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CLINICAL TRIAL

COOLHAIR: a prospective randomized trial to investigate the efficacy and tolerability of scalp cooling in patients undergoing (neo)adjuvant chemotherapy for early breast cancer

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Abstract

Purpose Chemotherapy-induced alopecia (CIA) is a distressing side effect for women with breast cancer undergoing chemotherapy. Scalp cooling is a method aiming to prevent CIA, but its efficacy is not well defined. Randomized trials until recently and at the time this trial was designed have been lacking.

Methods Patients undergoing (neo)adjuvant chemotherapy for early breast cancer (EBC) were randomized to scalp cooling (CAP) or observation (NoCAP). All patients received 18–24 weeks of anthracycline- and/or taxane-based chemotherapy. The primary endpoint was patient-reported rate of alopecia according to a modified version of the Dean Scale. Hair preservation was defined as hair loss ≤ grade 2 (≤ 50%). Secondary endpoints were rate of alopecia determined by medical staff, rate of wig/scarf use, tolerability as well as quality of life (QoL).

Results Seventy-nine patients were randomized. Hair preservation was observed in 39.3% of patients in the CAP arm versus 0% in the NoCAP arm ($p < 0.001$). Wig/scarf use was significantly less frequent in the CAP group (40.7% vs 95.5% outside home before cycle 3, $p < 0.001$). The drop-out rate was 31.7% and 34.2% in the CAP and NoCAP arm, respectively. Main reasons for drop-out were hair loss, adverse events (CAP), and randomization into control arm. We observed no differences in efficacy between anthracycline-based and non-anthracycline-based regimens. QoL did not differ between the study arms.

Conclusions This trial adds to the evidence that scalp cooling effectively prevents CIA in a meaningful number of patients. This option should be made available for patients undergoing (neo)adjuvant chemotherapy for EBC.

Keywords Alopecia · Breast cancer · Chemotherapy · Scalp cooling · Quality of life

Introduction

Breast cancer (BC) is the most common malignancy in women and (neo)adjuvant chemotherapy is offered to many patients to reduce the risk of recurrence [1]. The most frequently used regimens include anthracyclines and/or taxanes leading to alopecia in the vast majority of patients. Due to the ongoing improvement of therapy, overall and breast cancer-specific survival have never been higher than they are today [2] and quality of life (QoL) has moved into the focus as the absolute benefit from adjuvant chemotherapy is modest in most cases.

Chemotherapy-induced alopecia (CIA) remains one of the most distressing side effects for women with BC [3, 4]. CIA has a negative influence on body image and psychological well-being and is associated with depression [5].

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Scalp cooling has been used since the 1970s to reduce CIA [6], but efficacy data are inconsistent and difficult to interpret due to varying chemotherapy schedules, different methods of scalp cooling, and diverse endpoints. Its mode of action has been attributed to vasoconstriction leading to reduced concentration of chemotherapy at the hair follicle and a decrease in follicular metabolism [6, 7]. Scalp cooling can be administered through frozen caps, which have to be replaced regularly and result in fluctuating temperatures. More sophisticated scalp cooling devices are available with a customized cap and a control and cooling unit to circulate the cooling fluid in order to maintain a constant and predefined temperature and avoid fluctuations.

This study is one of the first prospective randomized trials with modern (neo)adjuvant chemotherapy containing sequential anthracycline–taxane-based regimens to examine the efficacy of scalp cooling.

Methods

Study design and patients

COOLHAIR is a monocentric prospective randomized open trial conducted at the National Center for Tumor Diseases, Heidelberg from August 2014 until December 2016. Patients with early breast cancer (EBC) undergoing (neo)adjuvant chemotherapy were eligible for the trial. The study protocol was approved by the ethical review committee of the Medical Faculty of Heidelberg. All patients signed written informed consent.

