# Results of the Dutch scalp cooling registry in 7424 patients: analysis of determinants for scalp cooling efficacy

BROOK, T.S., SEETSEN, T., DERCKSEN, M.W., VAN RIEL, A., DERLEYN, V.A., VAN DEN BOSCH, J., NORTIER, J., COLLETT, A., GEORGOPOULOS, Nikolaos, BRYK, J., BREED, W.P.M. and VAN DEN HURK, C.J.G.



**Published version**

BROOK, T.S., SEETSEN, T., DERCKSEN, M.W., VAN RIEL, A., DERLEYN, V.A., VAN DEN BOSCH, J., NORTIER, J., COLLETT, A., GEORGOPOULOS, Nikolaos, BRYK, J., BREED, W.P.M. and VAN DEN HURK, C.J.G. (2024). Results of the Dutch scalp cooling registry in 7424 patients: analysis of determinants for scalp cooling efficacy. The Oncologist, 29 (10), e1386-e1395. [Article]

# Results of the Dutch scalp cooling registry in 7424 patients: analysis of determinants for scalp cooling efficacy

BROOK, Toni S, SEETSEN, Tanja, DERCKSEN, Marcus W, VAN RIEL, Annemarie, DERLEYN, Veerle A, VAN DEN BOSCH, Johan, NORTIER, Johannes W R, COLLETT, Andrew, GEORGOPOULOS, Nikolas T, BRYK, Jarek, BREED, Wim P M and VAN DEN HURK, Corina J G <http://orcid.org/0000-0002-7802-1034>



**Published version**

BROOK, Toni S, SEETSEN, Tanja, DERCKSEN, Marcus W, VAN RIEL, Annemarie, DERLEYN, Veerle A, VAN DEN BOSCH, Johan, NORTIER, Johannes W R, COLLETT, Andrew, GEORGOPOULOS, Nikolas T, BRYK, Jarek, BREED, Wim P M and VAN DEN HURK, Corina J G (2024). Results of the Dutch scalp cooling registry in 7424 patients: analysis of determinants for scalp cooling efficacy. The Oncologist, 29 (10), e1386-e1395. [Article]

**Copyright and re-use policy**

*The Oncologist*, 2024, **29**, e1386–e1395
https://doi.org/10.1093/oncolo/oyae116
Advance access publication 13 June 2024
**Original Article**

# Results of the Dutch scalp cooling registry in 7424 patients: analysis of determinants for scalp cooling efficacy

**Toni S. Brook[1], Tanja Seetsen[2], Marcus W. Dercksen[3], Annemarie van Riel[4], Veerle A. Derleyn[5], Johan van den Bosch[6], Johannes W.R. Nortier[7], Andrew Collett[1], Nikolas T. Georgopoulos[1,8], Jarek Bryk[1], Wim P.M. Breed[9], Corina J.G. Van Den Hurk[*,2]**

[1]Department of Biological Sciences, School of Applied Sciences, University of Huddersfield, Huddersfield, United Kingdom,
[2]Research and Development Department, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands,
[3]Oncology Department, Maxima Medical Centre, Eindhoven, The Netherlands,
[4]Oncology Department, Elisabeth Twee Steden Hospital, Tilburg, The Netherlands,
[5]Oncology Department, Elkerliek Hospital, Helmond, The Netherlands,
[6]Oncology Department, Albert Schweitzer Hospital, Dordrecht, The Netherlands,
[7]Oncology Department, Leiden University Medical Centre, Leiden, The Netherlands,
[8]Biomolecular Sciences Research Centre, Industry and Innovation Research Institute, Sheffield Hallam University, Sheffield, United Kingdom,
[9]Oncology Department, Catharina Hospital, Eindhoven, The Netherlands

[*]Corresponding author: Corina J.G. Van Den Hurk, PhD, Research and Development Department, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, Godebaldkwartier 419, 3511DT Utrecht, The Netherlands (c.vandenhurk@iknl.nl).

## Abstract

**Background:** Chemotherapy-induced alopecia is a common consequence of cancer treatment with a high psychological impact on patients and can be prevented by scalp cooling (SC). With this multi-center patient series, we examined the results for multiple currently used chemotherapy regimens to offer an audit into the real-world determinants of SC efficacy.

**Materials and methods:** The Dutch Scalp Cooling Registry collected data on 7424 scalp-cooled patients in 68 Dutch hospitals. Nurses and patients completed questionnaires on patient characteristics, chemotherapy, and SC protocol. Patient-reported primary outcomes at the start of the final SC session included head cover (HC) (eg, wig/scarf) use (yes/no) as a surrogate for patient satisfaction with SC and WHO score for alopecia (0 = no hair loss up to 3 = total alopecia) as a measure of scalp cooling success. Exhaustive logistic regression analysis stratified by chemotherapy regimen was implemented to examine characteristics and interactions associated with the SC result.

**Results:** Overall, over half of patients ($n$ = 4191, 56%) did not wear a HC and 53% ($n$ = 3784/7183) reported minimal hair loss (WHO score 0/1) at the start of their final treatment. Outcomes were drug and dose dependent. Besides the chemotherapy regimen, this study did not identify any patient characteristic or lifestyle factor as a generic determinant influencing SC success. For non-gender specific cancers, gender played no statistically significant role in HC use nor WHO score.

**Conclusions:** Scalp cooling is effective for the majority of patients. The robust model for evaluating the drug and dose-specific determinants of SC efficacy revealed no indications for changes in daily practice, suggesting factors currently being overlooked. As no correlation was identified between the determinants explaining HC use and WHO score outcomes, new methods for evaluation are warranted.

**Key words:** CIA; Alopecia; chemotherapy; scalp cooling; hair loss; supportive care.

## Implications for practice

The most important clinical implication is that medical personnel involved in patient care need to be aware that males are also eligible for and benefit from scalp cooling. In addition, comprehensive standardized registration with more extensive outcome evaluation of hair loss and recovery is essential for long-term international protocol optimization and revealing the true determinants of SC efficacy to accelerate advances for individual patient care. Adding biomarkers, for example, scalp skin temperatures, to clinical studies will contribute to better predictions of who will experience hair loss and why.

## Introduction

Chemotherapy-induced alopecia (CIA) is a common yet unintended consequence of cytotoxic insult by chemotherapy agents to the mitotically active hair matrix keratinocyte cells. CIA is considered by many patients the most distressing side effect of cancer treatment; negatively affecting body image, self-esteem, social interactions, and health-related quality of life (HRQoL).[1-4] Utilizing scalp cooling (SC) preceding, during, and following chemotherapy infusions has shown a protective effect against CIA, with SC showing statistically

Received: 31 October 2023; Accepted: 9 April 2024.

significant higher hair retention rates comparable to the uncooled control groups in earlier SC trials.[5-11] The most documented understanding of the protective effect of SC against CIA is as a direct effect of vasoconstriction reducing blood perfusion within the hair matrix keratinocytes and decreased follicular metabolism.[6,12] However, it is becoming increasingly evident that scalp cooling is protected by a variety of mechanisms that may operate in combination to prevent hair follicle cytotoxicity.[13] Recent studies suggest that in vitro cooling to 18 °C provides cellular protection from drug-mediated apoptosis, reduces cellular drug uptake, upregulates the proliferative and metabolic capabilities of keratinocytes, and promotes quicker recovery.[14-16] Such findings lend support to the clinical observation that SC is more beneficial when the scalp skin is reduced to below 18 °C.[17] Additionally, SC provided superior regrowth even in patients who failed to retain their hair during treatment.[18,19] More research is needed to allow a better, more complete understanding of the mechanisms by which SC cyto-protects to improve clinical results.

