Scalp Cooling in Preventing Persistent Chemotherapy-Induced Alopecia: A Randomized Controlled Trial

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ABSTRACT

PURPOSE Current studies of the efficacy of scalp cooling are limited by short-term duration. Therefore, we conducted a randomized controlled trial to evaluate the efficacy of scalp cooling in reducing persistent chemotherapy-induced alopecia (PCIA) 6 months after chemotherapy.

METHODS We conducted an open-label randomized controlled trial comparing scalp cooling versus control in newly diagnosed patients with breast cancer stages I-III scheduled to receive neoadjuvant or adjuvant chemotherapy with curative intent between December 2020 and August 2021. Patients were randomly assigned (2:1 ratio) to scalp cooling or usual clinical practice. The primary outcome was PCIA 6 months after chemotherapy. Hair thickness and density were measured using Folliscope 5.0. CIA-related distress was assessed using the CIA distress scale (CADS), with a higher score reflecting higher stress.

RESULTS The proportion of patients with PCIA at 6 months was 13.5% (12/89) in the scalp-cooling group and 52.0% (26/50) in the control group. The average difference in the change in hair thickness from baseline between the scalp-cooling and control groups was 9.0 μm in favor of the intervention group. The average difference in the change in hair density between intervention and control at the end of the study was −3.3 hairs/cm². At 6 months after chemotherapy, the average difference in the change in CADS score between the intervention and control groups was −3.2 points, reflecting reduced CIA-related stress in the intervention group.

CONCLUSION Scalp cooling reduced the incidence of PCIA, primarily by increasing hair thickness compared with control. Scalp cooling is helpful in promoting qualitative hair regrowth. Yet, further research is necessary to observe longer-term benefits of scalp cooling.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

Chemotherapy-induced alopecia (CIA) is one of the most common and burdensome adverse events in patients undergoing chemotherapy.[1] Although CIA is often considered temporary,[2] some patients show complete or partial lack of hair regrowth even years after completion of chemotherapy, a phenomenon called persistent or permanent CIA (PCIA).[3] In a prospective study, 42.3% of patients with breast cancer had incomplete hair regrowth 3 years after chemotherapy.[4] In this cohort, the average hair density returned to baseline levels 6 months after chemotherapy, but the average hair thickness did not return to baseline levels,[4] suggesting chemotherapy damages hair follicle cells with a long-term impact on the quality of the hair shaft. Although pharmacologic and physical approaches have been developed for preventing or treating CIA, the effectiveness of most approaches to treat or prevent PCIA is limited.[2,5]

Studies have established the efficacy of scalp cooling in preventing hair loss during chemotherapy, but there is limited evidence of its efficacy on PCIA.[6-8] Previous studies evaluating scalp cooling assessed percent hair preservation 1-2 months after completion of chemotherapy (maximum of 12 weeks) and did not track long-term recovery to

CONTEXT

Key Objective

To evaluate the efficacy of scalp cooling in reducing persistent chemotherapy-induced alopecia (PCIA) 6 months after chemotherapy, presenting new insights into its benefits for hair preservation.

Knowledge Generated

Patients treated with scalp cooling showed a significant reduction in the incidence of PCIA 6 months after chemotherapy, compared with those in the control group. This intervention also resulted in a notable improvement in hair thickness and a significant decrease in psychological distress related to CIA.

Relevance *(G. Fleming)*

Even with scalp cooling, many patients have complete or partial hair loss. This manuscript provides additional information about the effects of scalp cooling, particularly on the thickness of individual hairs, at 6 months after chemotherapy.*

*Relevance section written by *JCO* Associate Editor Gini Fleming, MD.

baseline hair quality.[6-8] Therefore, we conducted a randomized controlled trial to evaluate the effectiveness of scalp cooling in preventing PCIA by promoting hair recovery among patients with breast cancer undergoing chemotherapy.

METHODS

Trial Design and Participants

We conducted an open-label, randomized, controlled trial. Participants were patients age 20-69 years with newly diagnosed stage I-III breast cancer scheduled to receive four or six cycles of anthracycline- and/or taxane-based chemotherapy either as neoadjuvant or adjuvant treatment with curative intent (eg, doxorubicin and cyclophosphamide, docetaxel and cyclophosphamide, or docetaxel, carboplatin, trastuzumab, and pertuzumab) between December 23, 2020, and August 27, 2021, at Samsung Medical Center (SMC) in Seoul, South Korea.

We excluded patients who had any other concurrent malignancy, including hematologic malignancies; elevated levels of liver enzymes or bilirubin, defined as three times the upper limit of normal; serum albumin level <3.0 g/dL; underweight, defined as BMI <17.5 kg/m^2; previous chemotherapy exposure; cold agglutinin disease or cold urticaria; thyroid disease, diabetes, or cardiac disease; autoimmune disease; history of treatment for alopecia; or scalp diseases such as seborrheic dermatitis, psoriasis, and infections.

The study was approved by the institutional review board (No. 2019-12-148). Participants provided written informed consent. The study protocol was registered at ClinicalTrials.gov (identifier: NCT04678544).