Inclusion criteria for the study were patients aged > 18 years, ECOG 0–1, with BC stage I–III, and planned chemotherapy with one of the following regimens: 4 × Epirubicin/Cyclophosphamide (q3w or q2w), followed by 12 × weekly Paclitaxel (plus anti-Her2-therapy for Her2-positive patients); 6 × Docetaxel/Carboplatin/Trastuzumab/Pertuzumab (q3w); or 6 × Docetaxel/Cyclophosphamide. Dose-dense dose-intense chemotherapy (iddETC) [8] or concurrent Docetaxel/Doxorubicin/Cyclophosphamide (TAC) [9] were not included due to expected limited efficacy of scalp cooling from previous reports [10]. Exclusion criteria comprised prior history of stroke, any scalp disease, cold agglutinin disease, cryoglobulinemia, or cryofibrinogenemia.

Randomization and intervention

Patients were randomized 1:1 to scalp cooling (CAP) or observation (NoCAP). We used sequentially numbered, opaque-sealed envelopes (SNOSE) for randomization and drawing was performed by personnel not involved in the study otherwise. Scalp cooling was performed by the DigniCap® System. Cooling started 30 min prior to each chemotherapy infusion and was maintained throughout and for 60–120 min after the completion of the treatment depending on the specific schedule. The pre-set temperature of the coolant was 3–5 °C.

Before each chemotherapy cycle, the following outcomes were evaluated: hair loss by patient-reported outcome measurements, staff assessment, and standardized photo documentation; QoL, adverse events, and patient preference with scalp cooling. Furthermore, hair pull tests and trichograms were performed as long as enough hair was available. The pull test is performed by tugging firmly on a group of about 50 hairs. It is positive if more than 10% of hair are pulled away. A trichogram is a semi-invasive method to evaluate hair follicle activity based on the microscopic examination of the proximal end of the hair shaft after plucking more than 50 hairs from the occipital region. Normally, an average of 89% of hair are in anagen (growth phase), 10% in telogen (resting phase), and 1% is catagen phase (transition phase) [11].

Follow-up was performed 3 and 6 months after completion of chemotherapy. At 12 months, a telephone survey was conducted to determine patient preference in the CAP arm.

Endpoints

The primary endpoint of the trial was patient-reported rate of alopecia according to a modified Dean Scale in patients completing the study per protocol [12, 13]. The Dean Scale is divided into five grades—Grade 0: no hair loss; 1: > 0–25%; 2: > 25–50%; 3: > 50–75%; 4: > 75% hair loss. Hair preservation was defined as hair loss ≤ grade 2 (≤ 50%) [14], using the worst grade reported in the course of the whole treatment.

Secondary endpoints were rate of alopecia determined by medical staff, wig/scarf use, tolerability of the scalp cooling device, QoL as well as changes in hair pull test and trichogram.

For assessment of QoL-selected scales of the European Organization for Research and Treatment of Cancer (EORTC), QLQ-C30 and its specific module for BC patients BR23 form version 3.0 were analyzed [15, 16]: Global Health Status (item 29 and 30), Emotional Functioning (item 21–24), Social Functioning (item 26, 27), and Body Image of the BR23 (item 9–12). Furthermore, we used a Summary Score with 13 items of the QLQ C30 [17]. For the analysis, the mean score difference from baseline was calculated for each time point in both study groups.

Sample size

A reduction of the alopecia rate from 99 to 70% was considered as clinical relevant. Based on a two-sided chi-squared test, a sample size of 25 patients per group was sufficient

to guarantee a power of 90% ($\alpha = 0.05$). With an expected drop-out of 35%, a total sample size of 78 patients was determined.

Statistical Analysis

Baseline characteristics of the study cohort were analyzed descriptively. Rates of alopecia between the two groups were compared using a chi-squared test and reported with 95% confidence intervals (CI). The results of the per-protocol analysis (PP) as primary endpoint were compared to a sensitivity analysis of a modified Intention-to-treat (mITT) sample, where drop-outs during therapy were treated as failures. Furthermore, the primary endpoint was analyzed in subgroups. For all secondary outcomes and subgroup analyses, descriptive *p* values were calculated applying t-tests for continuous data and chi-squared tests for binary data. Adverse events were reported with absolute and relative frequencies. All statistical analyses were performed using the statistical software R (Version 3.2.2).