In recent years, SC has been more broadly adopted, with comprehensive research into the safety profile of SC accelerating clinical acceptance.[20] As of 2023, SC devices are available in over 40 states in the US and in over 50 other countries across the globe.[21,22] Despite SC showing efficacy in most cases, also in controlled trials,[9,10,23] variabilities among SC protocols, infusion regimens, duration and temperature of SC, and outcome evaluation hinder large-scale meta-analysis review and thus the opportunity to learn from large numbers of patients how to increase SC efficiency.[24] Additionally, some clinicians still underestimate the high psychological impact of transient CIA on patients HRQoL, and healthcare insurers ignore the cost-effectiveness of SC related to societal willingness to pay for Quality Adjusted Life Years (QALYs).[25,26] This resulted in a minimal effort toward promoting SC as a preventative measure with reimbursement of its costs remaining difficult or unavailable in many countries, but also in many hospitals in countries where SC is already used.[27,28] Additionally, SC is still unavailable for many eligible patients with cancer, despite equipment availability. As SC is not actively offered to each patient, it introduces inequality of care.[29,30] Providing a comprehensive dossier with evidence of the efficacy of SC will provide a foundation for the wider global implementation of SC. Here, we, therefore, provide an audit into the real-world determinants of both the decision to use a head cover (HC) (eg, wig/scarf) as a surrogate for patient satisfaction with SC[31] and hair retention (self-reported WHO score for alopecia) as a measure of success after SC in the world's largest SC database.

## Materials and methods

The Dutch Scalp Cooling Registry (DSCR) commenced in January 2006 with 8 community hospitals and one academic hospital.[31] The data collected spans over 3 cohorts (2006-2009 (19%, $n = 1411$), 2009-2013 (68%, $n = 5035$), 2013-2019 (13%, $n = 978$)). The introduction of electronic recording from 2013 onwards facilitated a broader scope and minimized missing data. By its completion in December 2019, the registry included data from 68 clinical locations.

All patients commencing chemotherapy with SC during this time were asked to participate, regardless of whether they previously received alopecia-inducing chemotherapy treatment and whether treated in the (neo-)adjuvant or metastatic setting. Exclusion criteria included patients with prior cold sensitivity disorder, cold post-traumatic dystrophy, cold agglutinin disease, cryofibrinogenemia, and cryoglobulinemia and those under the age of 18 years. Upon inclusion in the DSCR, nurses documented the year of birth, gender, cancer type, chemotherapy regimen (sequential details available in Supplementary Table S1), dose (in mg/m$^2$ or AUC), and infusion time (minutes), treatment setting ((neo-) adjuvant/curative or palliative), and liver metastases (yes/no). In the latest cohort, nurses also reported (obligation-free) baseline blood test results.

In all 3 cohorts, during the first SC session patients self-reported their hair characteristics: the length (shorter/longer than 5 cm), density (low/moderate/high), hair type determined by ethnical background (West/East European, Asian, Afro-American, Other), and whether they had colored (yes/no), permed (yes/no), or bleached (yes/no) it within 2 months prior to the start of chemotherapy. They also reported previous chemotherapy (yes/no), whether they used SC (yes/no), and if they experienced earlier severe hair loss despite SC (yes/no). During all chemotherapy sessions, patients documented cap colors (cap size), pre- and post-infusion SC times, and prior hair dampening with water or conditioner (yes/no) (introduced as an adapted version of the questions during 2009, so therefore excluded for the first cohort). Hair dampening with water and/or conditioner to the hair prior to scalp fitting was subsequently merged into "dampening" (no/yes/intermittent) and dyed, bleached, and permed categories were combined into "chemical manipulation." Patients also reported tolerability, headaches, and the use of a regular painkiller to reduce headaches. All patients wishing to prematurely stop SC were asked to provide their reasoning for doing so (categories include severe hair loss/baldness, tolerability, stopping chemotherapy/disease progression, and other reasons). Nurses could also report reasons for ceasing SC under the same criteria. Only the latest cohort (2013-2019) included patient-reported anthropometric characteristics (height and weight), lifestyle tendencies (smoking and drinking frequencies), pre-treatment hair graying, natural hair shedding patterns, hair color, and potential technical problems with the SC machine. This cohort also included repeatedly documenting changes in growth, texture, color, and condition of the hair, barriers in access to SC, rating the expertise of SC provided by the nursing staff, and progressive evaluation of satisfaction and insecurity about the result to date. For information and future reference purposes, all content included in the DSCR has been described, but not all categories will be discussed below.

SC was performed using the Dignitana or Paxman (PSC1, PSC2, or Orbis) systems. Infusion time protocols were hospital-specific, and some chemotherapy regimens were sequential schemes [see Supplementary Table S1]. Pre-infusion cooling time was generally set at 30 minutes with a pre-cooled cap, (an additional 15 minutes for non-pre-cooled caps) and the infusion process started thereafter. Post-infusion cooling times (PICT) were standardized at 90 minutes; however, this was subject to implementation of independent treatment-specific protocols as per manufacturer advisement and at the hospital's discretion. From 2012, hospitals started to adapt the PICT for Docetaxel (D) towards 45 minutes[31] and from 2016 toward 20 minutes.[32] Jevtana (J) was introduced in cohort 2 and the combination therapy of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) was no longer administered

from 2014. Patients receiving docetaxel, doxorubicin, and cyclophosphamide (DAC) were recommended not to start SC from 2016, owing to earlier recognition of suboptimal responses sacrificing HRQoL.[33]

Patient-reported outcomes are the only feasible evaluation method in a large multi-center real-world SC cohort. SC efficacy was therefore measured by the patient's preference to wear an HC (including a wig) during their last reported scalp cooling session (yes/no). HC is commonly used as the most important outcome measure of efficacy because it represents perceived satisfaction with scalp cooling. Hair retention derived from the World Health Organization (WHO) score for alopecia offers a measure of SC success.[11] So, in addition, patients' self-reported WHO score (0: none, 1: minimal, 2: severe, and 3: total alopecia) was evaluated during the last reported session.[34] In the last cohort, the measure on head covering was corrected against use for religious reasons and whether the patient was bald but chose not to wear an HC. Both individual's preference to wear a HC and WHO score was evaluated to establish treatment-specific determinants of SC success. Final analyses included only patients who had completed at least 2 SC sessions or if they discontinued SC because of severe CIA after the first session. Drug categories with less than 25 patients were collated (mixed group) and the remaining uncategorized due to incomplete dosing schedules/small sample sizes ($n < 10$).

## Statistics

Patients within the dataset were stratified by chemotherapy regimen and dosages as chemotherapy-induced hair follicle damage and severity of CIA are understood to be drug and dosage-specific and the most important determinant of SC success.[35] Whether the patient, chemotherapy regimen, and SC characteristics were associated with HC use or WHO score after SC was evaluated by logistic regression analyses and expressed as odds ratios (OR). Continuous variables were grouped into categories, except for the number of cooling sessions. The correlation between HC uses and binary-WHO (yes (WHO 0/1) vs. no (WHO 2/3)) was determined by Kendall's rank correlation analysis. Separate analyses were conducted for the last cohort to assess the effect of lifestyle factors on final outcomes.

Independent multivariate analysis (MVA) was completed for each of the largest treatment categories (FEC, AC, D, and T; see Supplementary Table S1) to determine the relative drug-specific relationship between the variables and identify predictors of SC efficacy. Variables used as predictors included: clinical location, cancer type, dose, gender, treatment setting, age group, ethnic hair type, hair length, hair density, chemical manipulation, previous chemotherapy, infusion time group, PICT group, dampening, number of cooling sessions, HC use and WHO score. Outcomes were based on binary responses; HC (yes vs. no) and binary-WHO.