Random Allocation and Blinding

Patients were randomly assigned in a 2:1 ratio to scalp cooling or usual clinical practice using permuted blocks of sizes 3 and 6. Since aging and menopause could affect hair regrowth,[9] we stratified random assignment by age (<50 or ≥50 years).[10] To account for the reduced effectiveness of scalp cooling with anthracycline chemotherapy,[11] we also stratified random assignment–based anthracycline use. Study coordinators enrolling participants could not access the randomization codes. The locked information was not available until the last patient was recruited. Patients and investigators were not blinded during the trial, but outcome assessors and data analysts were blinded.

Scalp Cooling

We used the Paxman Scalp Cooling System 2 (PSCS2; Paxman Coolers Limited, Huddersfield, United Kingdom) as the investigational device. The PSCS2 is a freestanding, electrically powered, mobile refrigeration unit that circulates a liquid coolant at a preset temperature and flow rate through a cooling cap attached to the top of the patient's head. Potential side effects include discomfort due to cold, headache, dizziness, and vomiting.

Patients in the intervention group wore the cooling cap for 30 minutes before chemotherapy and then for an additional 20 minutes after taxane-based therapy and for an additional 90 minutes after doxorubicin-based or combination therapy. The additional times after chemotherapy were determined considering the pharmacokinetics of exposure of the hair follicles to the cytotoxic agent and its active metabolites on he basis of their peak plasma concentrations, drug half-life, and potential interactions.[12,13] The patients were allowed to move for 10 minutes while using the cooling cap. To improve

adherence, patients were asked to take pain medication before scalp cooling to prevent headache and pain caused by chills on the head. The intervention group also received a hair management kit containing a brush, a soft fabric headband, and one bottle each of shampoo and conditioner.

Control

Patients in the control group received the same clinical treatment (except for scalp cooling), educational materials, and hair management kit as those in the intervention group, including information on hair management during chemotherapy.

Follow-Up

Study visits were scheduled before chemotherapy (baseline), at the start date of the second cycle of chemotherapy, and then 1 month (±2 weeks) and 6 months (±2 months) after the completion of chemotherapy.

Study Outcomes

The primary outcome was PCIA, defined as absent or incomplete hair regrowth at 6 months after chemotherapy.[3] To establish the presence of PCIA, we adopted objective criteria on the basis of the fact that the two hallmarks of PCIA are reduced hair density and reduced hair thickness.[3,14] The presence of PCIA was established if, at the visit occurring 6 months after the completion of chemotherapy, hair density and hair thickness were more than two standard deviations (SDs) below their respective baseline means (before chemotherapy). The SDs were also on the basis of baseline data. This approach has been used in previous studies.[4,15] Hair thickness and density were measured using a Folliscope 5.0 (Lead M, Seoul, Korea). Hair density and thickness were measured at the midline of the vertex using a 60X lens to measure thickness and a 15X lens to measure density. To ensure the comparability of trichoscopic images during follow-up, we used a plastic headband connected to a tapeline by a snap mechanism using four reference points for reproducibility. We asked patients not to shave their head during the study.

To evaluate hair thickness, we measured the thickness of hairs from images of the vertex site (up to 50 hairs, limited by the Folliscope program). We selected the middle 50% of hairs (excluding the 25% thickest and the 25% thinnest hairs) and calculated their average thickness (μm) and the patient-specific SD. Hair density was calculated as the total number of hairs at the vertex site divided by surface area (hairs/cm^2). For hair density, the SD was calculated across all patients. We defined PCIA as a 6-month average hair thickness below the patient-specific baseline average minus two times the patient-specific baseline SD, or a 6-month hair density below the patient-specific baseline density minus two times the baseline SD. For hair thickness, the patient-specific baseline SDs ranged from 0.002 to 0.026 μm (average SD, 0.005 μm).

The secondary end points were hair density, hair thickness, and CIA-related distress during and after the completion of chemotherapy. To measure distress because of CIA, we used the CIA distress scale (CADS). The CADS was developed and validated in Korean[16] and adapted by US,[17] Japanese,[18] and Chinese investigators.[19] The CADS consists of 17 items in four domains: physical, emotional, daily activity, and relationships. Responses were based on a four-point Likert scale. The total CADS score was calculated as the sum of the scores of responses to all items and ranged from 0 to 51. Higher scores indicated higher levels of distress. In addition, we asked participants about their use of wigs, scarves, or caps at 6 months after chemotherapy.

At baseline, we collected sociodemographic information including marital status, education, and employment status, as well as behavioral information on smoking and drinking habits, using a questionnaire. Clinical information, including menopausal status, type of surgery, sequence of chemotherapy, type of chemotherapy, radiation therapy, hormone therapy, and ovarian function suppression, was obtained from electronic medical records. We collected expected adverse events using a 10-point visual analog scale.

Statistical Analyses

On the basis of our previous study,[4] we hypothesized that the proportion of patients with PCIA in the intervention and control groups would be 13% and 40%, respectively (absolute difference of 27%).[4] Assuming a probability of type-I error (α) of .05 (two-sided), a 2:1 intervention:control allocation ratio, and 90% power, we calculated a sample size of 90 patients for the intervention group and 45 for the control group. Considering a 20% loss to follow-up, we planned to enroll 170 patients.