Table 1 Demographics and baseline information (mITT)

	CAP	NoCAP	All
Overall patients No. (%)	36 (100.0)	27 (100.0)	63 (100.0)
Age			
Median (range)	53 (27–79)	56 (31–81)	54 (27–81)
Menopausal status			
Premenopausal	17 (47.2)	12 (44.4)	29 (46.0)
Postmenopausal	18 (50.0)	15 (55.6)	33 (52.4)
Perimenopausal	1 (2.8)	0 (0)	1 (1.6)
Ethnicity			
Caucasian	34 (94.4)	24 (88.9)	58 (92.1)
Mediterranean	1 (2.8)	3 (11.1)	4 (6.3)
Missing	1 (2.8)	0 (0)	1 (1.6)
CT setting			
Neoadjuvant	23 (63.9)	18 (66.7)	41 (65.1)
Adjuvant	13 (36.1)	9 (33.3)	22 (34.9)
CT regimen			
AT-based	14 (38.9)	16 (59.3)	30 (47.6)
AT-based + anti-HER2	2 (5.6)	2 (7.4)	4 (6.4)
T-based	3 (8.3)	2 (7.4)	5 (7.9)
T-based + anti-HER2	17 (47.2)	7 (25.9)	24 (38.1)

Results

Between August 2014 and January 2016, 79 patients were randomized, 41 into the CAP and 38 into the NoCAP arm. 16 patients were excluded from the analysis due to drop-out before starting chemotherapy (mITT sample). At the time of the analysis, all patients had completed (neo)adjuvant chemotherapy and were followed for 6 months after treatment.

Both arms were well balanced in terms of baseline patient and treatment characteristics (Table 1). In the mITT sample ($n = 63$) 54.0% of patients received sequential anthracycline–taxane-based regimes ($n = 34$), whereas 46.0% had anthracyclines-free taxane-based chemotherapies ($n = 29$). Patients with HER2-positive disease also received Trastuzumab ± Pertuzumab.

Altogether from all randomized patients ($n = 79$), 13 patients (31.7%) in the CAP arm were drop-outs. From the 13 drop-outs, 5 patients withdrew informed consent prior to the first therapy; 8 patients discontinued scalp cooling in the course of the treatment, mainly because of hair loss ($n = 3$) and adverse device events ($n = 2$). In the NoCAP arm also 13 patients (34.2%) withdrew consent, for the most part prior to therapy because of disappointment about allocation to the control arm ($n = 9$) (Fig. 1).

The analysis of the primary endpoint, the worst grade of patient-reported alopecia reported in the course of the treatment, was based on the per-protocol population ($n = 53$). In the CAP arm, 11 patients (39.3%, 95%-CI: 22%; 59%) had hair preservation in comparison to 0 (0%, 95%-CI: 0%; 14%) in the control arm ($p < 0.001$) (Table 2; Fig. 2). There was a near complete concordance between patient and staff evaluation (global weighted Cohen's kappa of all assessments: 0.92) (Fig. 2).

In the mITT analysis, 8 patients in the CAP arm, who discontinued scalp cooling early, were categorized as failures. This resulted in a success rate of 30.6% (95%-CI: 16%; 48%) which also differed significantly compared to the NoCAP arm (0%; 95%CI: 0%;14%; $p = 0.002$).

There were no differences in hair preservation between anthracycline–taxane-based and taxane-based chemotherapy regimens (p value = 0.80) or treatment with or without anti-Her2-therapy (p value = 0.93). However, these subgroup analyses are limited by small numbers (Table 3).

Wig/scarf use differed significantly between both arms. Before cycle 3, 81.5% of patients in the CAP arm never wore a head covering at home versus 9.1% in the NoCAP arm ($p < 0.001$). Outside home, still 59.3% never wore a wig or scarf in the CAP arm versus 4.5% in the control group ($p < 0.001$). During the entire course of the treatment, 64.3% in the CAP versus 0% in the NoCAP arm never used a head covering at home ($p < 0.001$). Outside, 21.4% in the CAP arm versus 0% in the NoCAP arm never used a head covering ($p < 0.001$) (Table 2). Wig use was strongly correlated with hair loss (Spearman´s correlation coefficient 0.73).