The more traditionally used stepwise (forward/backward) approaches to linear regression modeling are cumbersome for larger numbers of predictors and mixed model approaches are often flawed by premature convergence. In the current study, the use of machine learning (ML) models trained by ML algorithms allowed the so-called "brute force" exploration method for variable reduction and model refinement. This method facilitates exhaustive screening of all combinations of chemotherapy-, patient- and cooling characteristics and their interactions. Due to the limited sample sizes of many of the treatment categories ($n < 1000$), the more conservative Akaike's Information Criteria (AIC) model selection measure was used to select the optimum generalized linear model (GLM). Where in epidemiology the (adjusted) $R^2$ validation is used to evaluate the fitting of a model, AIC is used in statistics as an estimator of prediction error and used to determine the best of the many different models for a given dataset. Herein the lowest AIC yields the most accurate predictive power. Using this approach, the optimum GLM ultimately explains the largest proportion of variation using the fewest possible independent variables with a comparable level of precision.

First, chemotherapy regimen-specific model generation was constructed using a restricted version of the dataset (complete data only, missing variable's location and quantification see Supplementary Table S2). The remainder was retained as control data for later analyses. Second, the optimum model selection for HC use and WHO score for each treatment was finalized by internal cross-validation between the lowest AIC (+ 2 AIC units) models. The predictive performance of the optimum models was tested using the control data. This was assessed using confusion matrix analysis to quantify the proportion of correct predictions (see Supplementary Table S3 for a description of training and validation sets). Finally, the final optimum model results were recalculated using the original dataset, restricted only to missing data in the optimum model variables. Cohen's Kappa coefficient ($\kappa$) was used to measure inter-rater agreement within each model. 95% CIs and $P$-values were computed using a Wald $z$-distribution approximation. Statistical differences were indicated if $P < .05$ ($^*P < .05$, $^{**}P < .01$, $^{***}P < .001$) and reported $P$-values were 2-sided. Statistical analyses were performed using R software (V: 4.2.2) with the additional packages tidyverse and glmulti[36-38]

## Results

A total of 7424 patients were enrolled in the DSCR between 2006 and 2019. Most patients were female (87%), chemo-naïve (77%), breast cancer patients (73%), and treated in the adjuvant setting (61%) (see Table 1). The mean age was 55 years (range 18-98 years). The median pre-infusion cooling time was 36 minutes (SD 10, range 15-75) and the median PICT was 90 minutes (SD 23, range 15-124). The median number of cooling sessions was 16 (SD 10, range 1-44). In total 52 patients (0.7%) used a Dignitana SC machine.

Overall, over half of the patients ($n = 4191$, 56%) chose not to wear an HC and 53% ($n = 3784/7183$) reported good hair retention (WHO score 0/1) during the last SC session. For those with completed data, WHO scores for alopecia (WHO 0, 1, 2, 3) for patients wearing head covering ($n = 3127$), were 5%, 11%, 26%, and 58% ($n = 106$ missing). For patients not wearing HC scores were ($n = 4056$) 39%, 42%, 19%, and 0% ($n = 135$ missing). The correlation between HC uses and binary-WHO score for the whole patient series was 0.64, $z = -54.396$, $P = <.01$).

The proportion of patients choosing not to wear an HC at the start of their final session varied depending on the chemotherapy regimen and dosage; results ranged from 10% to 98% (see Table 2). Overall patients receiving taxanes had better results (78%) than patients receiving anthracyclines (40%) or combination therapies of anthracyclines and taxanes (45%). Patients receiving lower chemotherapy dosages

**Table 1.** Patient, treatment, scalp cooling characteristics, and scalp cooling efficacy ($n$ = 7424).

| | No HC/total (%) |
|---|---|
| Age | |
| Under 44 | 662/1377 (48) |
| 45-54 | 89/190 (47) |
| 55-64 | 1234/2302 (54) |
| Over 65 | 2189/3525 (62) |
| Missing | 17/30 (57) |
| Gender | |
| Female | 3359/6453 (52) |
| Male | 828/959 (86) |
| Missing | 4/12 (33) |
| Chemotherapy regimen | |
| A | 28/48 (58) |
| AC | 247/736 (34) |
| ACD[a] | 136/273 (50) |
| ACT[a] | 249/484 (51) |
| D[b] | 1028/1232 (83) |
| DAC | 17/166 (10) |
| FAC | 46/103 (45) |
| FEC | 597/1394 (43) |
| FECD[a] | 385/848 (45) |
| FECT[a] | 17/31 (55) |
| Gem[c] | 55/63 (87) |
| Irino | 95/295 (32) |
| J | 54/56 (96) |
| T[d] | 630/763 (83) |
| TCar | 340/584 (58) |
| Vino | 40/45 (89) |
| Mixed group[e] | 96/133 (72) |
| Uncategorized[f] | 131/170 (77) |
| Cancer type | |
| Breast | 2746/5408 (51) |
| Esophageal | 60/61 (98) |
| Gynecology[g] | 269/493 (55) |
| Lung | 185/216 (86) |
| Prostate | 624/646 (97) |
| Stomach/colorectal | 156/375 (42) |
| Other[h] | 151/225 (67) |
| Treatment setting | |
| Adjuvant | 2082/4489 (46) |
| Palliative | 2050/2818 (73) |
| Missing | 59/117 (50) |
| Prior chemotherapy | |
| No[i] | 2960/5624 (53) |
| Yes | 1148/1680 (68) |
| Missing | 83/120 (69) |
| Chemical manipulation | |
| No | 2442/3998 (61) |
| Dyed | 1025/2103 (49) |
| Bleached | 259/447 (58) |
| Permed | 44/97 (45) |
| Dyed/bleached | 109/203 (54) |
| Dyed/permed | 55/103 (53) |
| Bleached/permed | 21/43 (49) |
| Dyed/bleached/permed | 4/6 (67) |
| Missing | 232/424 (55) |
| Hair density | |
| Low | 1535/2870 (53) |
| Moderate | 1913/3316 (58) |
| High | 391/593 (66) |
| Missing | 352/645 (55) |
| Ethnic hair type | |
| Afro-American | 45/101 (45) |
| Asian | 87/208 (42) |
| Southern-European | 98/188 (52) |
| West-European | 3754/6521 (58) |
| Missing | 207/406 (51) |
| Dampening[j] | |
| No | 1524/2741 (56) |
| Intermittent | 183/397 (46) |
| Yes | 1776/2875 (62) |
| Missing | 708/1411 (50) |

[a]Sequential scheme detailed in Supplementary material (S1).
[b]Contains D25-60 ($n$ = 15), D70-90 ($n$ = 763), D100 ($n$ = 265), D(75)Combi ($n$ = 168), D(100)Combi ($n$ = 9), and other incomplete dosing schedules ($n$ = 12).
[c]Contains Gem1000 ($n$ = 15) and Gem(1000-1250)Combi ($n$ = 48).
[d]Contains T50-70 ($n$ = 23), T75-90 ($n$ = 684), T175 ($n$ = 27), T(75-90)Combi ($n$ = 6), and other unspecified dosages ($n$ = 23).
[e]Contains: Cae Mono ($n$ = 21), Cae Combi ($n$ = 14), Car/CisEto ($n$ = 23), CMF ($n$ = 21), E ($n$ = 12), Eri ($n$ = 21), FACD ($n$ = 11), and M ($n$ = 10) regimens.
[f]Collated due to incomplete dosing schedules/small sample sizes ($n$ < 10).
[g]Includes: ovary, cervix, endometrium, uterus, vulva and unspecified Female cancers.
[h]Includes blood, gall bladder, pancreas, sarcoma, skin, urinary bladder (bladder and urothelial cell/bladder) and other unspecified cancers.
[i]Includes missing values recategorized due to adjuvant setting.
[j]Adapted question for cohorts 2 and 3; the application of water and/or conditioner prior to cap fitting.
Abbreviations HC: head cover; A: doxorubicin (Adriamycin); C: cyclophosphamide; Car: carboplatin; D: docetaxel (Taxotere); E: epirubicin; F: 5-fluorouracil; Gem: gemcitabine; Irino: irinotecan (Campto); J: jevtana; T: paclitaxel (Taxol); Vino: vinorelbine. Further dosage breakdown detailed in Supplementary material (S1) and cohort-specific results detailed in (Supplementary material S5).

had better results than patients with higher dosages of the same chemotherapy (or combination). For the sequential schemes ACT (4× AC followed by 12 × T) did better than ACD (4× AC followed by 4× D) and both did better than AC alone. FECD (FEC 3× followed by D 3×) also had better results than FEC (6×) alone. Infusion times and PICTs varied considerably within chemotherapies.