Study participants were analyzed in the group that had been assigned by randomization, irrespective of treatment adherence. For the primary outcome, we used a χ^2 test to evaluate the difference in the proportion of PCIA at 6 months after chemotherapy between the intervention and control groups. For the secondary outcomes, which were measured at four visits, we used mixed-effect linear models including main effects for each visit and visit-scalp cooling interaction terms (visit × group) to assess the differences in the change in outcomes in the intervention and control groups. Random intercepts were included to allow for variations in outcomes across study participants at baseline. In a secondary analysis, we used log-transformed hair thickness and density as the outcomes and estimated the average difference in percent change from baseline (with 95% CIs) comparing intervention with control. In addition, we performed stratified analyses by age and type of chemotherapy.

Post hoc analyses were conducted for both primary and secondary outcomes adjusting for stratification factors. For the primary outcome, we estimated the marginally adjusted proportions of PCIA in each group (using stratification

factors in the adjustment model) and then calculated their ratio as the measure of efficacy of scalp cooling on PCIA. Statistical analyses were performed using R (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).[20]

RESULTS

We screened 216 patients with breast cancer between December 23, 2020, and August 27, 2021, of whom 188 met the eligibility criteria and 170 (90%) agreed to participate and were randomly assigned to the scalp-cooling (n = 113) or control (n = 57) groups. Before chemotherapy, seven participants in the intervention group and five participants in the control group withdrew their consent. In the intervention group, 16 patients withdrew during chemotherapy, and one patient withdrew 1 month after chemotherapy. The main reason cited for withdrawing was inconvenience resulting from the long postcooling time (n = 10). In the control group, two patients withdrew during chemotherapy (Fig 1).

The mean age (±SD) of the 139 study participants (89 in the intervention group and 50 in the control group) at baseline was 45.8 (±10.5) years; 12.9% of participants underwent chemotherapy that included an anthracycline drug (Table 1). The median follow-up from random assignment to the primary end point assessment visit was 8.9 months in the intervention group and 8.6 months in the control group, while the median follow-up from completion of chemotherapy to the primary end point assessment visit was 6.3 months in the intervention group and 6.1 months in the control group. Six months after chemotherapy, the proportions of patients with PCIA in the intervention and control groups were 13.5% (12/89) and 52.0% (26/50), respectively. The relative risk (RR) for PCIA comparing intervention versus control was 0.27 (95% CI, 0.11 to 0.43; Table 2). The effect was similar in patients younger than 50 and in patients age 50 years and older, and in those receiving and not receiving an anthracycline regimen.

From baseline to the 6-month visit, hair thickness decreased by 7.5 μm (95% CI, −11.9 to −3.0) in the control group and increased by 1.5 μm (95% CI, −2.8 to 5.8) in the intervention group (Table 3). Six months after chemotherapy, the average difference in the change in hair thickness between the intervention and control groups was 9.0 μm (95% CI, 4.0 to 14.0) in favor of the intervention group. Hair density decreased less in the intervention group than in the control group 1 month after chemotherapy and increased in both groups 6 months after chemotherapy. The average difference in the change in hair density between intervention and control at the end of the study was small (−3.3 hairs/cm²; 95% CI, −13.7 to 7.2; Table 3). The results were similar in secondary analysis using percent change from baseline in hair thickness and density (Appendix Table A1, online only).

Between the baseline and the 6-month visits, the CADS score increased by 3.9 points in the intervention group and by 7.0