Hair pull test and trichogram

Before chemotherapy, almost all patients had a negative hair pull test. Due to hair loss in the NoCAP arm, a pull test could only be performed in 5 patients at cycle 2, all demonstrating

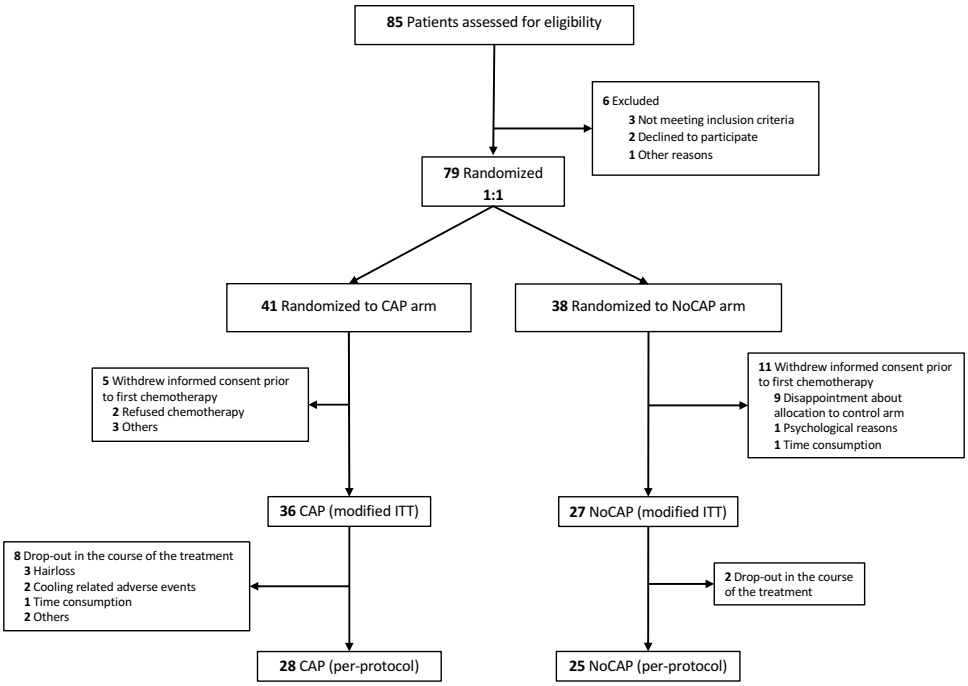


Fig. 1 Consort flow diagram of the study

Table 2 Success rates of the different endpoints in both study arms with or without Scalp cooling in the per-protocol analysis

Parameter	CAP $n=28$ (100%)	NoCAP $n=25$ (100%)	p value
Patient-reported hair loss by Dean Scale (Primary endpoint)			
Success	11 (39.3)	0 (0)	< 0.001
Failure	17 (60.7)	25 (100.0)	
Wig use			
Worst response at home			
Never	18 (64.3)	0 (0)	< 0.001
Sometimes	7 (25.0)	6 (24.0)	
Always	3 (10.7)	19 (76.0)	
Missings	0	0	
Worst response outside home			
Never	6 (21.4)	0 (0)	< 0.001
Sometimes	8 (28.6)	0 (0)	
Always	14 (50.0)	25 (100.0)	
Missings	0	0	
Before cycle 3 at home			
Never	22 (81.5)	2 (9.1)	< 0.001
Sometimes	3 (11.1)	11 (50.0)	
Always	2 (7.4)	9 (40.9)	
Missings	1	3	
Before cycle 3 outside home			
Never	16 (59.3)	1 (4.5)	< 0.001
Sometimes	7 (25.9)	1 (4.5)	
Always	4 (14.8)	20 (91.0)	
Missings	1	3	

a positive result. In the CAP arm, hair pull tests could be performed on 18 patients at cycle 2 with 38.9% of these still negative. A negative hair pull test was achieved at 3 and 6 months follow-up for 80% and 100%, respectively, with no differences between study arms.