For the specified chemotherapy regimens, models were generated to predict SC outcome (see Supplementary Table S3). Repeating the process by including interactions further improved the final model per chemotherapy regimen. The prediction accuracy of each training model was high (0.84-1.00) (Supplementary Table S3). Subsequently, final models represented 90% (for AC (binary-WHO)) to 98% (for D (HC)) of the total patients receiving FEC, AC, D, T within the DSCR, (see Table 3). See Supplementary Table S3 for full model parameters and extended validation data.

**Table 2.** Scalp cooling efficacy by chemotherapy regimen and dose ($n$ = 7338).

| | Dosage | No HC/Total (%) |
|---|---|---|
| Anthracycline Overall: 913/2267 (40%) | | |
| A | A20-50 | 14/15 (93) |
| A | A60 | 12/29 (41) |
| AC | A60C600 | 246/728 (34) |
| FAC | FA50-60C[a] | 41/92 (45) |
| FEC | FE50-70C[a] | 29/59 (49) |
| FEC | FE75-85C[a] | 26/46 (57) |
| FEC | FE90C[a] | 320/624 (51) |
| FEC | FE100C[a] | 215/647 (33) |
| FEC | Other[b] | 2/10 (20) |
| Anthracycline/taxane overall: 804/1792 (45%) | | |
| ACD | ACD70-90[a,c] | 11/28 (39) |
| ACD | ACD100[a,c] | 124/231 (54) |
| ACD | Other[b,c] | 1/11 (9) |
| ACT | ACT80-90[a,c] | 204/396 (52) |
| ACT | ACT100[a,c] | 14/19 (74) |
| ACT | ACT175[a,c] | 25/49 (51) |
| ACT | Other[b,c] | 6/17 (35) |
| DAC | D75A50C500 | 16/165 (10) |
| FECD | FE100CD[a,c] | 366/815 (45) |
| FECD | Other[b,c] | 19/29 (66) |
| FECT | FE100CT[a,c] | 11/23 (48) |
| Taxane overall: 1996/2574 (78%) | | |
| D | D25-60 | 14/15 (93) |
| D | D70-90 | 708/761 (93) |
| D | D100 | 189/265 (71) |
| D | D(75)Combi[d] | 106/168 (63) |
| D | Other[b] | 8/12 (67) |
| T | T50-70 | 20/23 (87) |
| T | T75-90 | 574/681 (84) |
| T | T175 | 17/27 (63) |
| T | Other[b] | 13/23 (57) |
| TCar | T50Car | 38/39 (97) |
| TCar | T70-100Car | 153/186 (82) |
| TCar | T175Car | 138/338 (41) |
| TCar | Other[b] | 11/21 (52) |
| Other overall: 469/755 (62%) | | |
| Gem | Gem1000 | 13/15 (87) |
| Gem | Gem1000-1250 Combi[e] | 42/47 (89) |
| Irino | Irino90-200 | 25/39 (64) |
| Irino | Irino210-300 | 10/29 (34) |
| Irino | Irino350 | 56/215 (26) |
| J | J20-55 | 52/53 (98) |
| Vino | Vino25-30 | 38/43 (88) |
| Mixed group | Cae30-50 | 20/21 (95) |
| Mixed group | Cae30-50 Combi[f] | 11/14 (79) |
| Mixed group | Car/CisEto[g] | 12/22 (55) |
| Mixed group | CM35-70F[a] | 16/21 (76) |
| Mixed group | E25-100 | 8/12 (67) |
| Mixed group | Eri | 16/21 (76) |
| Mixed group | FA50-100CD100[a,c] | 3/11 (27) |
| Mixed group | M10-30 | 10/10 (100) |
| Uncategorized[h] | - | 131/169 (78) |

Data not displayed due to small sample sizes ($n$ < 10) but included in overall calculations: A: other ($n$ = 2/3(67%)); AC: other ($n$ = 1/4(25%)); FAC: FA90-100C ($n$ = 4/7(57%)), other ($n$ = 1/3(33%)); FECT: FE75-90CT ($n$ = 6/8(75%)); D: D(100)Combi ($n$ = 3/9(33%)); T: T79-90Combi ($n$ = 4/6(67%)); Irino: other ($n$ = 2/9(22%)); Vino: other ($n$ = 2/2 (100%)).
[a]Unless otherwise listed above, additional dosage information: A50-80; C500/600; D30-100; F500/600; T70-100.
[b]Dosages other than those listed/incomplete dosing schedules.
[c]Sequential schemes detailed in Supplementary material (S1).
[d]D75 in combination: DC($n$ = 64); DCap($n$ = 4); DCar($n$ = 55); DM($n$ = 1), DMyo($n$ = 2), DPer($n$ = 8), DVino($n$ = 3), unspecified ($n$ = 31).
[e]Gem1000-1250 in combination: GemAbr($n$ = 2), GemCar($n$ = 31), GemCis($n$ = 8), GemCisEto($n$ = 2), GemD($n$ = 1) GemIrino($n$ = 1), GemT($n$ = 2).
[f]Cae30-50 in combination: CaeCar($n$ = 7); CaeCT($n$ = 4); CaeVino($n$ = 1); CaeCEto($n$ = 1), CaeCD($n$ = 1).
[g]Car/Cis in combination with Eto50-80: CarEto($n$ = 17), CisEto($n$ = 5).
[h]Collated due to small sample sizes ($n$ < 10).
Abbreviations: A, doxorubicin (adriamycin); C, cyclophosphamide; Cae, caelyx (pegylated liposomal doxorubicin); Cap, capecitabine; Car, carboplatin; D, docetaxel (taxotere); E, epirubicin; Eri, eribuline; Eto, etoposide; F, 5-fluorouracil; Gem, gemcitabine; HC, head cover; Irino, irinotecan (campto); J, jevtana; M, methotrexate; P, permexed; PICT, post infusion cooling time; SD, standard deviation; T, paclitaxel (taxol); Vino: vinorelbine.

Determinants per chemotherapy differed tremendously and trends were not analogous between primary outcomes (see Table 3; for full breakdowns see Supplementary Table S4). The most common predictor of both HC and binary-WHO outcomes was the number of SC sessions. In most cases, HC was a predictor of binary-WHO outcome and vice versa. Additional factors including age group, gender, dose, cancer type, treatment setting, previous chemotherapy, chemical manipulation, dampening, hair type, and PICT group were only selectively associated with the primary outcomes. Clinical location, hair length, and hair density failed to be included as predictor factors in any model. Intercept significance for AC and D refers to an unaccounted baseline effect which is not explained by the independent variables in the model. This is an indication that important working mechanisms have been overlooked.

For non-gender-specific cancer types, 81% ($n$ = 693/856) of the patients received comparable treatment regimens. Gender played no statistically significant role in the preference to wear an HC ($P$ = .912) nor the WHO score ($P$ = .393) nor an individual's decision to prematurely cease SC ($P$ = .329) (see Figure 1).

Of the 961 individuals in cohort 3 reporting lifestyle tendencies (smoking: yes, current ($n$ = 116), yes, ex-smoker ($n$ = 360), no ($n$ = 485); drinking: regularly ($n$ = 224), occasionally/socially ($n$ = 404), no, never ($n$ = 333)), neither smoking nor drinking habits showed significant impact on HC use, or WHO score when corrected for gender, age, cancer type, or chemotherapy regimen.