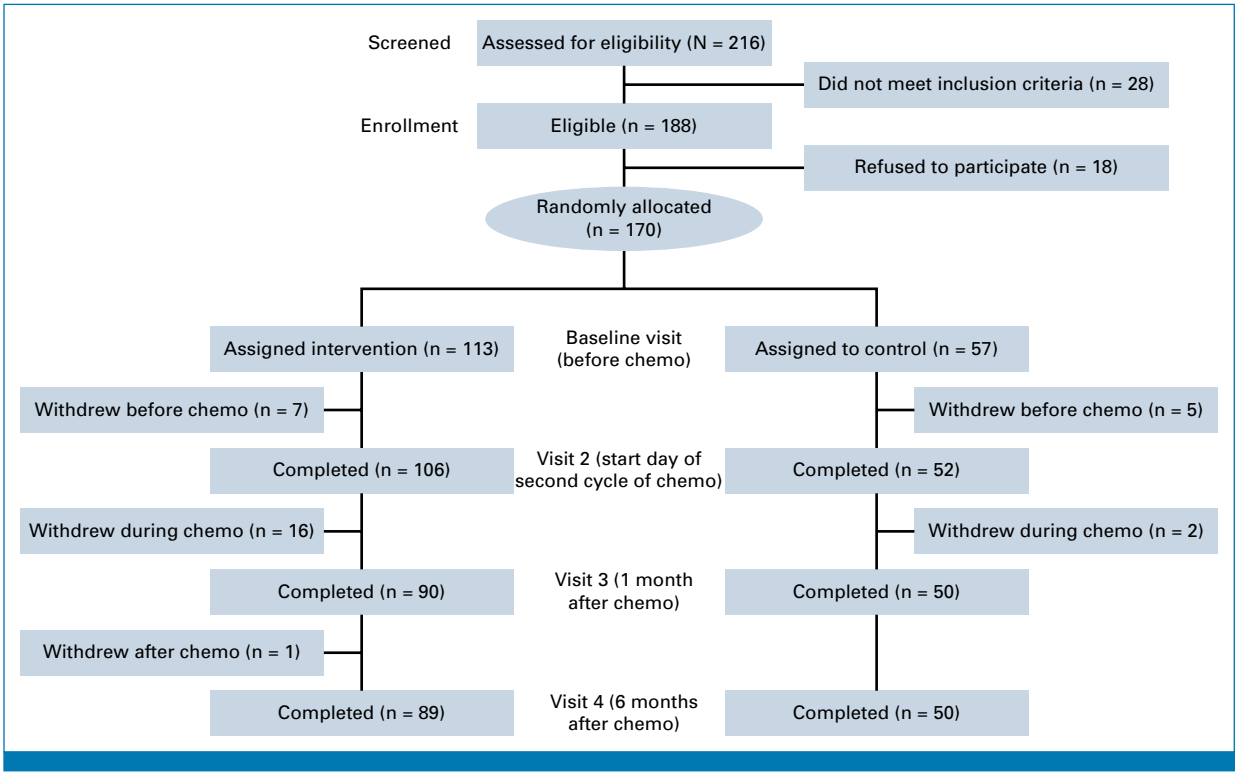

FIG 1. CONSORT diagram.

TABLE 1. Characteristics of Study Participants

Characteristic	Intervention	Control
No. of participants	89	50
Age at diagnosis, years, mean (SD)	45.3 (10.8)	46.9 (9.9)
Marital status, No. (%)		
Married	69 (77.5)	35 (70.0)
Unmarried	18 (20.2)	14 (28.0)
NA	2 (2.2)	1 (2.0)
Education, university, No. (%)	54 (60.7)	36 (72.0)
Employed, yes, No. (%)	27 (30.3)	14 (28.0)
Currently drinking, No. (%)	7 (7.9)	4 (8.0)
Current smoking status, No. (%)		
Never	81 (91.0)	46 (92.0)
Past	8 (9.0)	2 (4.0)
Current	0	2 (4.0)
Menopause, No. (%)	33 (37.1)	17 (34.0)
Type of surgery, lumpectomy, No. (%)	60 (67.4)	32 (64.0)
Sequence of chemotherapy, adjuvant, No. (%)	55 (61.8)	31 (62.0)
Type of chemotherapy, No. (%)		
AC (four cycles)	5 (5.6)	5 (10.0)
TC (four cycles)	46 (51.7)	22 (44.0)
TCHP (six cycles)	34 (38.2)	19 (38.0)
TAC (six cycles)	4 (4.5)	4 (8.0)
Radiation therapy, No. (%)	68 (76.4)	41 (82.0)
Hormone therapy, No. (%)	67 (75.3)	34 (68.0)
Tamoxifen	40 (44.9)	22 (44.0)
Aromatase inhibitor	30 (33.7)	13 (26.0)
Ovarian function suppression, No. (%)	31 (34.8)	15 (30.0)
Family history of alopecia, No. (%)	27 (30.3)	12 (24.0)
Hair thickness, μm, mean (SD)	98.1 (11.1)	98.2 (13.4)
Hair density, hairs/cm^2, mean (SD)	144.5 (26.6)	151.0 (27.1)

Abbreviations: AC, doxorubicin + cyclophosphamide; NA, not available; TAC, docetaxel + doxorubicin + cyclophosphamide; TC, docetaxel + cyclophosphamide; TCHP, docetaxel + carboplatin + trastuzumab + pertuzumab; SD, standard deviation.

TABLE 2. Effect of Scalp Cooling on Primary Outcome (PCIA at the 6-month visit)

Outcome	Intervention	Control
Overall		
No. of cases of PCIA/total	12/89	26/50
Proportion (95% CI)	0.14 (0.06 to 0.21)	0.52 (0.38 to 0.66)
RR (95% CI)	0.26 (0.11 to 0.41)	1.00 (reference)
By age group		
Age <50 years		
No. of cases of PCIA/total	7/59	15/30
Proportion (95% CI)	0.12 (0.04 to 0.20)	0.50 (0.32 to 0.68)
RR (95% CI)	0.24 (0.05 to 0.42)	1.00 (reference)
Age ≥50 years		
No. of cases of PCIA/total	5/30	11/20
Proportion (95% CI)	0.17 (0.03 to 0.30)	0.55 (0.33 to 0.77)
RR (95% CI)	0.30 (0.03 to 0.58)	1.00 (reference)
By type of chemotherapy		
No anthracycline (TC or TCHP)		
No. of cases of PCIA/total	11/80	20/41
Proportion (95% CI)	0.14 (0.06 to 0.21)	0.49 (0.33 to 0.64)
RR (95% CI)	0.29 (0.10 to 0.47)	1.00 (reference)
Anthracycline (AC or TAC)		
No. of cases of PCIA/total	1/9	6/9
Proportion (95% CI)	0.11 (0.04 to 0.32)	0.67 (0.35 to 0.98)
RR (95% CI)	0.17 (0.02 to 0.48)	1.00 (reference)

NOTE. Proportions obtained as proportions from logistic regression models.
Abbreviations: AC, doxorubicin + cyclophosphamide; PCIA, persistent chemotherapy-induced alopecia; RR, relative risk; TAC, docetaxel + doxorubicin + cyclophosphamide; TC, docetaxel + cyclophosphamide; TCHP, docetaxel + carboplatin.

points in the control group (Table 3). At 6 months after chemotherapy, the average difference in the change in CADS score between intervention and control was −3.2 points, reflecting reduced PCIA-related stress in the intervention group. When comparing the scores by domain, the intervention group exhibited reduced scores in the emotional and activity domains (Appendix Table A2). At 6 months after chemotherapy, 17% of patients in the intervention group reported wearing wigs to conceal hair loss, compared with 32% in the control group (RR of 0.53 [95% CI, 0.20 to 0.85]). Similarly, a smaller proportion of patients in the intervention group resorted to scarves or caps to hide hair loss (RR, 0.66 [95% CI, 0.47 to 0.84]; Table 4). The post hoc analysis showed similar results of the primary and secondary outcomes (Appendix Tables A3 and A4).

