

PAXMAN SCALP COOLING SYSTEM **CLINICAL EFFICACY**

US UK ROW ISSUE 2 1020



PAXMAN[®]

Select treatment

Standard treatment stage 1 to 3

Pre infusion cooling and infusion cooling stage 1 to 2

Post infusion cooling stage 3 only

Patient 1 Screen

Select treatment

Standard treatment stage 1 to 3

Pre infusion cooling and infusion cooling stage 1 to 2

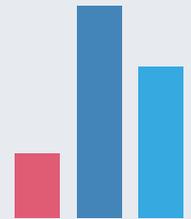
Post infusion cooling stage 3 only

System Status 

Patient 2 Screen

PAXMAN[®]

PIONEERS IN SCALP COOLING



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NCCN
RECOMMENDED

NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) now recommend scalp cooling as a category 2A treatment option for patients with invasive breast cancer and ovarian cancer, fallopian tube cancer and primary peritoneal cancer. To reduce incidence of chemotherapy- induced alopecia in those receiving chemotherapy.



INTRODUCTION

Since the 1990s, Paxman have been worldwide pioneers in scalp cooling, currently the only available treatment that offers patients undergoing cancer chemotherapy a safe and FDA-cleared way of combating chemotherapy induced alopecia (CIA) and maintaining their hair (Dunnill et al., 2018).

The collaboration between Paxman and biologists at the University of Huddersfield, initiated in 2011, has involved extensive laboratory research aimed at providing a deeper mechanistic understanding for how cooling prevents CIA. Using cultured cells from human hair follicles (Fig 1), these laboratory studies demonstrated that cooling directly blocks drug toxicity (Fig 2), and that this protection occurs, at least in part, via a reduction in drug accumulation within the cells. In fact, intracellular drug concentrations are >5-times lower in cooled vs. non-cooled cells.

This fundamental finding demonstrates that the protective impact of scalp cooling goes beyond the indirect effects previously assumed to result from vasoconstriction and reduced of blood flow to the scalp hair follicles. Importantly, these studies have also provided the first demonstration that temperature is critical in achieving adequate protection, with a difference of just 3-4 °C substantially altering cell survival (Al-Tameemi et al., 2014).

Overall, these biological studies have shed light on the mechanisms by which cooling protects against drug-induced toxicity and are in direct support of the established clinical efficacy of cooling.

Publications

*1 Dunnill CJ, Al-Tameemi W, Collett A, Haslam IS, Georgopoulos NT. (2018). A Clinical and Biological Guide for Understanding Chemotherapy-Induced Alopecia and Its Prevention. *The Oncologist*. 23:84-96.

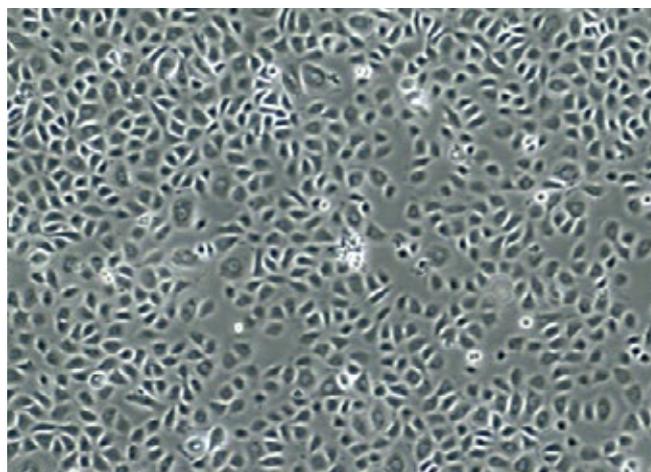
*2 Al-Tameemi W, Dunnill C, Hussain O, Komen MM, van den Hurk CJ, Collett A, Georgopoulos NT. (2014). Use of in vitro human keratinocyte models to study the effect of cooling on chemotherapy drug-induced cytotoxicity. *Toxicol In Vitro*. 28: 1366-76.

Paxman are committed to further improvement in scalp cooling efficacy and continue to collaborate closely with the University of Huddersfield. In particular recent biological discoveries have identified that combining cooling with a topically applied compound has the potential to substantially enhance protection. Strikingly, results have shown the ability to not only reduce but, for some chemotherapy drugs, completely prevent cell toxicity.

The collaboration of Paxman with the University of Huddersfield is now entering an exciting new phase, with a long-term programme of research that will utilise the clinically-relevant culture of human hair follicles (Fig 3) to gain deeper insights into how scalp cooling works and develop novel methods for increasing scalp cooling efficacy for an expanded range of chemotherapeutics. This collaboration will a) support Paxman in becoming the only provider worldwide with a science-based, biological research-driven approach to scalp cooling, and b) be a stepping stone in Paxman's commitment to working on improving scalp cooling to 80/20 by 2020 and 'zero hair loss' in the near future.

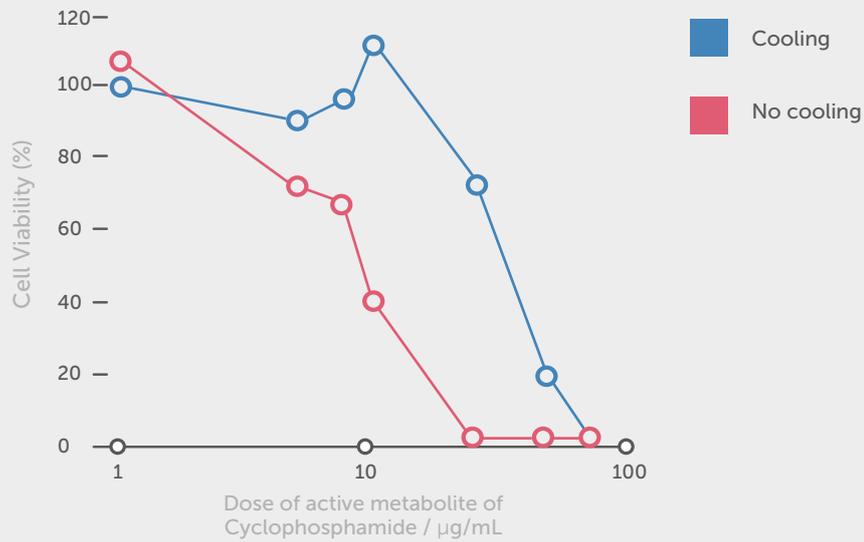
Human hair follicle-derived cells cultured in the laboratory

FIG 1.



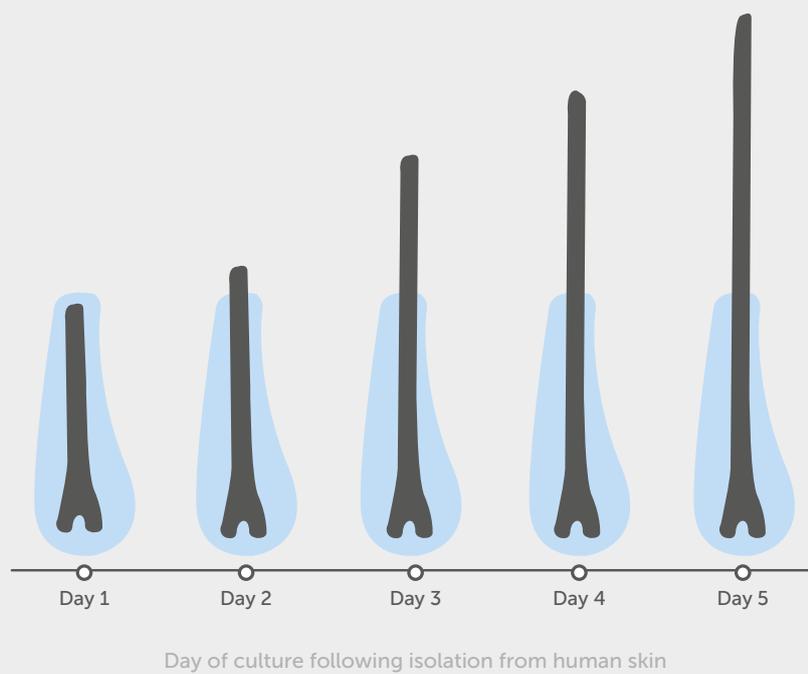
Treatment of human hair follicle cells with the active metabolite of Cyclophosphamide

FIG 2.



Schematic representation of human hair follicle organ cultures

FIG 3.



Prolonging the duration of post-infusion scalp cooling in the prevention of anthracycline-induced alopecia: a randomised trial in patients with breast cancer treated with adjuvant chemotherapy.