Trichograms showed normal rates of anagen (80.7%) and telogen (17.5%) hair prior to treatment in both arms. In the CAP arm, the ratio of anagen to telogen hair shifted at the expense of anagen hair with a maximum at cycle 3 (50.5% anagen and 40.8% telogen). Due to hair loss in the NoCAP arm, between cycle 3 and completion of the chemotherapy no trichograms could be performed. At cycle 2 a stronger decline of anagen hair is shown in the NoCAP arm in comparison to the CAP arm. Three months after the end of therapy, trichograms had recovered to a normal distribution in both study arms (Fig. 3).

Quality of life

In all selected scales of the EORTC QLQ-C30 and BR23, no significant difference between the arms were observed. However, the small number of patients in both study arms has to be considered. Only in the emotional and social functioning scale a trend to a better functioning could be seen in the respective graphs for the patients in the CAP arm at the end of the treatment and the follow-up (Fig. 4).

Adverse device events/tolerability

Altogether, 86.8% of the patients had device-related adverse events in the mITT analysis. The most distressing

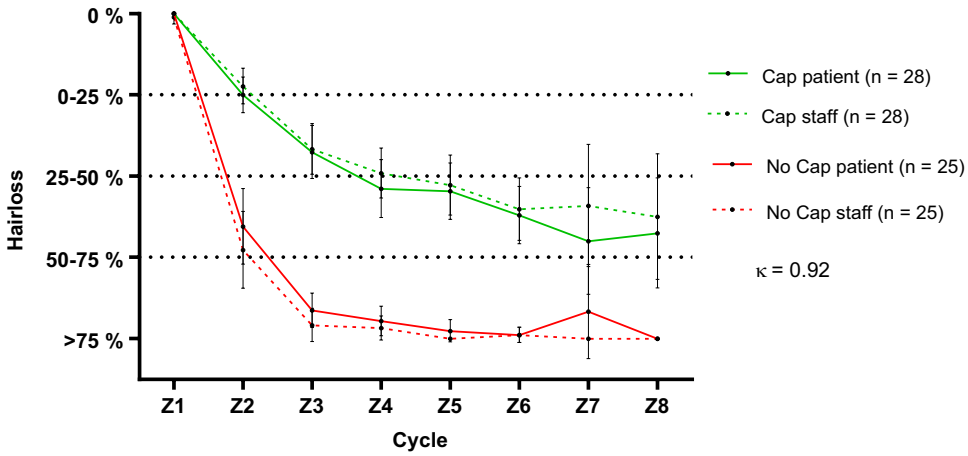


Fig. 2 Hair loss by patient and staff evaluation in the course of the treatment. Data are presented as mean values of the per-protocol analysis (incl. 95% CI). The graph shows a near complete concordance between patient and staff evaluation (global weighted Cohen's kappa of all assessments: 0.92)

Table 3 Patient-reported hair loss in subgroups in the per-protocol analysis

Parameter	CAP *n* (%)	*p* Value
AT-based regimen		
Success	4 (36.4)	0.80
Failure	7 (63.6)	
T-based regimen		
Success	7 (41.2)	
Failure	10 (58.8)	
Anti-HER2		
Success	6 (40.0)	0.93
Failure	9 (60.0)	
No anti-HER2		
Success	5 (38.5)	
Failure	8 (61.5)	

adverse event was chills, which was reported as severe in 63.1% of the patients ($n=24$). 18.4% ($n=7$) of the patients reported severe headaches. Worst grades of adverse events per patient are given in Table 4. Two patients stopped scalp cooling due to device-related adverse events.

Follow-up and patient preference of scalp cooling

Follow-up was performed at 3 and 6 months after chemotherapy. Hair regrowth > 75% was reported by 66.7% ($n=12$) and 75.0% ($n=12$) at 3 months and 94.7% and 100% at 6 months in the CAP and NoCAP arms, respectively.

81.5% of the patients were satisfied with scalp cooling and 66.7% of the patients would have chosen scalp cooling again as demonstrated by results of a telephone survey at 12 months.