The intervention group was more likely to experience chills, dizziness, and pain than the control group at all visits. The most common reported side effects were pain followed by dizziness and chills. None of the participants experienced any severe unexpected adverse event (Appendix Table A5).

DISCUSSION

Patients with breast cancer assigned to scalp cooling demonstrated a highly reduced incidence of PCIA 6 months after chemotherapy compared with the control group. The intervention group had a faster recovery in hair density than the control group, as evidenced by the differences between baseline and 1 month after chemotherapy. At 6 months, the intervention group showed greater improvement in hair thickness compared with the control group. These effects were consistent across the different chemotherapy regimens. Patients in the intervention group also experienced significantly reduced psychological distress related to CIA

TABLE 3. Effect of Scalp Cooling on Secondary Outcomes

Outcome	Intervention		Control		Difference in Difference, Intervention – Control (95% CI)
	Observed Mean (SD)	Estimated Difference From Baseline (95% CI)	Observed Mean (SD)	Estimated Difference From Baseline (95% CI)	
Hair thickness, μm					
Baseline	98.1 (11.1)	0.0 (reference)	98.2 (13.4)	0.0 (reference)	0.0 (reference)
During chemo	80.3 (20.2)	−17.9 (−22.3 to −13.6)	77.4 (21.8)	−20.8 (−25.5 to −16.2)	2.9 (−2.3 to 8.1)
After chemo					
1 month	53.8 (13.5)	−44.4 (−48.7 to −40.1)	49.9 (11.1)	−48.3 (−52.9 to −43.8)	3.9 (−1.2 to 9.1)
6 months	99.7 (12.3)	1.6 (−2.7 to 5.9)	90.6 (14.6)	−7.6 (−12.0 to −3.1)	9.1 (4.1 to 14.2)
Hair density, hairs/cm^2					
Baseline	144.5 (26.6)	0.0 (reference)	151.0 (27.1)	0.0 (reference)	0.0 (reference)
During chemo	100.5 (33.3)	−45.4 (−54.0 to −36.7)	113.4 (45.8)	−35.4 (−44.8 to −26.1)	−9.9 (−20.6 to 0.8)
After chemo					
1 month	113.6 (32.0)	−32.4 (−41.0 to −23.8)	85.0 (32.3)	−63.0 (−72.2 to −53.8)	30.6 (20.0 to 41.1)
6 months	151.5 (30.7)	5.5 (−3.1 to 14.1)	157.4 (32.0)	9.1 (0.1 to 18.2)	−3.7 (−14.1 to 6.8)
CADS total score					
Baseline	4.0 (5.7)	0.0 (reference)	4.7 (7.4)	0.0 (reference)	0.0 (reference)
During chemo	18.1 (9.6)	13.9 (11.8 to 16.0)	19.0 (10.5)	14.6 (12.4 to 16.8)	−0.7 (−3.3 to 1.9)
After chemo					
1 month	16.0 (7.8)	11.8 (9.7 to 13.9)	17.4 (9.4)	13.0 (10.8 to 15.2)	−1.2 (−3.8 to 1.4)
6 months	8.1 (7.6)	3.9 (1.8 to 6.0)	11.4 (7.1)	7.0 (4.8 to 9.2)	−3.1 (−5.7 to −0.5)

NOTE. Results on the basis of mixed linear models. The scalp-cooling group (n = 89) had no missing values. The control group (n = 50) had four missing on the values during chemotherapy (n = 46) and two missing values 1 month after chemotherapy (n = 48).
Abbreviations: CADS, chemotherapy-induced alopecia distress scale; SD, standard deviation.

compared with those in the control group 6 months after chemotherapy.

Previous randomized controlled trials have confirmed the effectiveness of scalp cooling in preventing CIA,[21,22] but these studies did not evaluate long-term outcomes. Most studies focused on assessing the degree of hair loss during chemotherapy.[23,24] For instance, in one trial that followed up patients for 12 weeks after chemotherapy, 85.7% (24/28) of patients in the scalp-cooling group and 50.0% (6/12) of patients in the control group showed an increase of ≥50% in hair volume.[6]

TABLE 4. Effect of Scalp Cooling on Primary Outcome (PCIA at the 6-month visit), Which Is Defined as Wear Wig, Scarves, or Cap to Hide Hair Loss

Outcome	Intervention	Control
Wear wig to hide hair loss		
No. of cases of PCIA/total	15/89	16/50
Adjusted proportion (95% CI)	0.17 (0.09 to 0.25)	0.32 (0.19 to 0.45)
RR (95% CI)	0.53 (0.20 to 0.85)	1.00 (reference)
Wear scarves or cap to hide hair loss		
No. of cases of PCIA/total	41/89	35/50
Adjusted proportion (95% CI)	0.46 (0.35 to 0.56)	0.71 (0.58 to 0.83)
RR (95% CI)	0.65 (0.46 to 0.84)	1.00 (reference)

Abbreviations: PCIA, persistent chemotherapy-induced alopecia; RR, relative risk.