## Discussion

To the best of our knowledge, this is the largest prospective multi-center patient series on SC. The DSCR data showed that SC results of individuals not wearing an HC at the start of their final treatment varied per chemotherapy regimen,

**Table 3.** Significant determinants of multivariate analyses on scalp cooling efficacy per chemotherapy regimen for head cover use and binary-WHO.

| | FEC[a] | | AC[a] | | D | | T | |
|---|---|---|---|---|---|---|---|---|
| **Determinants** | **HC** | **Binary-WHO** | **HC** | **Binary-WHO** | **HC** | **Binary-WHO** | **HC** | **Binary-WHO** |
| Intercept | | | 1.00*** | | | 1.00*** | | |
| WHO score [2] | | | 0.85*** | | 0.05*** | | 0.03*** | |
| WHO score [3] | | | 0.00*** | | 0.00*** | | 0.00*** | |
| Head cover [yes] | | 0.01*** | | 0.11*** | | 0.02*** | | 0.02*** |
| Head cover [yes] × dampening [yes] | | 3.38*** | | | | | | |
| Head cover [yes] × dampening [intermittent] | | 2.18* | | | | | | |
| Head cover [yes] × number SC sessions | | | | | | | | 1.07*** |
| Age group [55-64] | | | 5.06* | | | | | |
| Gender [male] | | | | | | | | 5.10*** |
| Gender [male] × head cover [yes] | | | | | | | | 0.10* |
| Dose [FE100C] | 0.30* | | | | | | | |
| Cancer type [lung] | | | | | | | 2.79*** | |
| Cancer type [prostate] | | | | | | | 3.61*** | |
| Previous chemo [yes] | | 1.43* | | | | 0.78*** | | |
| Hair type [Afro-American] × number SC sessions | | | | | 0.44* | | | |
| Dampening [yes] | | | | | | 0.77*** | | |
| Dampening [intermittent] × head cover [yes] | | | | 0.05* | | | | |
| PICT80 | | | | | 5.22* | | | 1.55* |
| Number SC sessions | 1.65* | | 4.00*** | 1.00*** | 0.91*** | | 0.80*** | |
| Number SC sessions × head cover [yes] | | 0.81*** | | | | | | |
| Number SC sessions × setting [palliative] | | | | | 0.54* | | | |
| Number SC sessions × previous chemo [Yes] | 0.78* | | | | | | | |
| Number SC sessions × Prior chemo [yes] | | | | 1.16* | | | | |
| Number SC sessions × chemical manipulation [bleached] | | | | | | | 1.03* | |
| Number SC sessions × chemical manipulation [dyed/permed] | | | | | | | 0.30* | |
| Number SC sessions × dampening [yes] | | 0.51* | | | | | | |

For all groups, the reference category was corrected for age group [Under 44], Gender [Female], Dose [FEC = FE50-70C; AC = A60C600 only; D = D25-60, T = T50-70], Cancer Type [Breast], Setting [Adjuvant], previous chemo [No], chemical manipulation [No], hair length [shorter than 5cm], hair density [low], Hair type [West-European], dampening [No], Infusion time group [15] and PICT group [90]. WHO score [1] and Head cover [no] were only included in models for opposing outcomes.
Outcomes were based on binary responses; head cover (yes vs. no) and retention success (Binary-WHO; WHO 0/1 vs. WHO 2/3). OR reported relative to the reference category in each chemotherapy group. Statistical differences were indicated if $P < .05$ ($^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$). Non-significant parameters are not displayed -see Supplementary material for complete MVA output breakdown (Supplementary material S4).
[a]Only females with breast cancer were analyzed.
[b]Best model: HC ~ Dose + WHO score + Number SC Sessions + Previous Chemo:Number SC Sessions + WHO score:Number SC Sessions. ($n$ = 1325/1377 (96%); accuracy = 0.896, [95% CI: 0.851-0.931]; $P$ = <.001)).
[c]Best model: Binary-WHO ~ Previous Chemo + Number SC Sessions + HC + HC:Number SC Sessions + Dampening:Number SC Sessions + Dampening:Chemical Manipulation. ($n$ = 1325/1377 (96%); accuracy = 0.992, [95% CI: 0.971-0.999]; $P$ = <.001).
[d]Best model: HC ~ Age Group + WHO score + Number SC Sessions. ($n$ = 698/730 (96%); accuracy = 0.835, [95% CI: 0.746-0.903]; $P$ = .021).
[e]Best model: Binary-WHO ~ Infusion Time Group + Dampening + Number SC Sessions + HC + Setting:Number SC Sessions + Previous Chemo:Number SC Sessions + Dampening:HC. ($n$ = 659/730 (90%); accuracy = 1, [95% CI: 0.938-1]; $P$ = <.001).
[f]Best model: OH ~ Cancer Type + Dampening + WHO score + Number SC Sessions + WHO score:Dampening + Chemical Manipulation:Number SC Sessions. ($n$ = 1205/1232 (98%); accuracy = 0.925, [95% CI: 0.877-0.958]; $P$ = <.001).
[g]Best model: Binary-WHO ~ Gender + Setting + PICT Group + HC + HC:Number SC Sessions + Gender:HC. ($n$ = 1167/1232 (95%): accuracy = 0.993, [95% CI: 0.963-1]; $P$ = <.001).
[h]Best model: OH ~ Ethnic Hair Type + PICT Group + WHO score + Number SC Sessions + Gender:Number SC Sessions + Setting:Number SC Sessions + Ethnic Hair Type:Number SC Sessions + PICT Group:Number SC Sessions ($n$ = 691/763 (91%): accuracy = 0.891, [95% CI: 0.788-0.955]; $P$ = 0.599 (ns)).
[i]Best model: Binary-WHO ~ Gender + Previous Chemo + Dampening + HC + Dampening:Previous Chemo. ($n$ = 703/763 (92%): accuracy = 0.987, [95% CI: 0.929-1]; $P$ = <.001).
**Abbreviations:** A, doxorubicin (adriamycin); C, cyclophosphamide; D, docetaxel (Taxotere); E, epirubicin; F, 5-fluorouracil; HC, head cover; OR, odds ratio; PICT, post-infusion cooling time; SC, scalp cooling; T, paclitaxel (Taxol).