(Komen et al., 2018)

150 mins

For FEC patients, a lengthened post-infusion time of 150 minutes improved the grade of alopecia, however, it did not improve the use of a wig/head covering.

Methods:

This prospective, multi-centre, randomised study in the Netherlands aimed to determine if increasing the post-infusion cooling time by 1 hour improved hair retention efficacy for breast cancer patients on FEC chemotherapy regimens.

The patients' hair was assessed against the World Health Organisation's (WHO) scale for alopecia (0 = no change; 1 = minimal hair loss; 2 = moderate hair loss; 3 = complete alopecia).

Patients also assessed their tolerance to the treatment against a visual analogue scale (10 = most tolerable). Patient's headaches were also reported.

Method of scalp cooling: Paxman Scalp Cooler (PSC-1).

Type of Chemotherapy: FEC with an epirubicin dose of 90-100mg/m².

Patients:

102 female breast cancer patients prescribed adjuvant FEC chemotherapy regimens. Half of the patients were assigned a post-infusion time of 90 minutes and the other half were assigned 150 minutes.

Results:

No significant difference was found between the 90- and 150-minute groups with respect to wig/head cover usage (figure 1), however, the 150- minute group showed a significantly higher proportion of patients with grade 0-1 alopecia on the WHO scale (figure 2).

The dosage of chemotherapy (90 vs 100mg/m²) and the number of cycles (3, 5 or 6) did not significantly affect the percentage of patients needing to use a wig/head cover.

Tolerability:

Scalp cooling was tolerated well by most patients. The mean VAS score was 7.4 (10 being the most comfortable).

Three patients discontinued scalp cooling due to intolerance.

Headaches were mentioned in 327 chemotherapy sessions, patients graded the severity, the results are shown in figure 3.

No cases of scalp metastases were reported during the follow up time (median 47 months).

Limitations:

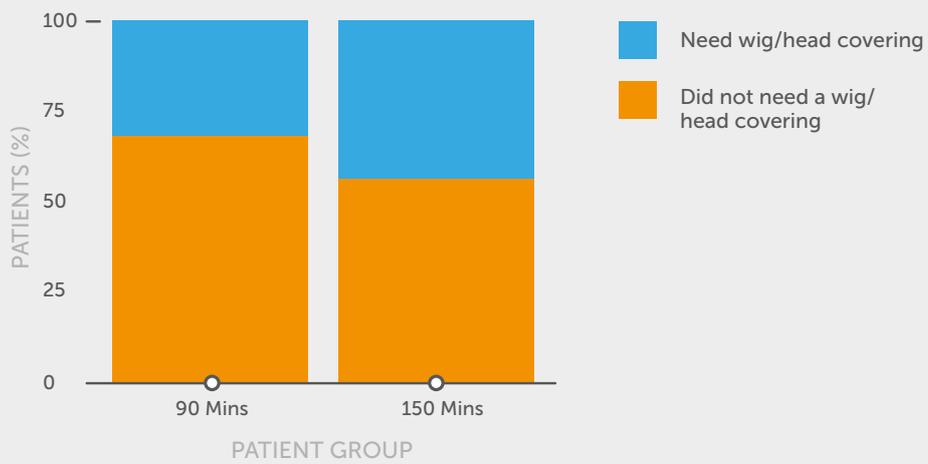
This study may have been underpowered to detect a small difference in efficacy between the drug regimen groups.

The significance between post-infusion times should be further investigated on a larger scale before it is adopted into practice.

"No significant difference was found between the 90- and 150-minute groups."

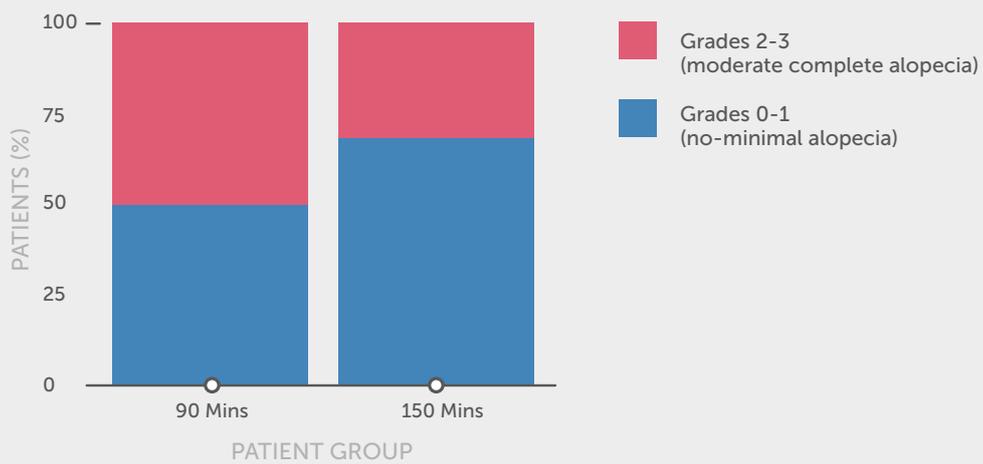
Wig/Head Cover Usage

FIG 1.



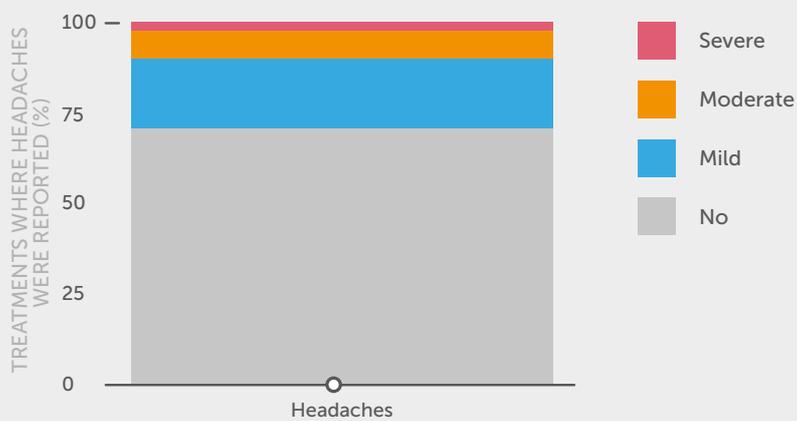
WHO Alopecia Grade Results

FIG 2.



Severity of Headaches During 327 Sessions

FIG 3.



Scalp cooling successfully prevents alopecia in breast cancer patients undergoing anthracycline/taxane-based chemotherapy.

(Vasconcelos, Wiesske & Schoenegg, 2018).

88%

German study shows scalp cooling giving an 88% success rate with paclitaxel and an overall success rate of 71% in patients treated with chemotherapy for breast cancer.

Methods:

A single-centre, prospective, observational study aimed to assess the success rates of scalp cooling in breast cancer patients undergoing chemotherapy.

The 131 participants independently decided if they felt the need to wear a wig or head covering. The perceived percentage of hair loss was assessed by the oncology study nurse through an empirical visual evaluation.

Drug regimens: both anthracycline/taxane-based chemotherapy (74%) and taxane-monotherapy chemotherapy (26%) included.

Timing of chemotherapy: both neoadjuvant and adjuvant patients included.

Method of scalp cooling: Paxman Scalp Cooling System.

Results:

93 participants (71%) had successful treatment, meaning they did not require a wig and retained over 50% of their hair.

Table 1 shows the successes and failures.

The degree of success varied greatly between chemotherapy regimens (table 2 & figure 2).

5 participants also received a carboplatin-anthracycline combination, however the small group size (n=5) impedes the analysis of success rates.

Tolerability:

The participants rated the scalp cooling procedure as reasonably comfortable. This is reflected as only 9 participants (7%) discontinued the treatment due to adverse effects (headaches/nausea/discomfort).

Additional information: The fit of the cap was found to be very important. The nurses on site were highly trained in the fitting of the cap and used a wrapping technique to improve cap fit.

Only appropriate candidates were selected for this trial. Patients were assessed on their baseline alopecia and given empirically based advice on success rates. This was to manage patient expectations, particularly as the cost of scalp cooling is not covered by health insurance in Germany.