We found that the scalp-cooling group recovered hair thickness by 6 months after chemotherapy. These results were consistent with a previous pilot study to evaluate impact of scalp cooling on PCIA.[25] Usually, DNA is repaired and the hair bulb structure is restored within 96 hours after completion of chemotherapy, and new hair becomes visible within 3-6 months.[26] Scalp cooling helps protect hair follicle stem cells and their associated structure and reduce the risk of apoptosis, thereby promoting the survival of essential stem cells.[27] Our results indicate that the beneficial effects of scalp cooling extend beyond the initial 3 months after chemotherapy, but additional research is needed to establish long-term benefits.

In previous studies, quality of life (QoL) was assessed using general QoL questionnaires instead of hair-specific questionnaires, which may not be sensitive enough to detect the impact of alopecia on QoL.[6,8] In this study, we used the CADS, a validated and reliable tool for evaluating the influence of CIA on psychosocial well-being and QoL.[16] We demonstrated that the intervention group had significantly less CIA-related stress 6 months after chemotherapy than the control group. The observed differences were also clinically meaningful.[28] Moreover, at 6 months after chemotherapy, there was a significant reduction in the need for concealment strategies including wigs and scarves in the intervention

group. These results suggest that scalp cooling may also reduce the psychosocial burden associated with visible signs of alopecia. CIA is a public and private sign of illness and can be a source of emotional distress and stigma related to social activities.[29] Thus, scalp cooling could facilitate return to normal life in patients after chemotherapy. In addition, since CIA-related stress is associated with lower QoL[30] and adverse psychosocial consequences, early recovery from alopecia in patients using a scalp-cooling device may help improve QoL.

This study had some limitations. First, patients with more sensitive hair or those who were more interested in hair conditions were more likely to participate. However, study patients were randomly assigned to the two study groups, and their sociodemographic and clinical characteristics at baseline did not differ between the groups. Second, the study was restricted to female patients with breast cancer. Because PCIA depends on the chemotherapy agents rather than the cancer type, our results may be applicable to other patients receiving the same chemotherapy agents. Third, because of the nature of the scalp-cooling intervention, it was impossible to perform a blinded trial. To minimize biases, we chose a primary outcome on the basis of objective measurements of hair density and thickness, and we blinded assessment of outcomes during follow-up. Fourth, a higher proportion of participants withdrew after the start of chemotherapy in the intervention compared with the control group, which may have introduced selection biases. Fifth, the follow-up of our study was restricted to 6 months after chemotherapy. Studies with additional follow-up will be needed to establish the long-term effect of scalp cooling on PCIA. Sixth, although the CADS was designed to measure distress because of CIA and we instructed patients to answer the questionnaire on the basis of changes because of chemotherapy, we cannot exclude that the results of the CADS can be affected by other sources of stress. However, the results of the CADS were consistent with behavioral changes that reflect distress caused by PCIA. Finally, this study was conducted among Koreans. Although there are well-established differences in hair characteristics across race/ethnicity groups,[31] it is unknown how these differences may translate into differences in the efficacy of scalp cooling for PCIA. Further research is necessary to confirm our findings with other treatment regimens for various cancers as well as for other race/ethnicity groups.

In conclusion, this randomized clinical trial showed that scalp cooling reduced the incidence of PCIA, primarily by increasing hair thickness compared with control. Scalp cooling is helpful in promoting qualitative hair regrowth. This effect on hair quality is perceived by the patients and significantly enhances their social and psychological QoL. Yet further research is necessary to observe longer-term benefits of scalp cooling.

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DISCLAIMER

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EQUAL CONTRIBUTION

D.K. and J.C. contributed equally to this work as cofirst authors.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

The data that support the findings of this study are not openly available because of reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled-access data storage at Samsung Medical Center. J.S.A. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Scalp Cooling in Preventing Persistent Chemotherapy-Induced Alopecia: A Randomized Controlled Trial

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APPENDIX

TABLE A1. Percent Change on Secondary Outcomes by Intervention Group

Outcome	Intervention Group of Percent Change From Baseline (95% CI)	Control Group of Percent Change From Baseline (95% CI)	Difference in Percent Change, Intervention − Control (95% CI)
Hair thickness, μm			
Baseline	0.0 (reference)	0.0 (reference)	0.0 (reference)
During chemo	−20.5 (−24.9 to −15.7)	−23.7 (−28.2 to −18.8)	3.2 (−3.8 to 9.8)
After chemo			
1 month	−46.2 (−46.2 to −43.0)	−49.8 (−52.8 to −46.7)	3.6 (0.1 to 7.0)
6 months	1.5 (−4.2 to 7.5)	−8.1 (−13.5 to −2.5)	9.6 (4.6 to 14.7)
Hair density, hairs/cm^2			
Baseline	0.0 (reference)	0.0 (reference)	0.0 (reference)
During chemo	−33.9 (−39.0 to −28.3)	−29.1 (−35.0 to −22.6)	−4.8 (−14.3 to 4.3)
After chemo			
1 month	−24.3 (−30.2 to −17.9)	−45.8 (−50.3 to −41.0)	21.5 (14.5 to 27.9)
6 months	3.4 (−4.6 to 12.1)	5.7 (−2.8 to 15.1)	−2.4 (−10.4 to 4.7)
CADS total score			
Baseline	0.0 (reference)	0.0 (reference)	0.0 (reference)
During chemo	481.0 (356.1 to 640.2)	503.6 (369.3 to 676.3)	−3.7 (−27.7 to 28.2)
After chemo			
1 month	427.1 (314.1 to 570.9)	460.4 (335.7 to 620.8)	−5.9 (−29.4 to 25.2)
6 months	112.1 (66.7 to 170.0)	240.5 (164.8 to 338.0)	−37.7 (−53.2 to −17.1)