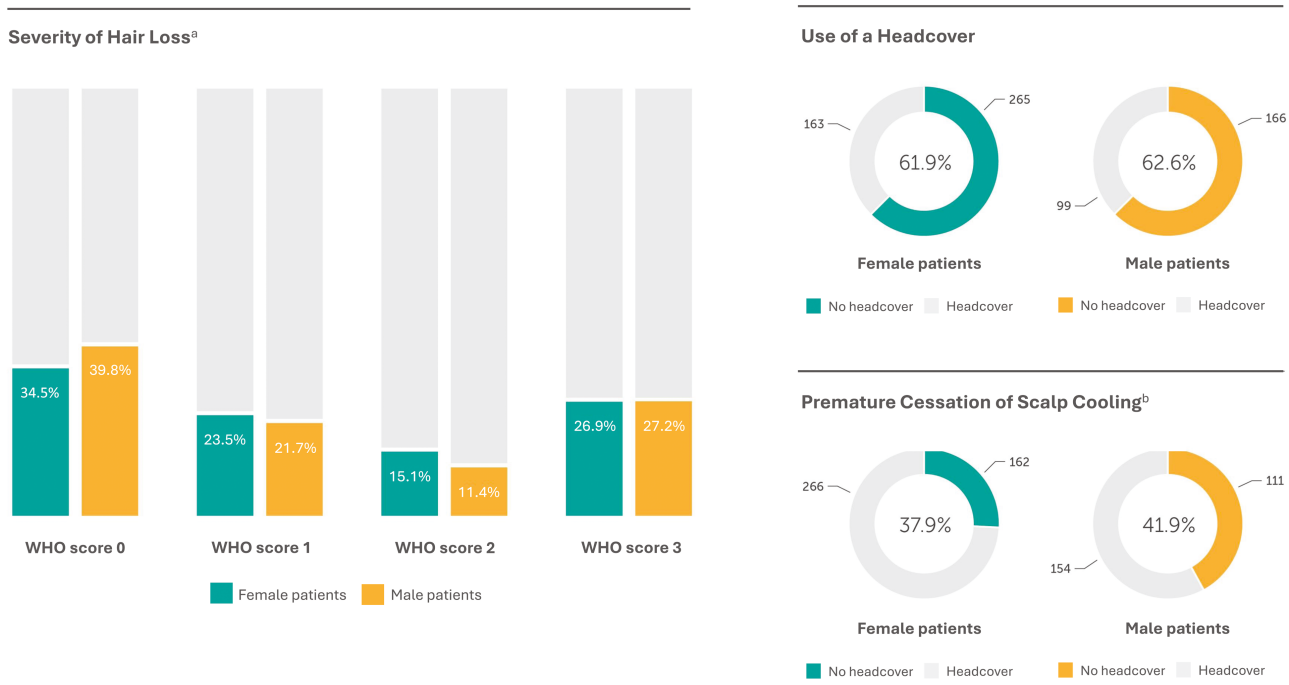


**Figure 1.** Non-gender specific cancer results of scalp cooling ($n$ = 693). Abbreviations: A, doxorubicin (Adriamycin); Car, carboplatin; Cis, cisplaitin; D, docetaxel (Taxotere); E, epirubicin; Eto, etoposide; Gem, gemcitabine; HC, Head cover; Irino, irinotecan (Campto); T, paclitaxel (Taxol); Vino, vinorelbine. Cancer types: lung ($n$ = 192), oesophageal ($n$ = 55), pancreas ($n$ = 11), sarcoma ($n$ = 12), skin ($n$ = 8), stomach/colorectal ($n$ = 314), urothelial cell/bladder ($n$ = 7), and other ($n$ = 86). Treatment regimens: A60 ($n$ = 13), Car/CisEto ($n$ = 22), D70-90 ($n$ = 146), D(75) in combination ($n$ = 33), D100 ($n$ = 28), E ($n$ = 4), Gem in combination ($n$ = 24), Irino90-200 ($n$ = 39), Irino210-300 ($n$ = 29), Irino < 300 ($n$ = 215), T50-70 ($n$ = 4), T75-90 ($n$ = 39), T50Car ($n$ = 38), T70-100Car ($n$ = 32), T175Car ($n$ = 23), Vino25-30 ($n$ = 8); dosages in mg/m$^2$. [a] World Health Organisation (WHO) score for alopecia (0: none, 1: minimal, 2: severe, and 3: total alopecia). 22 patients (11F, 11M) were omitted due to incomplete data. [b]Positive results for premature cessation included reasons of tolerability, hair loss/baldness, and other. Stop chemotherapy/disease progression was deemed a negative result. For non-gender-specific cancer types, 81% ($n$ = 693/856) of the patients received comparable treatment regimens. Gender played no statistically significant role in the preference to wear an HC ($P$ = .912) nor the WHO score ($P$ = .393) nor an individual's decision to prematurely cease SC ($P$ = .329).

as reported in the global SC literature.[9,39,40] Despite the substantial number of patients, our robust models did not show any patient, cancer, or treatment characteristic as a generic determinant influencing SC success. This is parallel to earlier smaller studies.[41] In contrast with another study where nicotine abuse was linked to suboptimal hair retention rates,[42] our results did not link lifestyle characteristics with SC efficacy. The lack of significance indicates that there will be other -yet unknown-factors primarily differentiating patients with good and suboptimal outcomes. Also dampening the hair did not show convincingly improved results.

For the whole patient series, better responses for FECD than FEC show that the switch to a taxane (D) is less cytotoxic to the follicles than continuing with an anthracycline. Also, ACT and ACD performed better than AC with SC in terms of hair retention derived from the WHO score, although dosages were comparable. There might be a 2-fold explanation; first, it might be attributed to information bias, that is, nurses might have registered patients on the sequential scheme in the AC group because that was the chemotherapy at SC initiation. Second, it is known that hair grows during taxane treatment with SC,[15,18,43-45] so the added 3 months before the final review may account for the improved outcome; camouflaging incomplete hair loss within AC treatments. Therefore, patients should be encouraged to continue SC, also if the result is not satisfactory during AC.

The correlation between HC use and WHO score was moderate, however, both were each other's predictors. Head covering is a logical consequence of hair loss severity, however, this holds true for many but not all patients, as described in earlier studies.[11,46] In addition, determinants influencing SC success differed between both primary outcomes, indicating that these are really 2 different measures. It endorses that outcome measures for SC, irrelevant to logical psychological assumptions, should not be combined in meta-analyses. In addition, as both HC and binary-WHO outcomes are fitted to different data, models cannot be directly compared. Here, the HC use training models had lower AIC scores and incorporated fewer variables whereas binary-WHO models with more variables were more accurate predictors of outcome, with almost perfect to perfect inter-rater agreement. Because the preference for providing scores is different for many patients, a combination of methodologies could be a solution. An example is to allow patients to rate hair loss based on pre-defined images in combination with a numerical and a categorical score like used in the HAIR-QoL measure for alopecia.[47,48] Other aspects of evaluation are the pattern and the course of hair loss over time.

For non-gender-specific cancer types, gender played no statistically significant role in the outcomes of SC success nor prematurely ceasing it. This is in contrast with previous notions that higher success rates in the small proportion of men undertaking SC (overall no HC average of 86% vs 52% for females—see Table 1) are attributed to a combination of factors including short hair, hormone levels, lower dose

regimens (eg, D for prostate cancer vs breast cancer), and societal acceptance of male baldness as fashionable.[49]

For many chemotherapies, the extent of hair loss without SC is unknown, with data mostly being drawn from pharmaceutical trials and practice-based information from medical personnel. Randomized control trials are now scarcely performed owing to earlier recognition of the benefits of SC against CIA.[9,10,23] Consequently, the extent of the added value of SC for chemotherapies with less pronounced hair loss is unknown. Moreover, it is less clear how effective the use of an HC is as a surrogate for patient satisfaction with SC for these chemotherapy treatments. Furthermore, with the increasing research into SC preventing persistent-CIA, previous assumptions of ineligibility based on chemotherapy regimens need to be revisited.[33]

A strength of this study is the extent of the database with high completeness of data, especially for patient-reported data from multiple centers. The increased completeness in the second and third cohorts (see Supplementary Table S5) reflects the benefits of forced response electronic data collection. However, despite this being a relatively large study, and advancements being made to standardize SC procedures (PICT, outcomes, etc.), hospital-specific variabilities between SC protocols, dosages, infusion regimens, and pre- and post-infusion cooling times still makes interpretation of significant determinants for outcomes challenging (see Supplementary Table S6). This would argue for even more detailed guidelines, preferably specified for each drug regimen. A disadvantage for this and many other SC studies is the primary endpoint. For large multicenter studies, reliable clinical evaluation of hair loss is not feasible. Furthermore, physical hair checks are possible for trials but are labor intensive and not practical for real-world cohorts.[46] Patient-reported outcome data collection is challenging to implement; however, its recurrent application limits recall bias and it bypasses medical personnel inter-rater variability.[46] The currently used end-point evaluation may not be optimal for SC efficacy review, and it should preferably be measured some weeks after treatment completion instead of during chemotherapy. Another limitation is that for ML preferably larger patient samples are used to enable methodologies that further improve model sensitivity, for example, Bayesian Information Criterion or least absolute shrinkage and selection operator. Besides, ML methods are generally not built with *P*-values to check statistical thresholds but assess predictive ability through self-learning. As such, further evaluation using the more commonly used Shapley value may improve understanding of ML model predictions.[50]

The most important clinical implication is that medical personnel involved in patient care need to be aware that males are also eligible for and benefit from scalp cooling. In addition, comprehensive standardized registration with more extensive outcome evaluation of hair loss and recovery is essential for long-term international protocol optimization and for revealing the true determinants of SC efficacy to accelerate advances in individual patient care. Adding biomarkers, for example, scalp skin temperatures, to clinical studies will contribute to better predictions of who will experience hair loss and why.[51]

## Conclusion

We have described and validated a robust model for evaluating the chemotherapy-specific determinants of SC efficacy. This study implies that apart from the chemotherapy regimen, no specific characteristics were universal determinants of SC efficacy. While currently, unknown determinants may be exerting a baseline influence on efficacy outcomes, gender plays no significant role. SC is effective for the majority of patients, and it offers patients the opportunity for privacy, identity, and control in their cancer treatment journey.