Limitations:

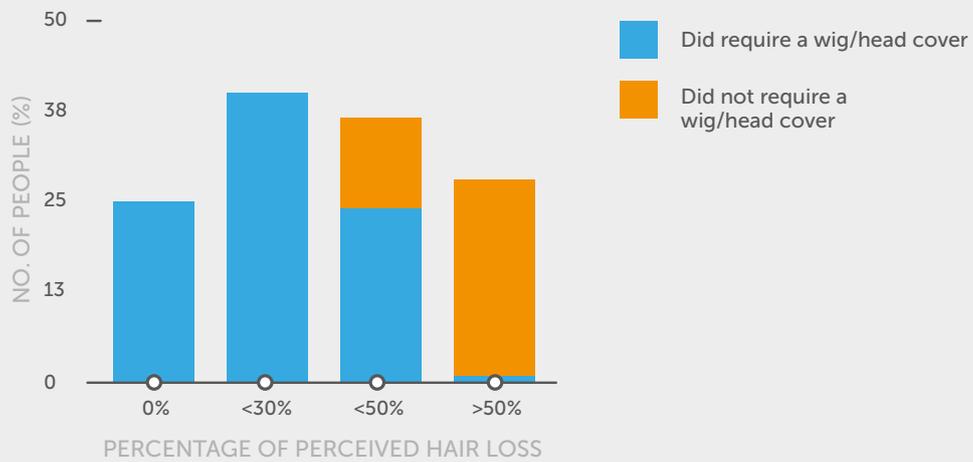
This trial did not use standardised photographs when grading the hair loss, a control group was not recorded, and the patients were not randomised. The sample size was also relatively small.

TABLE 1.

Percentage of perceived hair loss across all drug types	No. of patients	No. of patients not requiring a wig/head cover	No. of patients requiring a wig/head cover
0	25	25	0
<30	42	42	0
<50	35	26	9
>50	29	1	28
Total	131	94	37

No. of Patients Requiring a Wig/Head Cover Dependent on Perceived Hair Loss

FIG 1.



Success and Failure Between Different Drug Regimens

FIG 2.

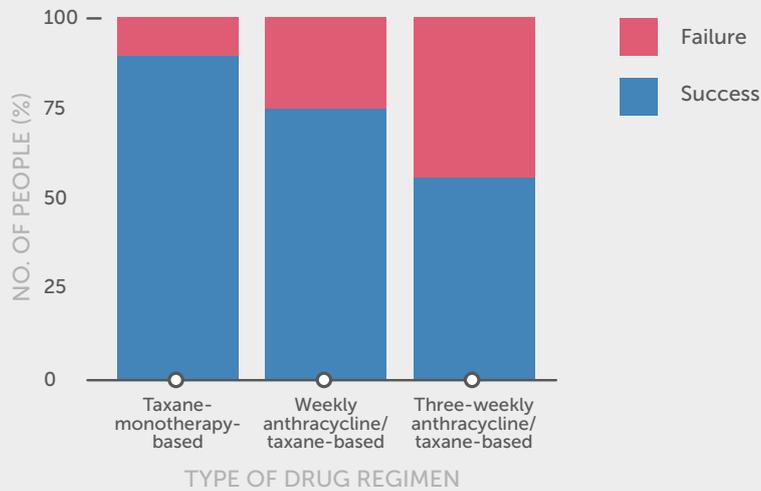


TABLE 2.

Drug Regimen	Success rate (%)
Taxane-monotherapy-based	88.0%
Weekly anthracycline/taxane-based	76.0%
Three-weekly anthracycline/taxane-based	59.0%

Effect of a Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer. The SCALP Randomized Clinical Trial

(Nangia et al., 2017)

50%

Seven trial sites across the USA found scalp cooling to improve hair retention by 50%.

Methods:

A multicentre, randomised, non-blinded study on women undergoing chemotherapy for Stage I or II breast cancer treatment in the adjuvant or neo-adjuvant setting.

Patients were randomly assigned scalp cooling or no scalp cooling on a 2:1 ratio.

Type of chemotherapy: both taxane and anthracycline regimens included.

Method of scalp cooling: Paxman Scalp Cooler (Orbis).

The data are from 3 sets of alopecia assessments using the CTCAE scale v4.0 by clinicians (blinded and unblinded to treatment assignment) and a self-assessment by the participant. Patients were also asked if they needed to use a wig or head covering. Success was defined as no hair loss (CTCAE grade 0) or less than 50% hair loss (grade 1) not requiring a wig; failure was defined as more than 50% hair loss, requiring a wig or head covering.

The scalp cooling group completed a comfort assessment after each treatment. Patients were also asked questions about quality of life, hospital anxiety, depression and body image at baseline, after four cycles of chemotherapy and at the end of their treatment.

Patients will have routine follow up visits for 5 years after finishing treatment to assess safety and overall survival.

Patients:

182 patients were assigned a group in this trial. Of these, 95 scalp cooling patients completed the first chemotherapy cycle, as did 47 in the non-scalp cooling group. 89 and 45 patients completed treatment to the fourth cycle in the scalp cooling and non-scalp cooling groups respectively.

Results:

Success rates were statistically higher in the scalp cooling group compared to the control group (figure 1). The difference in success rate between the two groups was 50.5%, giving patients a significantly better chance at retaining their hair if scalp cooling is used with chemotherapy treatment. Analysis showed that of the successful 50.5% of patients in the cooling group, 5 patients had grade 0 alopecia and 43 patients had grade 1 alopecia.

The success rates between drug regimens varied significantly. A post hoc analysis estimated the overall success rates for two different drug categories (figure 2).

* An update from the authors of this paper was presented at ASCO. It was shown that the difference in success rates between the cooling and non-cooling groups had improved to 53.1% (figure 1). Within the cooling group, it was shown that the success rates for taxanes and anthracyclines were 63% and 24.1% (figure 2). Both of which are above the values in the post hoc analysis (Nangia, et al. ASCO Poster 2017).

Quality of life

No significant difference was found in the change in emotional and social functioning and patient body image, between the patients in the cooling group (with and without hair preservation) and the control group after 4 cycles of chemotherapy.

Tolerability:

No serious adverse events were reported. 54 minor adverse events were reported including: chills, dizziness, headache, nausea, paresthesia, pruritus, sinus pain, skin and subcutaneous tissue disorder and skin ulceration.

The majority of patients reported feeling comfortable, reasonably comfortable or very comfortable. (figure 4)

6 patients discontinued scalp cooling treatment due to intolerance.

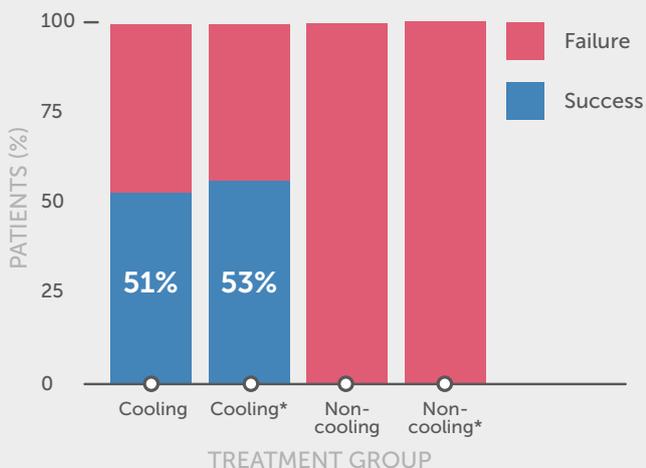
Limitations:

The results varied between sites which could be due to differences in cap fitting, and type of drug regimen used, therefore, overall some sites may have a success rate of above or below 50%. The patients were assessed for hair retention after 4 cycles; patients receiving more than 4 cycles may have seen further hair loss.

The cap fit is thought to be critical to the success of retaining hair with scalp cooling. As the clinicians became more familiar with the caps the process is thought to have improved, giving a higher chance of better success rates.

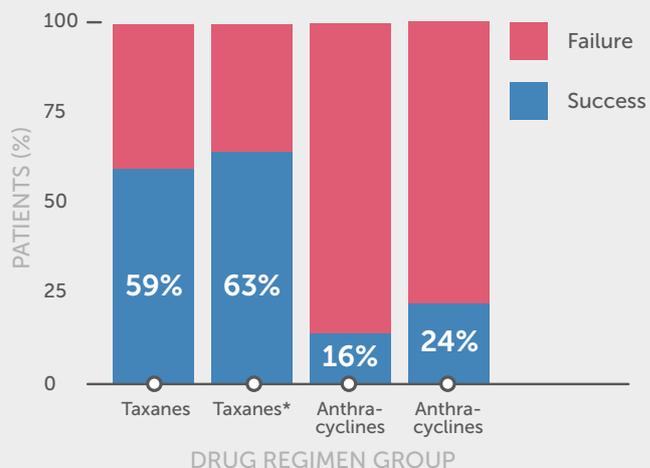
Clinician Assessed Hair Preservation

FIG 1.



Drug Regimen Success Rates

FIG 2.



Alopecia Grading Example

FIG 3.