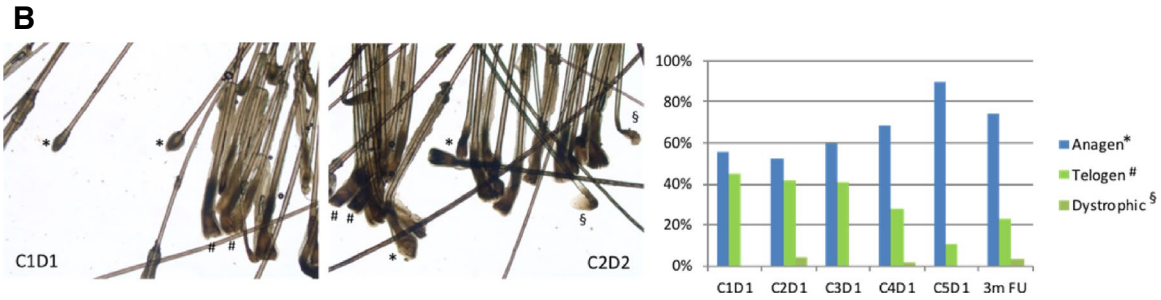
Missing values

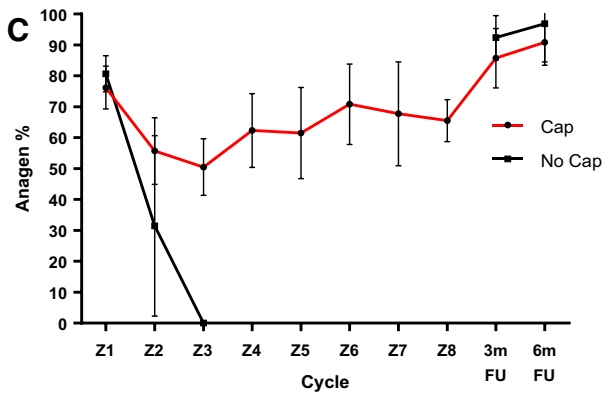
No missing values occurred in primary endpoint of the study. In the secondary endpoints, missing values occurred completely at random and no relation to any other study variable was found. Occurrence and number of missing values in selected secondary endpoints are given in Table 2.

Discussion

COOLHAIR is a prospective randomized trial including 79 patients to evaluate the efficacy of scalp cooling for patients receiving (neo)adjuvant chemotherapy for EBC. The study is one of the first randomized trials with modern chemotherapy regimens, including sequential anthracycline–taxane-based protocols in over 50% of patients.

Hair preservation was achieved in 39.3% of patients in the CAP compared to 0% in the NoCAP arm in the per-protocol analysis ($p<0.001$). These results were confirmed by the analysis of the mITT sample (30.6% vs 0%; $p=0.002$). The efficacy of scalp cooling can be influenced by many factors, including ethnicity, age, infusion time, scalp temperature, and chemotherapy agents, dose as well as regimen [18–20]. This limits the comparison of hair preservation rates between different studies. Nangia et al. reported a success rate of 50.5% in a randomized trial of patients receiving either anthracyclines or taxanes. In anthracycline-treated patients, the success rate was only 16% compared to 59% in the taxane group [21]. In contrast, 54.0% of the patients in our study received a sequential anthracycline **and** taxane-based regimen. In addition, we did not observe differences between patients with anthracycline-containing and anthracycline-free regimens, in line with observational studies [20, 22]. Another multicenter prospective study using the same scalp cooling device, only included taxane-based chemotherapy and achieved a success rate of 66.3% [23]. However,





CAP	26	19	17	16	13	12	7	6	13	11
NoCAP	19	6	1	0	0	0	0	0	5	3

Number of patients with trichogram

◂**Fig. 3** **a** Standardized photo documentation of patients with Scalp cooling (A, B and C) and no Scalp cooling (D) Patient A and B show a successful hair preservation (Dean Scale grade ≤ 2). Patient C shows no success with scalp cooling (Dean Scale grade > 2). Patient D shaved the head after cycle 2 because of complete alopecia. *CT* chemotherapy, *FU* follow-up. **b** Trichogram of patient A with Scalp cooling during treatment [*Anagen hair; #Telogen hair; §Dystrophic hair (×10 magnification)]. **c** Rate of anagen hair during treatment in both study arms. Data are shown as mean values of the mITT analysis (incl. 95%-CI). *FU* follow-up