NOTE. Results on the basis of mixed linear models adjusted for randomization stratification variables: age (<50 or ≥50 years) and chemotherapy type (no anthracycline or anthracycline). The scalp-cooling group (n = 89) had no missing values. The control group (n = 50) had four missing on the values during chemotherapy (n = 46) and two missing values 1 month after chemotherapy (n = 48).
Abbreviation: CADS, chemotherapy-induced alopecia distress scale.

TABLE A2. Effect of Scalp Cooling on CADS

CADS Subscore	Intervention		Control		Difference in Difference, Intervention − Control (95% CI)
	Observed Mean (SD)	Estimated Difference From Baseline (95% CI)	Observed Mean (SD)	Estimated Difference From Baseline (95% CI)	
Physical					
Baseline	0.2 (0.5)	0.0 (reference)	0.2 (0.6)	0.0 (reference)	0.0 (reference)
During chemo	2.1 (1.5)	2.57 (2.23 to 2.91)	2.8 (1.7)	1.87 (1.52 to 2.22)	0.70 (0.32 to 1.08)
After chemo					
1 month	0.7 (0.8)	0.76 (0.42 to 1.10)	1.0 (1.2)	0.49 (0.15 to 0.84)	0.26 (−0.11 to 0.65)
6 months	0.6 (0.9)	0.45 (0.12 to 0.79)	0.7 (1.0)	0.35 (0.01 to 0.70)	0.10 (−0.27 to 0.48)
Emotional					
Baseline	1.7 (3.3)	0.0 (reference)	1.5 (2.3)	0.0 (reference)	0.0 (reference)
During chemo	7.1 (4.9)	5.32 (4.31 to 6.34)	6.9 (4.5)	5.52 (4.46 to 6.58)	−0.20 (−2.43 to 1.02)
After chemo					
1 month	7.2 (4.8)	4.48 (3.47 to 5.49)	6.1 (3.9)	5.58 (4.52 to 6.64)	−1.10 (−2.32 to 0.12)
6 months	4.0 (3.0)	1.16 (0.14 to 2.17)	2.7 (3.1)	2.42 (1.36 to 3.48)	−1.27 (−2.49 to −0.04)
Activity					
Baseline	2.1 (3.6)	0.0 (reference)	1.6 (2.8)	0.0 (reference)	0.0 (reference)
During chemo	8.2 (4.4)	5.80 (4.82 to 6.79)	7.6 (4.1)	6.28 (5.24 to 7.32)	−0.47 (−1.68 to 0.74)
After chemo					
1 month	7.9 (3.8)	6.41 (5.42 to 7.39)	8.1 (3.7)	6.03 (5.00 to 7.08)	0.37 (−0.83 to 1.58)
6 months	5.9 (3.4)	2.38 (1.40 to 3.37)	4.1 (4.1)	4.04 (3.00 to 5.08)	−1.65 (−2.86 to −0.45)
Relationship					
Baseline	0.6 (1.4)	0.0 (reference)	0.7 (1.6)	0.0 (reference)	0.0 (reference)
During chemo	1.6 (2.2)	0.22 (−0.22 to 0.65)	0.9 (1.4)	0.96 (0.51 to 1.42)	−0.75 (−1.27 to −0.22)
After chemo					
1 month	1.6 (2.2)	0.16 (−0.27 to 0.59)	0.8 (1.3)	0.94 (0.49 to 1.40)	−0.79 (−1.31 to −0.27)
6 months	0.9 (1.5)	−0.11 (−0.54 to 0.32)	0.5 (1.3)	0.26 (−0.19 to 0.72)	−0.38 (−0.90 to 0.14)

NOTE. Results on the basis of mixed linear models adjusted for randomization stratification variables: age (<50 or ≥50 years) and chemotherapy type (no anthracycline or anthracycline). The scalp-cooling group (n = 89) had no missing values. The control group (n = 50) had four missing on the values during chemotherapy (n = 46) and two missing values 1 month after chemotherapy (n = 48).
Abbreviations: CADS, chemotherapy-induced alopecia distress scale; SD, standard deviation.