Scalp Cooling Example 1



Scalp Cooling Example 2



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Comfort scale: the average rating was reasonably comfortable

FIG 4.



Results of 20- versus 45-min post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia.

(Komen et al., 2016)

20 mins

For hair retention, a post infusion time of 20 minutes is as effective as 45-minute treatments for docetaxel 3-weekly schedules, leading to shorter hospital stays.

Methods:

A prospective, multicentre and randomised study to test if 20-minute post-infusion scalp cooling was as effective as 45-minute post infusion treatments for 3-weekly docetaxel treatments.

Treatment type: docetaxel 75-100mg/m² 3-weekly schedule only.

Patients who opted to use scalp cooling treatment were assigned either 45 or 20-minute post infusion treatment sessions on a 1:1 ratio. A pre-infusion time of 30 minutes was always given, and the standard infusion time was 60 minutes.

Success was defined if the patient decided not to wear a wig/head covering. Patients also assessed their perceived hair loss on the World Health Organisation's 4-point alopecia scale (0 = no change; 1 = minimal hair loss; 2 = moderate hair loss; 3 = patchy alopecia; 4 = complete alopecia)

Patient tolerability was measured on a visual analogue scale of 1-10 where 0 was intolerable and 10 was very tolerable.

Method of scalp cooling: Paxman Scalp Cooler (PSC-1)

Patients:

134 patients of 18 years or older were identified for the study.

11 patients were withdrawn from the study for reasons unrelated to scalp cooling. 26 patients withdrew due to intolerance.

97 patients were evaluated for tolerance and hair preservation.

61% of participants were male.

Results:

No significant difference was found in the need to wear a head covering between the 45- and 20-minute groups with respect to clinical characteristics and treatment (figure 1). However, a significant difference was found in the need to wear a head covering between genders (figure 2).

Komen et al. (2016) reported that men are generally less inclined to wear a wig/head covering, therefore the results may be overestimated.

Tolerability:

5 patients discontinued treatment due to intolerance during the first chemotherapy cycle.

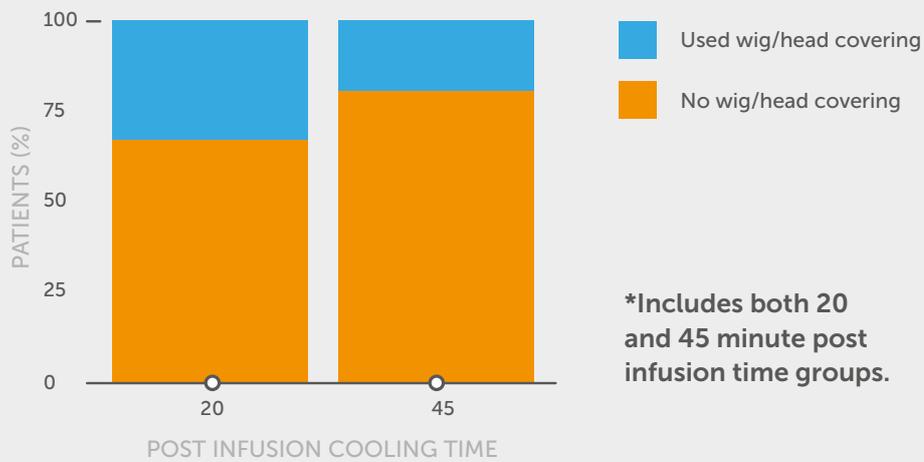
21 patients discontinued chemotherapy before completing the second cycle.

The mean score for tolerability was 8.3, showing a positive experience for most patients. Figure 3 shows how the patients rated their headaches.

"No significant difference was found in the need to wear a head covering between the 45- and 20-minute groups"

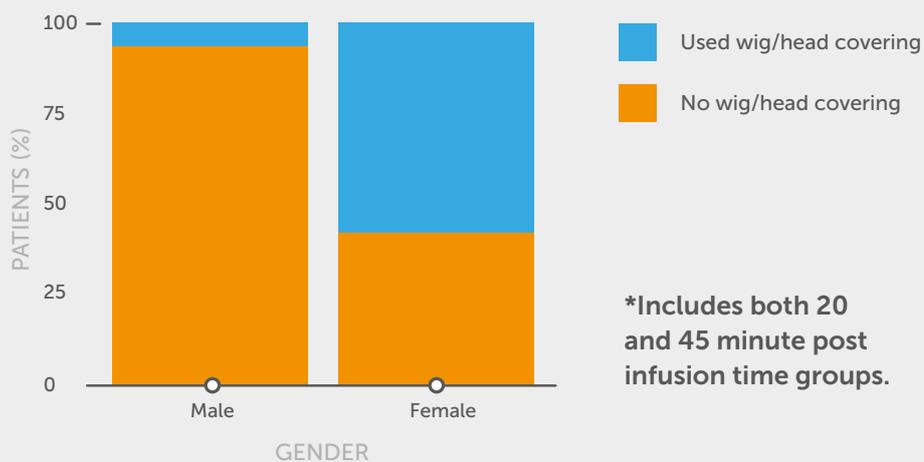
Decision on the Use of a Wig/Head Covering at Post Infusion Time of 20 or 45 Minutes

FIG 1.



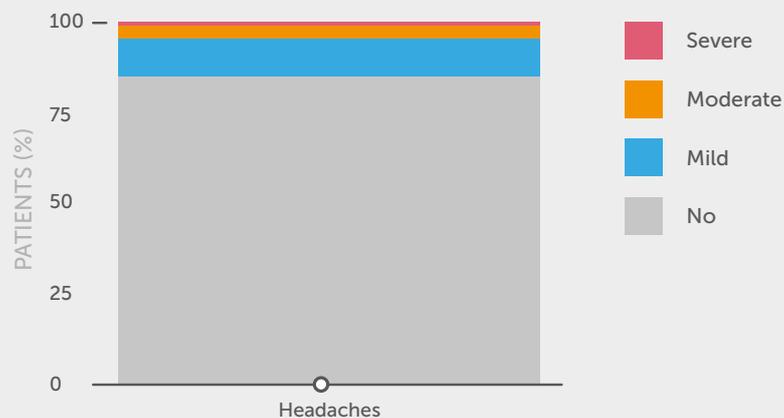
Decision to Use Wig/Head Covering *Includes both 20 and 45 minute post infusion time groups

FIG 2.



Severity of Headaches During 327 Sessions

FIG 3.



Impact of scalp cooling on chemotherapy induced alopecia, wig use and hair growth of patients with cancer.

(van den Hurk et al., 2013a)

40%

Scalp cooling has reduced the use of a wig or head cover by 40% when using the Paxman system.

Methods:

An observational study of 246 patients to determine the degree of success of scalp cooling in reducing chemotherapy induced alopecia in chemotherapy patients.

The patients completed 4 questionnaires between the start of, and a year after finishing, treatment.

Patients evaluated the degree of hair loss with the use of the World Health Organisation's scale for alopecia (0 = no hair loss; 1 = mild; 2 = pronounced; 3 = total alopecia) and by using a Visual Analogue Scale (0 = no alopecia; 100 = total alopecia).

Patients also reported on if they had used a wig/head covering, if they had noticed hair regrowth and if they were satisfied with their hair style.

Drug regimens: Taxane and/or anthracycline-based regimens included.

The number of patients on each type of drug regimen in the scalp cooling and non-scalp cooling groups were not of equal proportion and there was a lack of detail given about the drug dosages. It is widely known that the efficacy of scalp cooling depends on the drug regimen therefore, this study is limited.

Method of scalp cooling: Paxman Scalp Cooler (PSC-1 or PSC-2).

Patients:

160 patients used scalp cooling with their chemotherapy treatment and 86 patients did not use scalp cooling.

Only 6 patients were male.

93% of patients had breast cancer.

Results:

Scalp cooling during chemotherapy significantly reduced the need to purchase a wig/head covering.

Of the 160 scalp cooling patients, 84 purchased a wig. Among these 84, 32 did not use the wig and therefore made the purchase unnecessarily. In total, 51% of patients in the cooling group used a type of head cover vs 91% who used a head cover in the noncooling group (figure 1).

Hair regrowth was reported in 24% and 7% of the scalp cooled and non-scalp cooled groups respectively.

Most patients who had tried scalp cooling were satisfied with their hair style three weeks (85%) and six months (94%) after chemotherapy.

Not all of the patients who did not receive scalp cooling purchased a wig or head cover.

The author of this study concluded that patients should be advised not to buy a wig as a precaution, but to wait until it becomes necessary.

Tolerability:

Only 4 patients (3%) discontinued scalp cooling treatment due to intolerance.