endpoints differ considerably between these trials. We chose a rigid definition of hair preservation based on worst grade of hair loss reported during all cycles of therapy. Other trials defined a specific time point at which hair loss was evaluated (e.g., end of cycle 4 or 4 weeks after the last chemotherapy) [21, 23], which would assume that hair loss develops in a very similar pattern over time in all patients and is highest at the selected point. This might also explain some of the observed differences. Maybe more important than the actual grade of hair loss is its relevance for patient's daily activities. In our study, the patients in the CAP arm never used a wig/scarf outside home before cycle 3 in 59.3% or at any time during chemotherapy in 21.4%, compared to 4.5% and 0% of patients not undergoing scalp cooling. A registry including 1411 patients used head covering as an endpoint and reported an overall success rate of 50% for scalp-cooled patients after their last chemotherapy [10].

Hair pull tests and trichograms were selected as more objective tools to investigate the influence of scalp cooling on the changes in the hair follicle [24]. We observed a faster and stronger deterioration in the pull test and trichogram in the control group. However, the hair reconstituted at the 3- and 6-month follow-up to normal results in both study arms. The data in our control arm are in line with data from Kanti et al. on the influence of CIA on the hair follicle with trichological parameters [25]. However, to the best of our knowledge, we report the first analysis of the impact of scalp cooling on trichological parameters. These findings support the results of the primary endpoint.

The lack of impact of scalp cooling on QoL observed in our study has to be interpreted in the light of the small sample size. In addition, the drop-outs in the experimental and control arm might have led to a selection bias. It could be speculated, that those patients who were the least concerned about CIA would be more likely to drop out of the CAP arm, whereas those strongly concerned about CIA might have selectively dropped out of the control arm. However, it is in line with the randomized trial by Nangia et al. [21]. In BC treatment, QoL is influenced by a variety of factors including the diagnosis itself, multiple side effect of chemotherapy, and the aesthetic outcome after BC surgery [26–29]. With a non-specific QoL questionnaire developed for cancer patients, changes by scalp cooling are difficult to evaluate. However, various studies have shown that CIA ranges under the most distressing side effects leading to decreased body image, stigmatization, and depression [4, 5]. The Chemotherapy-Induced Alopecia Distress Scale proposed by Cho et al. is a validated and reliable instrument to evaluate the influence on CIA on psychosocial well-being and QoL which could be used in further studies [30].

Limitations

Due to the small sample size of the study, the conclusions especially in the subgroups of the secondary endpoints are limited. Although the trial met its primary endpoint, for further studies the primary endpoint should be QoL and not hair preservation, making bigger sample sizes necessary. Another limitation of the study is the high drop-out rate in both study arms with possible bias in patient cohorts.

Conclusion

Scalp cooling can prevent hair loss in a clinically relevant number of patients and should be made available for patients undergoing modern (neo)adjuvant chemotherapy regimens for EBC. Despite a relevant failure rate and adverse events, 66.7% would opt for scalp cooling again.