## Author contributions

Toni S. Brook (Conceptualization, Formal Analysis, Methodology, Validation, Visualization, Writing—original draft), Tanja Seetsen (Data curation, Writing—review & editing), M.W. Dercksen (Data curation, Investigation, Writing—review & editing), Annemarie van Riel (Data curation, Investigation, Writing—review & editing), Veerle A. Derleyn (Data curation, Investigation, Writing—review & editing), Johan van den Bosch (Data curation, Investigation, Writing—review & editing), Johannes W.R. Nortier (Data curation, Investigation, Writing—review & editing), Andrew Collett (Formal analysis, Writing—review & editing), Nikolas T. Georgopoulos (Formal analysis, Supervision, Writing—review & editing), Jarek Bryk (Formal analysis, Methodology, Supervision, Writing—review & editing), Wim P.M. Breed, Corina J.G. Van Den Hurk (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing—review & editing)

## Funding

None declared.

## Conflicts of interest

The authors declare no conflicts of interest.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

## Supplementary material

Supplementary material is available at *The Oncologist* online.

## References

1. Choi EK, Kim IR, Chang O, et al. Impact of chemotherapy-induced alopecia distress on body image, psychosocial well-being, and depression in breast cancer patients. *Psychooncology*. 2014;23(10):1103-1110. https://doi.org/10.1002/pon.3531
2. Freites-Martinez A, Chan D, Sibaud V, et al. Assessment of quality of life and treatment outcomes of patients with persistent post-chemotherapy alopecia. *JAMA Dermatol*. 2019;155(6):724-728. https://doi.org/10.1001/jamadermatol.2018.5071
3. Ozusaglam E, Can G. The impact of the perception of chemotherapy-induced alopecia on psychosocial life. *Flor Night J Nurs*. 2021;29(3):361-370. https://doi.org/10.5152/FNJN.2021.19098
4. Wils R, Jacob A, Daniel E, Chacko R, Reka S. Distress and coping in cancer patients experiencing chemotherapy-induced alopecia [Research in Brief]. *Indian J Contin Nurs Educ*. 2019;20(1):60-64. https://doi.org/10.4103/ijcn.ijcn_4_19
5. Betticher DC, Delmore G, Breitenstein U, et al. Efficacy and tolerability of two scalp cooling systems for the prevention of alopecia associated with docetaxel treatment. *Support Care Cancer*.

2013;21(9):2565-2573. https://doi.org/10.1007/s00520-013-1804-9
6. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol*. 2005;16(3):352-358. https://doi.org/10.1093/annonc/mdi088
7. Kargar M, Sarvestani RS, Khojasteh HN, Heidari MT. Efficacy of penguin cap as scalp cooling system for prevention of alopecia in patients undergoing chemotherapy. *J Adv Nurs*. 2011;67(11):2473-2477. https://doi.org/10.1111/j.1365-2648.2011.05668.x
8. Lemieux J, Maunsell E, Provencher L, et al. Prospective cohort study of chemotherapy-induced alopecia with or without scalp cooling. *J Clin Oncol*. 2012;30(15_suppl):9138-9138. https://doi.org/10.1200/jco.2012.30.15_suppl.9138
9. Nangia J, Wang T, Osborne C, et al. Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer: The SCALP Randomized Clinical Trial. *JAMA*. 2017;317(6):596-605. https://doi.org/10.1001/jama.2016.20939
10. Rugo HS, Klein P, Melin SA, et al. Clinical performance of the DigniCap system, a scalp hypothermia system, in preventing chemotherapy-induced alopecia. *J Clin Oncol*. 2015;33(15_suppl):9518-9518. https://doi.org/10.1200/jco.2015.33.15_suppl.9518
11. van den Hurk CJ, van den Akker-van Marle ME, Breed WP, et al. Impact of scalp cooling on chemotherapy-induced alopecia, wig use and hair growth of patients with cancer. *Eur J Oncol Nurs*. 2013;17(5):536-540. https://doi.org/10.1016/j.ejon.2013.02.004
12. Janssen FP, Rajan V, Steenbergen W, van Leeuwen GM, van Steenhoven AA. The relationship between local scalp skin temperature and cutaneous perfusion during scalp cooling. *Physiol Meas*. 2007;28(8):829-839. https://doi.org/10.1088/0967-3334/28/8/006
13. Dunnill CJ, Al-Tameemi W, Collett A, Haslam IS, Georgopoulos NT. A clinical and biological guide for understanding chemotherapy-induced alopecia and its prevention. *Oncologist*. 2018;23(1):84-96. https://doi.org/10.1634/theoncologist.2017-0263
14. Al-Tameemi W, Dunnill C, Hussain O, et al. Use of in vitro human keratinocyte models to study the effect of cooling on chemotherapy drug-induced cytotoxicity. *Toxicol In Vitro*. 2014;28(8):1366-1376. https://doi.org/10.1016/j.tiv.2014.07.011
15. Bajpai J, Kagwade S, Chandrasekharan A, et al. "Randomised controlled trial of scalp cooling for the prevention of chemotherapy induced alopecia". *Breast*. 2020;49:187-193. https://doi.org/10.1016/j.breast.2019.12.004
16. Dunnill C, Ibraheem K, Peake M, et al. Cooling-mediated protection from chemotherapy drug-induced cytotoxicity in human keratinocytes by inhibition of cellular drug uptake. *PLoS One*. 2020;15(10):e0240454. https://doi.org/10.1371/journal.pone.0240454
17. Komen MMC, Smorenburg CH, Nortier JWR, et al. Results of scalp cooling during anthracycline containing chemotherapy depend on scalp skin temperature. *Breast*. 2016;30:105-110. https://doi.org/10.1016/j.breast.2016.09.007
18. Kinoshita T, Nakayama T, Fukuma E, et al. Efficacy of scalp cooling in preventing and recovering from chemotherapy-induced alopecia in breast cancer patients: The HOPE Study. *Front Oncol*. 2019;9:733. https://doi.org/10.3389/fonc.2019.00733
19. Ohsumi S, Kiyoto S, Takahashi M, et al. Prospective study of hair recovery after (neo)adjuvant chemotherapy with scalp cooling in Japanese breast cancer patients. *Support Care Cancer*. 2021;29(10):6119-6125. https://doi.org/10.1007/s00520-021-06168-y
20. Enzlin R, van den Waarts H, Hurk C, Breed W, Kloeze C. *Development of Personalized Scalp Cooling by Prediction and Adjustment of Scalp Skin Temperatures*. *Supportive Care in Cancer*. 2023;31(Suppl 1):S399.
21. DigniCap. *Where is DigniCap Available?* 2022. Accessed October 15, 2023. https://dignicap.com/locations/
22. Paxman. *Paxman Installations*; 2020. Accessed October 15, 2023. https://paxmanscalpcooling.com/wp-content/uploads/2022/09/Paxman-Installations-2020psc.pdf
23. Zhou T, Han S, Zhu Z, Hu Y, Xing W. Interventions for preventing chemotherapy-induced alopecia: a systematic review and network meta-analysis of randomized controlled trials. *Cancer Nurs*. 2021;44(6):E567-E577. https://doi.org/10.1097/ncc.0000000000000899
24. Breed WPM, van den Hurk CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss: scalp cooling potentials and limitations. *Expert Rev Dermatol*. 2011;6(1):109-125. https://doi.org/10.1586/edm.10.76
25. Mulders M, Vingerhoets A, Breed W. The impact of cancer and chemotherapy: perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nurs*. 2008;12(2):97-102. https://doi.org/10.1016/j.ejon.2007.10.002
26. van den Hurk CJ, van den Akker-van Marle ME, Breed WP, et al. Cost-effectiveness analysis of scalp cooling to reduce chemotherapy-induced alopecia. *Acta Oncol*. 2014;53(1):80-87. https://doi.org/10.3109/0284186X.2013.794955
27. Paxman. *Paxman Announces that US Centers for Medicare and Medicaid Services (CMS) has Reassigned Payment for Scalp Cooling*; 2021. Accessed October 15, 2023. https://www.ipohub.io/render/3f5850b0-cef7-4a6c-b36d-33447be03fbc.pdf?original=-paxman-announces-that-us-centers-for-medicare-and-medicaid-services-cms-has-reassigned-payment-for-scalp-cooling
28. Singer S, Tkachenko E, Sharma P, et al. Geographic disparities in access to scalp cooling for the prevention of chemotherapy-induced alopecia in the United States. *J Am Acad Dermatol*. 2021;85(5):1248-1252. https://doi.org/10.1016/j.jaad.2020.06.073
29. Keim S, Hempel L, Ebner F, et al. Scalp cooling for prevention of chemotherapy-induced alopecia for women and men with various cancer entities: a two-year survey of an outpatient cancer center in Germany. *Oncol Res Treat*. 2022;45(7-8):395-399. https://doi.org/10.1159/000523759
30. Komen MMC, Smorenburg CH, van den Hurk CJ, Nortier JW. Factors influencing the effectiveness of scalp cooling in the prevention of chemotherapy-induced alopecia. *Oncologist*. 2013;18(7):885-891. https://doi.org/10.1634/theoncologist.2012-0332
31. van den Hurk CJ, Breed WP, Nortier JW. Short post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia. *Support Care Cancer*. 2012;20(12):3255-3260. https://doi.org/10.1007/s00520-012-1465-0
32. Komen MMC, Breed WP, Smorenburg CH, et al. Results of 20- versus 45-min post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia. *Support Care Cancer*. 2016;24(6):2735-2741. https://doi.org/10.1007/s00520-016-3084-7
33. van den Hurk CJ, Mols F, Vingerhoets AJ, Breed WP. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psychooncology*. 2010;19(7):701-709. https://doi.org/10.1002/pon.1615
34. World Health, O. *WHO Handbook for Reporting Results of Cancer Treatment*. World Health Organization; 1979. https://iris.who.int/handle/10665/37200
35. Haque E, Alabdaljabar MS, Ruddy KJ, et al. Management of chemotherapy-induced alopecia (CIA): a comprehensive review and future directions. *Crit Rev Oncol Hematol*. 2020;156:103093. https://doi.org/10.1016/j.critrevonc.2020.103093
36. Calcagno V, de Mazancourt C. glmulti: An R package for easy automated model selection with (generalized) linear models. *J Stat Softw*. 2010;34(12):1-29. https://doi.org/10.18637/jss.v034.i12
37. R-Core-Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2022. https://www.R-project.org/
38. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. *Int J Open Source Softw*. 2019;4(43):1-6. https://doi.org/10.21105/joss.01686
39. Martín M, de la Torre-Montero JC, López-Tarruella S, et al. Persistent major alopecia following adjuvant docetaxel for breast cancer: Incidence, characteristics, and prevention with scalp cooling. *Breast Cancer Res Treat*. 2018;171(3):627-634. https://doi.org/10.1007/s10549-018-4855-2