"Scalp cooling during chemotherapy significantly reduced the need to purchase a wig/head covering."

TABLE 1.

Purchase/use	Scalp-cooled (n ¼ 160) n (%)	Non scalp-cooled (n ¼ 86) n (%)	p-Value
Purchased wig	84 (53)	66 (77)	0.0002
Used wig	52 (33)	59 (69)	<0.0001
Purchased head cover ^a	117 (73)	83 (97)	<0.0001
Used head cover ^a	81 (51)	78 (91)	<0.0001

Regrowth	Scalp-cooled (n ¼ 160) n (%)	Non scalp-cooled (n ¼ 86) n (%)	p-Value
During chemotherapy	31 (24)	5 (7)	
Within 3 weeks after chemotherapy	19 (19)	10 (16)	
3-6 weeks after chemotherapy	45 (46)	27 (43)	
6-8 weeks after chemotherapy	18 (18)	18 (28)	
8 weeks after chemotherapy	17 (17)	8 (18)	
Missing	30	18	

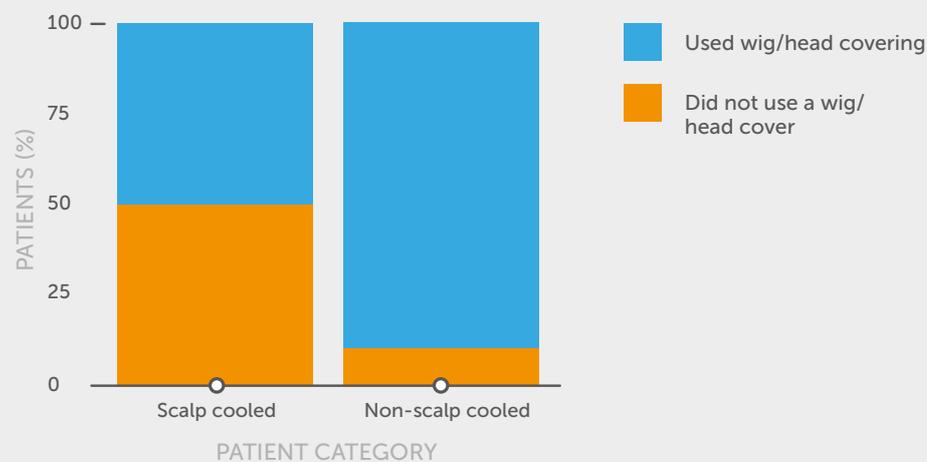
Satisfied with current hair style? ^b	Scalp-cooled (n ¼ 160) n (%)	Non scalp-cooled (n ¼ 86) n (%)	p-Value
3 weeks after chemotherapy	111 (85)	57 (78)	0.23
6 months after chemotherapy	111 (94)	50 (86)	0.08

^a Wig included.

^b n < 246 because measured in M3 and M4.

% OF PATIENTS THAT USED A WIG/HEAD COVER

FIG 1.



Efficacy and tolerability of two scalp cooling systems for the prevention of alopecia associated with docetaxel treatment.

(Betticher et al., 2013)

93.7%

93.7% of patients reported to feel reasonably well or better when using the Paxman Scalp Cooler.

Methods:

The aim of this trial was to investigate two options of scalp cooling treatments and assess the tolerance and efficacy.

This study was a nonrandomised, prospective, controlled study on 238 patients across 27 facilities in Switzerland.

Data were collected at the screening visit, treatment visits and at an end of study visit.

Hair loss was graded against the World Health Organisation's (WHO) scale for alopecia (0 = no hair loss; 1 = mild; 2 = pronounced; 3 = total, reversible alopecia, 4 = total, irreversible alopecia).

The scalp cooling patients were also asked to complete an additional questionnaire including questions about tolerance, side effects, hair loss, hair regrowth and general impression of treatment.

Method of scalp cooling: Paxman Scalp Cooler (PSC-2) (PAX) or a cold cap (CC).

The treatment was deemed a success if the patient did not need to wear a wig at the end of treatment.

Drug regimens: docetaxel 55-60mg/day on weekly basis or 135-140mg/day on three-weekly basis.

Patient tolerability was measured on a visual analogue scale of 1-10 where 0 was intolerable and 10 was very tolerable.

Patients:

All patients received docetaxel palliative, first-line chemotherapy for a solid tumour. 238 patients took part in the trial (128 – PAX, 71 – CC, 39 – no cooling).

The cooling protocol was amended during the study. September 2009: the post-infusion cooling time for both the CC and PAX groups was reduced from 90 to 45 minutes due to new research (van den Hurk et al., 2012a). September 2010: inclusion criteria were updated to include patients with metastases treated with docetaxel-based regimens.

Results:

No significant difference was found for hair retention between the CC and PAX groups. The patients being treated on a weekly basis with docetaxel showed a lower incidence of CIA than patients treated on a three-weekly basis (figure 1).

Tolerability:

93.7% of patients rated their scalp cooling treatment as reasonably well or better when using the Paxman Scalp Cooler (figure 2).

8 patients from the scalp cooled groups reported adverse events; most prominently, a cold sensation.

Limitations:

30 patients (13%) discontinued scalp cooling after cycle 1.

Limitations: This study was open and unrandomized therefore patients could have been biased when choosing their method of treatment.

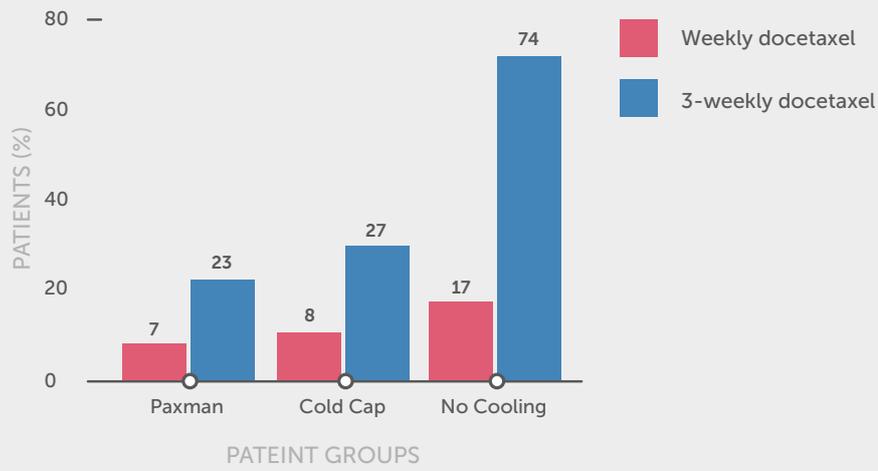
The grading of alopecia against the WHO scale is subjective, as is the choice to wear a wig.

The protocol used in this trial is now slightly outdated as the protocol for scalp cooling recommended by Paxman has been updated to a longer pre-cooling time (30 minutes) and shorter post cooling time (20 minutes).

“No significant difference was found for hair retention between the CC and PAX groups.”

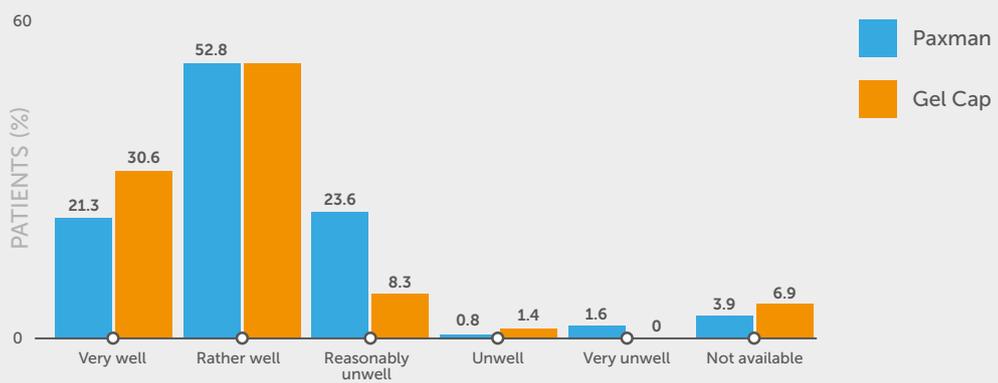
Patients Requiring a Wig and/or had Grade 3 or 4 Alopecia on the WHO Scale.

FIG 1.



Patients consistently reported feeling well after treatment (After Cycle 1)

FIG 2.



Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - Results of the Dutch Scalp Cooling Registry

(van den Hurk et al., 2012b)

50%

50% of 1411 patients treated with a range of alopecia causing chemotherapy regimens, did not require a head covering while using scalp cooling.