TABLE A3. Adjusted Analysis of the Effect of Scalp Cooling on the Primary Outcome at the 6-Month Visit

Outcome	Intervention	Control
Overall		
No. of cases of PCIA/total	12/89	26/50
Adjusted proportion (95% CI)	0.14 (0.07 to 0.21)	0.51 (0.37 to 0.65)
RR (95% CI)	0.27 (0.11 to 0.43)	1.00 (reference)
By age group		
Age <50 years		
No. of cases of PCIA/total	7/59	15/30
Adjusted proportion (95% CI)	0.12 (0.04 to 0.20)	0.50 (0.32 to 0.68)
RR (95% CI)	0.24 (0.05 to 0.43)	1.00 (reference)
Age ≥50 years		
No. of cases of PCIA/total	5/30	11/20
Adjusted proportion (95% CI)	0.17 (0.03 to 0.31)	0.54 (0.32 to 0.77)
RR (95% CI)	0.31 (0.03 to 0.59)	1.00 (reference)
By type of chemotherapy		
No anthracycline (TC or TCHP)		
No. of cases of PCIA/total	11/80	20/41
Adjusted proportion (95% CI)	0.14 (0.06 to 0.21)	0.49 (0.33 to 0.64)
RR (95% CI)	0.29 (0.10 to 0.47)	1.00 (reference)
Anthracycline (AC or TAC)		
No. of cases of PCIA/total	1/9	6/9
Adjusted proportion (95% CI)	0.11 (0.04 to 0.32)	0.67 (0.35 to 0.99)
RR (95% CI)	0.17 (0.02 to 0.48)	1.00 (reference)

NOTE. Proportions obtained as marginally adjusted proportions from logistic regression models adjusted for randomization stratification variables: age (<50 or ≥50 years) and chemotherapy type (no anthracycline or anthracycline).
Abbreviations: AC, doxorubicin + cyclophosphamide; PCIA, persistent chemotherapy-induced alopecia; RR, relative risk; TAC, docetaxel + doxorubicin + cyclophosphamide; TC, docetaxel + cyclophosphamide; TCHP, docetaxel + carboplatin.

TABLE A4. Adjusted Analysis of the Effects of Scalp Cooling on Secondary Outcomes

Outcome	Intervention		Control		Difference in Difference, Intervention − Control (95% CI)
	Observed Mean (SD)	Estimated Difference From Baseline (95% CI)	Observed Mean (SD)	Estimated Difference From Baseline (95% CI)	
Hair thickness, μm					
Baseline	98.1 (11.1)	0.0 (reference)	98.2 (13.4)	0.0 (reference)	0.0 (reference)
During chemo	80.3 (20.2)	−17.9 (−22.2 to −13.5)	77.4 (21.8)	−20.7 (−25.3 to −16.1)	2.9 (−2.3 to 8.0)
After chemo					
1 month	53.8 (13.5)	−44.5 (−48.8 to −40.1)	49.9 (11.1)	−48.3 (−52.8 to −43.7)	3.8 (−1.3 to 8.9)
6 months	99.7 (12.3)	1.5 (−2.8 to 5.8)	90.6 (14.6)	−7.5 (−11.9 to −3.0)	9.0 (4.0 to 14.0)
Hair density, hairs/cm^2					
Baseline	144.5 (26.6)	0.0 (reference)	151.0 (27.1)	0.0 (reference)	0.0 (reference)
During chemo	100.5 (33.3)	−45.1 (−53.7 to −36.5)	113.4 (45.8)	−35.7 (−45.0 to −26.4)	−9.4 (−20.1 to 1.3)
After chemo					
1 month	113.6 (32.0)	−32.3 (−40.9 to −23.7)	85.0 (32.3)	−63.3 (−72.5 to −54.1)	31.0 (20.5 to 41.5)
6 months	151.5 (30.7)	5.6 (−3.0 to 14.2)	157.4 (32.0)	8.9 (−0.2 to 17.9)	−3.3 (−13.7 to 7.2)
CADS total score					
Baseline	4.0 (5.7)	0.0 (reference)	4.7 (7.4)	0.0 (reference)	0.0 (reference)
During chemo	18.1 (9.6)	13.9 (11.8 to 16.0)	19.0 (10.5)	14.6 (12.4 to 16.8)	−0.7 (−3.3 to 1.9)
After chemo					
1 month	16.0 (7.8)	11.8 (9.7 to 13.9)	17.4 (9.4)	13.0 (10.8 to 15.2)	−1.2 (−3.8 to 1.4)
6 months	8.1 (7.6)	3.9 (1.8 to 6.0)	11.4 (7.1)	7.0 (4.8 to 9.3)	−3.2 (−5.7 to −0.6)

NOTE. Results on the basis of mixed linear models adjusted for randomization stratification variables: age (<50 or ≥50 years) and chemotherapy type (no anthracycline or anthracycline). The scalp-cooling group (n = 89) had no missing values. The control group (n = 50) had four missing on the values during chemotherapy (n = 46) and two missing values 1 month after chemotherapy (n = 48).
Abbreviations: CADS, chemotherapy-induced alopecia distress scale; SD, standard deviation.

TABLE A5. Proportion of Adverse Events With Score ≥5 by Treatment Group

Adverse Event	Intervention (n = 89), No. (%)	Control (n = 50), No. (%)
During chemotherapy		
Expected events		
Chills	25 (28.1)	2 (4.0)
Dizziness	29 (32.6)	3 (6.0)
Pain	47 (52.8)	11 (22.0)
Unexpected events	0	0
After chemotherapy		8
Expected events		
Chills	5 (5.6)	2 (4.0)
Dizziness	13 (14.6)	16 (32.0)
Pain	20 (22.5)	19 (38.0)
Unexpected events	0	0