiencing substantial physical complaints following their breast cancer treatment. The most important reason given was burden of high treatment intensity. The population-level effect of offering HBOT to women with late toxic effects seems modest, as the ITT analysis reflects daily clinical practice involving nonacceptance and nonadherence. Women who accepted the HBOT invitation were younger, underwent more comprehensive breast cancer treatment, and more often tried treatments for relief of late toxic effects, suggesting a higher (perceived) disease burden.

Limitations

A number of limitations of the HONEY trial should be noted. First, reporting bias among HBOT-adherent patients cannot be ruled out, as these women may be influenced by their expectations toward treatment efficacy. The control group was not informed about the trial, as a result of which patient-reported outcomes were not affected. The risk of reporting bias could have been reduced by conducting a classic sham-controlled RCT. However, we chose not to do so due to complicated logistics and ethical considerations, as participants would unnecessarily be exposed to a high treatment burden.[42] Second, the late toxic effects questionnaire was not filled out at exactly 6 months postrandomization by all participants; there was some variation in the start of HBOT, and not all participants completed the questionnaire immediately after it was sent. The median time between randomization and filling out the follow-up questionnaire was 8 months for both the HBOT-invitation and control groups and 10 months for the HBOT-adherent patients. As all women experienced moderate or severe pain at baseline, a later than expected completed follow-up questionnaire would most likely be associated with a larger reduction in pain in both groups. Sensitivity analysis, where data were analyzed excluding HBOT-adherent patients who started treatment more than 6 months postrandomization, yielded comparable results. Third, this trial was underpowered due to a smaller than anticipated number of participants both randomized into the trial and willing to undergo HBOT. Furthermore, although power analysis assumed 1-sided testing at a 5% significance level, we performed conventional 2-sided testing to reduce risk of type I error.

Conclusions

In this RCT, 1 in 4 women who was offered HBOT for treatment of late local toxic effects after breast irradiation was prepared to undergo treatment. In ITT, offering HBOT was not significantly associated with a reduction in pain, but a significant reduction in fibrosis was observed. Completing HBOT was associated with a significant reduction in pain and fibrosis until at least 3 months posttreatment. The current findings therefore indicate that HBOT is beneficial for the subgroup of women with late local toxic effects who would complete HBOT if offered.

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