The Dutch Scalp Cooling Registry started in 2006 and has been ongoing and expanding since.

Methods:

The Dutch Scalp Cooling Registry collected data from 28 Dutch hospitals. Questionnaires were completed by nurses and patients to examine the success of scalp cooling and any side effects.

Method of scalp cooling: Paxman Scalp Cooler (PSC-1 or PSC-2)

Patients:

The majority of patients were women (96%) with breast cancer (86% being treated in the adjuvant setting (69%). The severity of chemotherapy induced alopecia without scalp cooling was not evaluated as a control group; the severity of alopecia can vary greatly for such patients.

Results:

Success rates varied according to different regimens (figure 1). The best results were shown in patients on monotherapy taxane drug regimens. 94% of patients on a certain docetaxel regimen and 81% of patients on paclitaxel did not feel the need to wear a head cover. The lowest success rate (8%) was seen with TAC (a mixture of taxanes and anthracyclines).

Patients with chemically manipulated, long or thick hair did not have a statistically higher use of head coverings.

Tolerability:

Only 3% of patients discontinued scalp cooling treatment due to intolerance of the procedure.

Additional: Doses of chemotherapy drugs were generally higher than in previous studies and several new chemotherapy drugs were evaluated giving a low success rate.

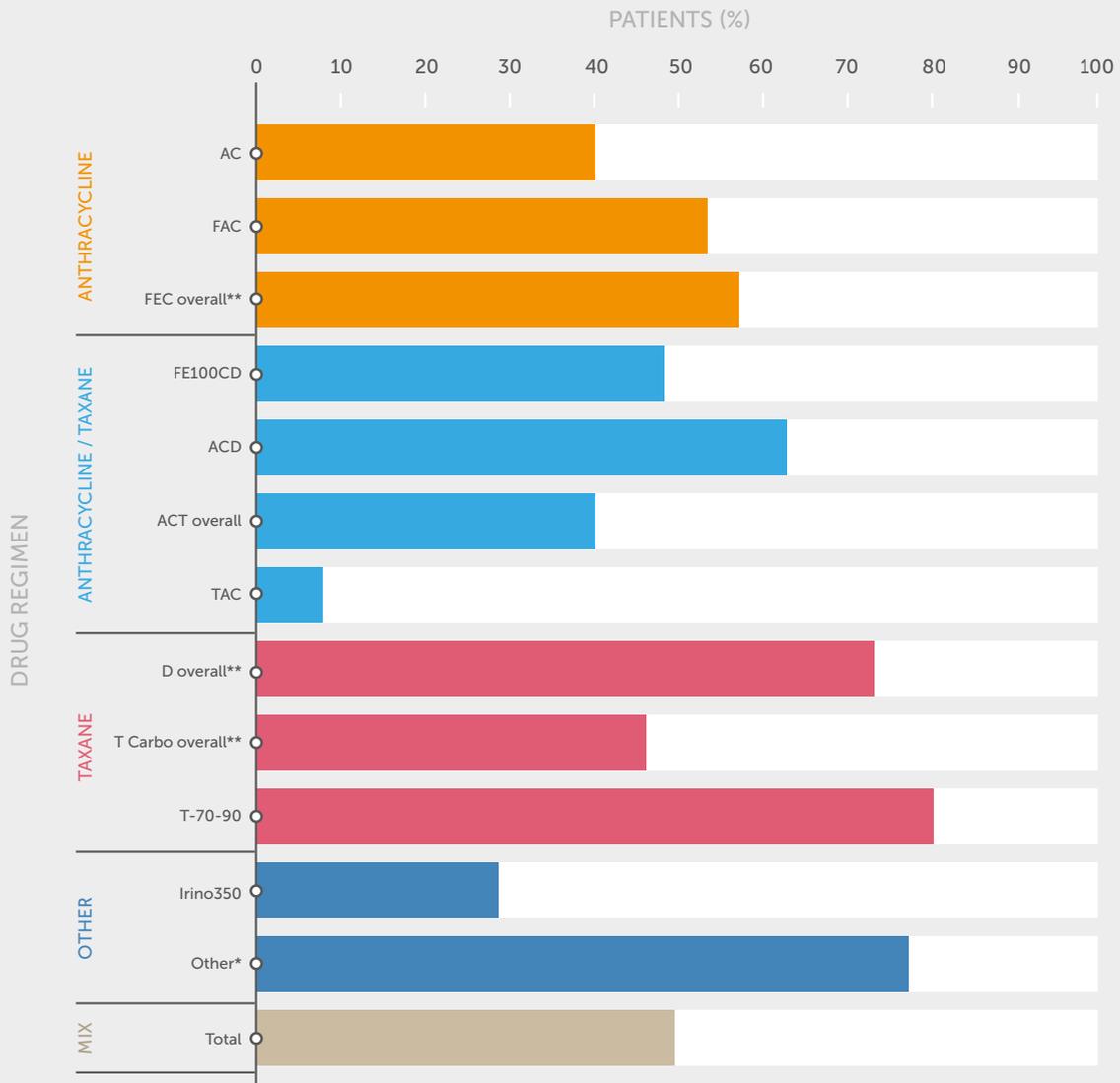
** = Including also other dosages than specified in this table

* = other: <10 patients had a particular regimen with a specific dose

"The best results were shown in patients on monotherapy taxane drug regimens."

% of Patients Not Requiring a Head Cover

FIG 1.



Persistent major alopecia following adjuvant docetaxel for breast cancer: incidence, characteristics, and prevention with scalp cooling.

(Martín et al., 2018)

2 weeks

Scalp cooling reduces the prevalence of persistent alopecia in breast cancer patients.

In most cases, chemotherapy induced alopecia starts 2 weeks after the initial chemotherapy session and starts to reverse 3-4 months after the termination of the final treatment.

However, it was hypothesised that, the incidence of persistent alopecia (PA) for breast cancer patients, treated with adjuvant docetaxel chemotherapy, was high.

Methods:

Patients undergoing scalp cooling with their chemotherapy treatment had follow-up visits every 6 months to determine the grade of hair loss.

Grade 1 persistent alopecia was defined as "weakening of the hair or partial alopecia, not leading to the use of a wig after 18 months from the end of adjuvant chemotherapy"

Grade 2 persistent alopecia was defined as "complete alopecia that requires a wig after 18 months from the end of adjuvant chemotherapy".

Drug regimen: cumulative docetaxel dose of $\geq 400\text{mg/m}^2$.

Timing of chemotherapy: adjuvant treatment.

Method of scalp cooling: Static refrigerated cold caps

Patients:

492 breast cancer patients.

Results:

It was found that grade 2 PA was only seen in chemotherapy regimens containing docetaxel and that these treatments also had a significantly higher proportion of patients showing grade 1 PA to treatments not containing docetaxel.

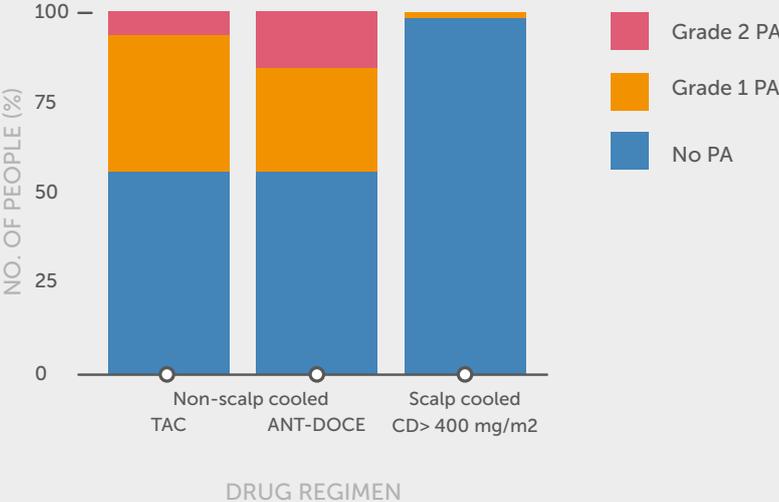
When scalp cooling was used, no incidences of grade 2 persistent alopecia were seen with docetaxel. Only 1 patient (0.8%) showed grade 1 PA (figure 1). Therefore, it can be said that scalp cooling is effective at preventing persistent alopecia in breast cancer patients on docetaxel chemotherapy regimens.

Tolerability:

No significant side effects were recorded. All patients tolerated scalp cooling well, and therefore, completed all scheduled appointments. 10% of patients reported mild headaches but did not discontinue treatment.

% of PA on Patients Given Docetaxel Chemotherapy Drug Regimens

FIG 1.



Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis.