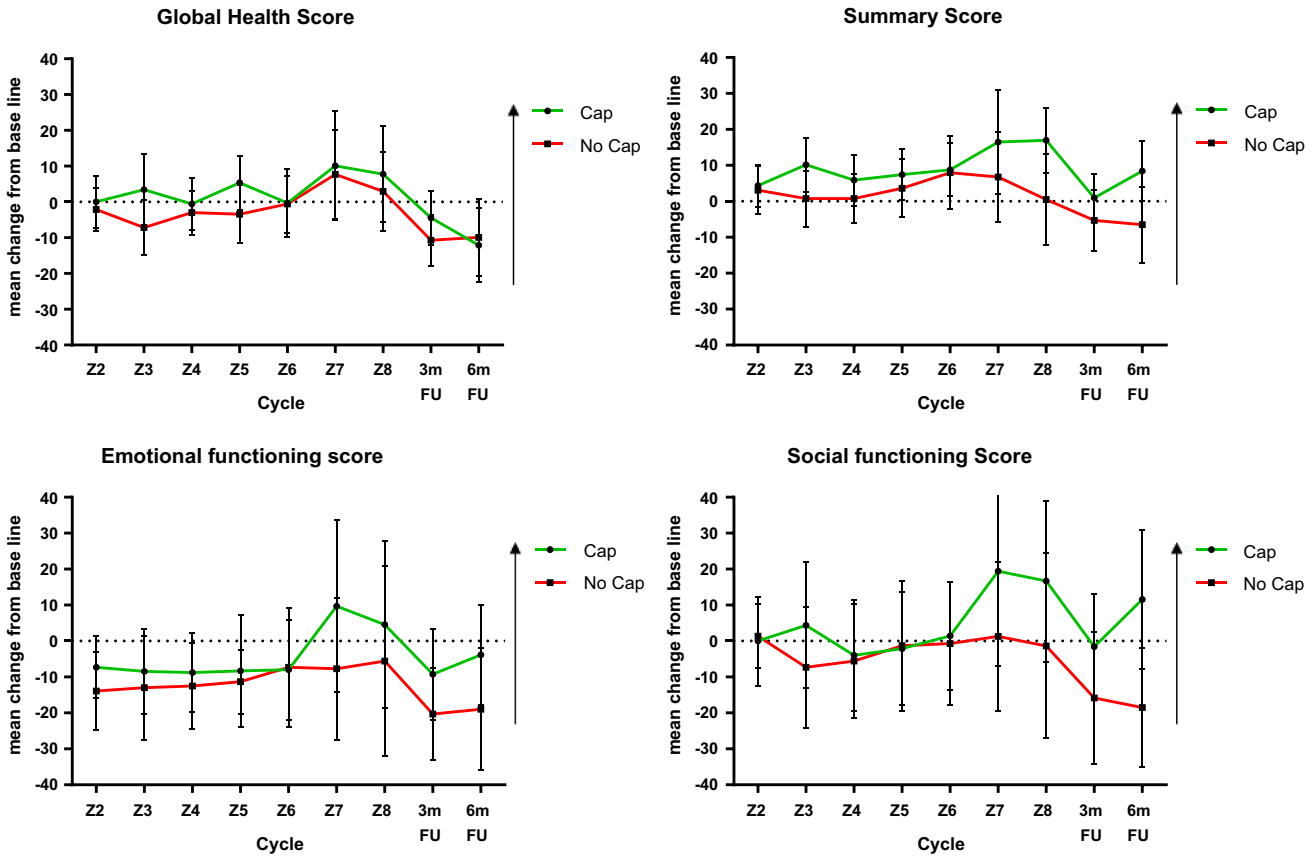


Fig. 4 Global health, summary, emotional, and social functioning score. Data are shown as mean change from baseline before CT (incl. 95%-confidence intervals). Changes > 0 indicate improvement from baseline. Arrow denotes direction of improved outcome. *FU* follow-up

Table 4 Adverse events of Scalp cooling

Adverse device event No.* (%)	Not at all	A little	Quite a bit	Very much
Any adverse device events	5 (13.2)	4 (10.5)	22 (57.9)	7 (18.4)
Headache	9 (23.7)	1 (2.6)	21 (55.3)	7 (18.4)
Chills	7 (18.4)	2 (5.3)	5 (13.2)	24 (63.1)
Feeling of heaviness of the head	12 (31.6)	5 (13.2)	13 (34.2)	8 (21.0)
Scalp pain	14 (36.8)	2 (5.3)	13 (34.2)	9 (23.7)
Neck pain	18 (47.4)	4 (10.5)	10 (26.3)	6 (15.8)

*Percentage refer to patients who answered (missings excluded); grade of maximal severity per patient in the course of the treatment

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Compliance with ethical standards

Conflict of interest Jessica C. Hassel has had a paid consulting role with Merck and Amgen, and has received honoraria from Bristol-Myers Squibb, Merck, Novartis, Roche, and Pfizer. Dirk Jaeger received honoraria from Bayer, Amgen, MSD, CureVac, Roche, BMS, and Definiens. Andreas Schneeweiss received honoraria from Roche, Celgene, Pfizer, AstraZeneca, and Novartis. Frederik Marmé has received honoraria and travel expenses from Roche, Amgen, AstraZeneca, Eisai, and Celgene. Novartis, Pfizer, PharmaMar, Genomic Health, and CureVac. All remaining authors have declared no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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