40. Vasconcelos I, Wiesske A, Schoenegg W. Scalp cooling successfully prevents alopecia in breast cancer patients undergoing Anthracycline/Taxane-based chemotherapy. *Breast*. 2018;40:1-3. https://doi.org/10.1016/j.breast.2018.04.012
41. Pedersini R, Fornaro C, di Mauro P, et al. Efficacy of the DigniCap system in preventing chemotherapy-induced alopecia in breast cancer patients is not related to patient characteristics or side effects of the device. *Int J Nurs Pract*. 2021;27(3):e12888. https://doi.org/10.1111/ijn.12888
42. Schaffrin-Nabe D, Schmitz I, Josten-Nabe A, von Hehn U, Voigtmann R. The influence of various parameters on the success of sensor-controlled scalp cooling in preventing chemotherapy-induced alopecia. *Oncol Res Treat*. 2015;38(10):489-495. https://doi.org/10.1159/000440636
43. de Barros Silva G, Donati A, van den Hurk CJ. Comments regarding "Hair regrowth during chemotherapy after scalp cooling technique". *Int J Dermatol*. 2017;56(3):e57-e59. https://doi.org/10.1111/ijd.13526
44. Fushimi A, Shinozaki N, Takeyama H. Hair regrowth using a properly fitted scalp cooling cap during adjuvant chemotherapy for breast cancer. *Int Canc Conf J*. 2019;8(4):181-184. https://doi.org/10.1007/s13691-019-00380-8
45. Sahadevan SW, Ding SR, Del Priore G. Hair "regrowth" during chemotherapy after scalp cooling technique. *Int J Dermatol*. 2016;55(8):e463-e465. https://doi.org/10.1111/ijd.13261
46. Komen MMC, van den Hurk CJG, Nortier JWR, et al. Patient-reported outcome assessment and objective evaluation of chemotherapy-induced alopecia. *Eur J Oncol Nurs*. 2018;33:49-55. https://doi.org/10.1016/j.ejon.2018.01.001
47. van den Hurk C, Libreros-Peña L, Winstanley J, et al. The HAIR-QoL measure Part 1: What are the quality of life issues for people with cancer with chemotherapy-induced alopecia? *Meas Eval Cancer Care*. 2023;1:100002. https://doi.org/10.1016/j.ymecc.2023.100002
48. Winstanley J, Libreros-Peña L, Schaffrin-Nabe D, et al. The HAIR-QoL measure Part 2: validation of an instrument to measure of the severity and impact of Chemotherapy-Induced Alopecia (CIA). *Meas Eval Cancer Care*. 2023;1:100003. https://doi.org/10.1016/j.ymecc.2023.100003
49. van den Hurk C, Peerbooms M, van de Poll-Franse LV, Nortier JW, Coebergh JWW, Breed WP. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients—results of the Dutch Scalp Cooling Registry. *Acta Oncol*. 2012;51(4):497-504. https://doi.org/10.3109/0284186X.2012.658966
50. Rodríguez-Pérez R, Bajorath J. Interpretation of machine learning models using shapley values: application to compound potency and multi-target activity predictions. *J Comput Aided Mol Des*. 2020;34(10):1013-1026. https://doi.org/10.1007/s10822-020-00314-0
51. van de Poll-Franse LV, Horevoorts N, Schoormans D, et al; PROFILES Registry Group. Measuring clinical, biological, and behavioral variables to elucidate trajectories of patient-reported outcomes: The PROFILES registry. *J Natl Cancer Inst*. 2022;114(6):800-807. https://doi.org/10.1093/jnci/djac047