(Rugo, Melin & Voigt, 2017)

0.61%

An American meta-analysis shows no difference in the incidence of scalp metastases between scalp cooled and non-scalp cooled patients.

Methods:

A systematic review and meta-analysis evaluated the risk of scalp metastases in breast cancer chemotherapy patients undergoing and not undergoing scalp cooling.

Several electronic databases were searched for information relating to chemotherapy, breast cancer and scalp metastases.

Timing of chemotherapy: Adjuvant chemotherapy patients included.

Patients:

3197 breast cancer patients treated with chemotherapy, both with and without the use of scalp cooling. Patients who did not have enough follow up information were excluded from the study.

Results:

Scalp metastases incidence rates were found to be very low for both groups.

After following the scalp cooled and non-scalp cooled patients for an estimated mean average of 43.14 and 87.4 months respectively, in total the study found 17 cases of scalp metastases in 3197 patients. Only 0.61% (figure 1) of the scalp cooled group and 0.4% (figure 2) of the non-scalp cooled group showed signs of scalp metastases, therefore showing no statistical difference between the groups.

This study is in agreement with van den Hurk et al. (2013b) showing a low incidence rate of scalp metastases in general and that scalp cooling does not increase the risk of scalp metastases.

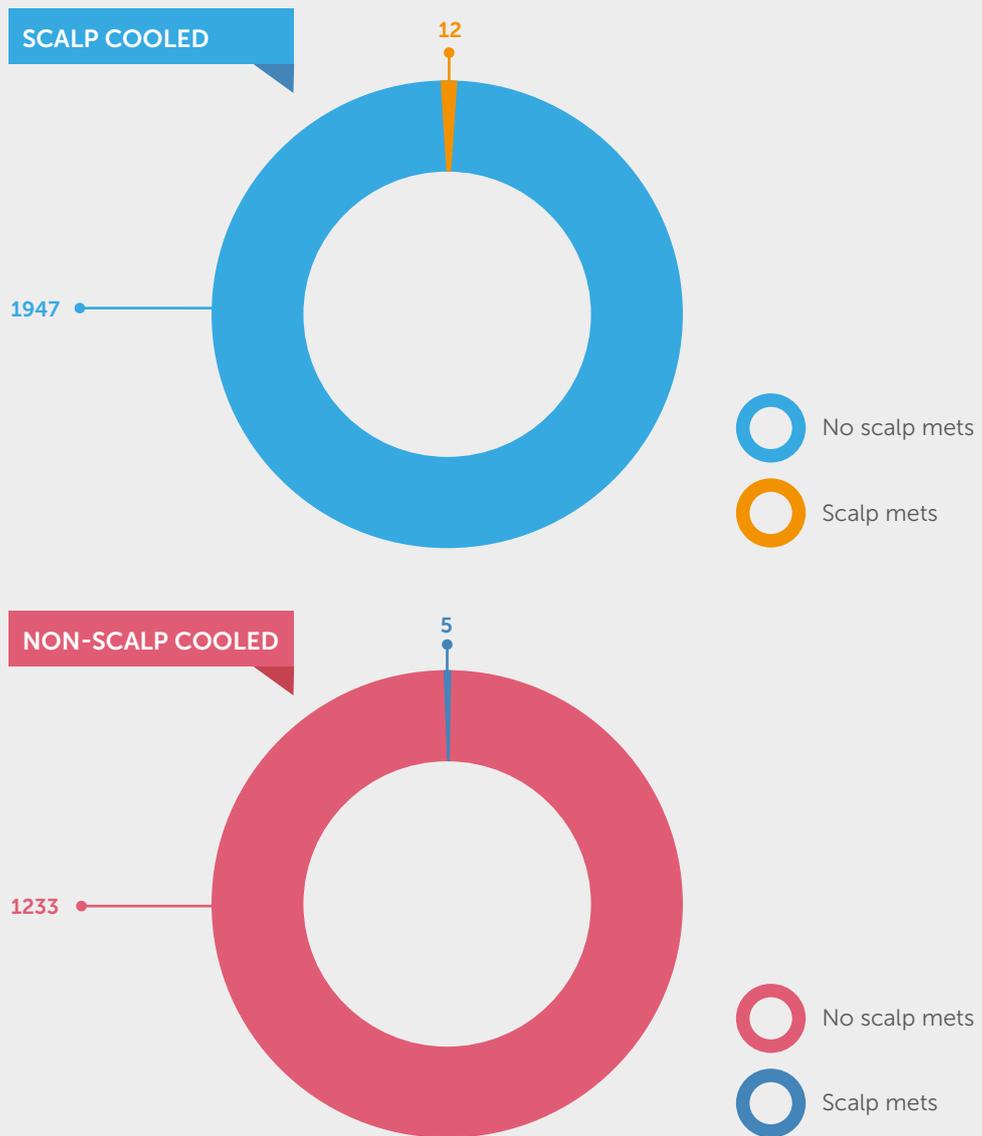
Limitations: Retrospective studies use pre-recorded data, therefore most studies used did not specifically assess scalp metastasis as a primary end point.

The follow up time is presented as an estimated weighted mean. This is due to the times varying between each patient, however the average is thought to be a good representation of the follow up time, as the groups were large, and the distribution was assumed to be normal.

“Scalp metastases incidence rates were found to be very low for both groups.”

Scalp metastases incidence rates

FIG 1.



No effect of scalp cooling on survival among women with breast cancer.

(Lemieux et al., 2014)

533

Scalp cooling does not impact the survival of chemotherapy patients.

Methods:

A retrospective, multicentre cohort study based on two cohorts comparing the survival of 553 women who used scalp cooling to that of 817 women who did not, while undergoing chemotherapy for non-metastatic breast cancer in Quebec, Canada.

Drug regimens: Both anthracycline and taxane chemotherapy included.

Timing of chemotherapy: both neoadjuvant and adjuvant patients included.

The median follow-up times for the scalp-cooled and non-scalp cooled groups were 6.3 years and 8.0 years respectively.

The following variables were considered during analysis: age at diagnosis, stage of cancer (AJCC v5), grade, presence of lymphovascular invasion, type of chemotherapy, oestrogen receptor status, timing of chemotherapy given (adjuvant, neoadjuvant).

Scalp cooling method: cold cap changed at regular intervals or a cap that constantly circulates coolant around the patient's scalp.

Participants:

Information on the patients taking part can be found in figure 1.

Results:

This study found no negative impact on the survival of female patients undergoing scalp cooling during chemotherapy treatment.

During the follow up time, 19.3% of the scalp cooled group and 24.4% of the non-scalp cooled group had died, however, their exact cause of death was unknown.

Limitations: The study was underpowered to detect small differences in survival rates between the scalp cooled and non-scalp cooled groups.

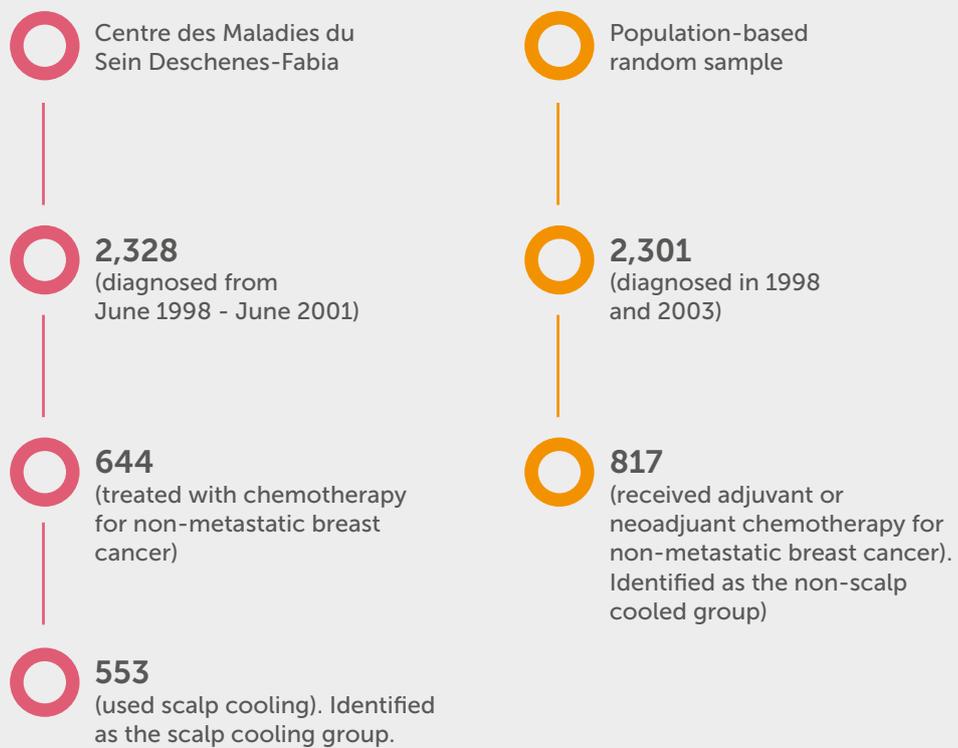
Important prognostic factors and treatment characteristic differed between the groups. The results were adjusted to reduce this limitation, but the conclusion remained the same.

There may be differences between the two groups as different sites may use different techniques of scalp cooling.

"This study found no negative impact on the survival of female patients undergoing scalp cooling during chemotherapy treatment."

Patients Taking Part

FIG 1.



Efficacy of Scalp Cooling in Preventing and Recovering from Chemotherapy-Induced Alopecia in Breast Cancer Patients: The HOPE Study.

(Kinoshita et al., 2019)

60%

Japanese study shows a minimum of 27% success rate in breast cancer patients treated with anthracycline-taxane-based therapy when assessed by two clinical assessors in combination and a 60% success rate when efficacy was determined by each assessor independently.

Methods:

This multicentre, controlled trial in 5 clinical sites in Japan aimed to assess the efficacy of the Paxman scalp cooling (SC) system in preventing chemotherapy-induced alopecia in Japanese breast cancer patients, and to also investigate whether the device improved hair volume recovery 12 weeks following completion of chemotherapy.

The study involved women the majority of whom underwent SC during adjuvant combinatorial anthracycline- and/or taxane-based chemotherapy. Patients were allocated to SC vs Control groups at a 2:1 ratio per regimen at each clinical site in a sequential, non-randomized manner.

The severity of hair loss was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. To determine SC efficacy, no CIA was defined as Grade 0 (no hair loss) or Grade 1 (no wig needed, hair loss <50%), in contrast to alopecia defined as Grade 2 (≥50% hair loss, wig needed). Two independent assessors evaluated alopecia based on photographs of the patient's head taken from five angles (front, back, right, left, and above). The highest grade from the five photographs was adopted as the alopecia outcome by each assessor.

For hair recovery assessment, the study evaluated the proportion of patients with a hair volume of Grade 0, 1, and 2, which took place every 4 weeks and for a total period of 12 weeks after the end of chemotherapy.

Method of SC: Paxman Hair Loss Prevention System.

Type of Chemotherapy: anthracycline- and/or taxane-based chemotherapy (results provided for patients treated with AC and TC). SC was initiated 30min prior to each chemotherapy

infusion and continued until at least 90min following completion.

Patients:

For the evaluation of the efficacy of SC, a total of 43 breast cancer patients were assessed, divided into a SC group (n=30) and a control group (n=13). More than 60% of patients were treated with a docetaxel/cyclophosphamide (TC) regimen (SC group: 75.0%; control group: 64.3%) and the remaining patients received a doxorubicin/cyclophosphamide (AC) regimen (SC group: 25.0%; control group: 35.7%). To determine hair recovery from alopecia, a total of 40 patients were followed-up (SC group n=28 and Control group n=12).

Results:

26.7% (8/30) of patients in the SC group and 0% (0/13) in the control group were judged to have no alopecia by two independent clinical assessors at the end of chemotherapy. This result was obtained if both assessors determined alopecia to be ≤Grade 1, in which case that patient was judged as having no alopecia (FIG 1).

However, 60.0% (18/30) of patients in the SC group and 0% (0/13) in the control group were judged to have no alopecia when success was determined by either clinical assessor independently (FIG 2).

The proportion of patients with alopecia who experienced an increase in hair volume of ≥50% within 12 weeks after chemotherapy was 85.7% (24/28) in the SC group and 50.0% (6/12) in the Control group.

For patients who were judged as having alopecia at the end of chemotherapy, post-hoc analysis was conducted on alopecia recovery. The proportion of patients who recovered from Grade 2 to Grade 0 over the 12 weeks following the end of chemotherapy was 25% (5/20) in the SC group and 8.3% (1/12) in the Control group.

Overall, scalp cooling resulted in faster recovery of hair volume after chemotherapy, even in patients for whom scalp cooling failed to prevent chemotherapy-induced alopecia (FIG 3).

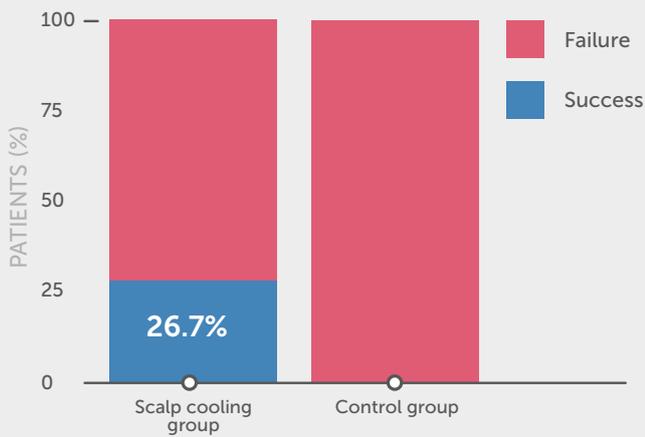
Tolerability: Any minor adverse effects or discomfort were successfully managed with appropriate treatment. No patient developed serious adverse events related to the scalp-cooling device.

Additional information: In this study, two independent assessors evaluated the degree of the alopecia using photographs of the patient's head taken from five directions, and the worst assessment was judged as the outcome. This may represent the main factor for the lower success rate (26.7%) of this study compared to other studies. In support of this notion, when efficacy was judged independently by the assessors the success rate was 60%. Despite this rather strict definition of successful hair preservation, however, the study provides strong evidence to support the efficacy of scalp cooling.

Limitations: The difference of the Japanese head shape is expected to have influenced the efficacy of SC in the study. The Japanese head is more brachycephalic than that of Caucasians, yet the cap used was originally designed for Caucasian head shapes. Achieving a good cap fit required tightening the cap strap to provide adequate pressure, which may have resulted in increased hair loss in the patients as proper cap fitting is crucial for successful SC. A new cap better suited to a Japanese head shape has recently been developed, which is expected to be more effective than the current cap. In addition to this, a limitation of the study was the small sample size.

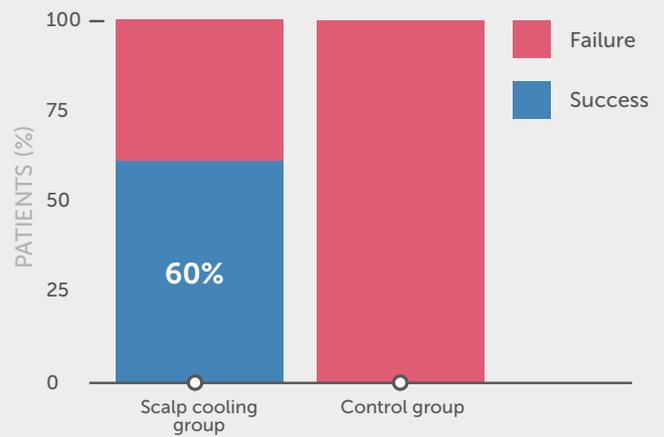
SC success rate by two assessors combined

FIG 1.



SC success rate determined by assessors independently

FIG 2.



Drug regimen-specific hair recovery following completion of chemotherapy

FIG 3.

A. AC (doxorubicin + cylophosphamide)



B. AC (doxorubicin + cylophosphamide)



Randomised controlled trial of scalp cooling for the prevention of chemotherapy induced alopecia.

(Bajpai et al., 2020)

56%

Study shows a 56.3% success rate and more rapid hair regrowth with anthracycline and taxane-based chemotherapy in Indian breast cancer patients.

Methods:

An open label randomised single centre study with 51 female Indian breast cancer patients was used to evaluate the effect of the Paxman scalp cooling device on preventing CIA among women undergoing (neo) adjuvant chemotherapy (CT) containing both anthracyclines and taxanes. Subjects were stratified by the sequence of CT (A or T first) and randomised to scalp cooling (SC) or no scalp cooling (control) arm in a 2:1 ratio. SC was initiated 30 min prior to each treatment cycle, with scalp temperature maintained throughout infusion and for 90 min afterwards.

The primary end point (PEP) was successful hair preservation (HP) assessed clinically and by review of 5 photographs, using the CTCAE version 4.0 scale for alopecia (grade 0 = no hair loss, grade 1 = < 50% hair loss, not requiring a wig) after 4 cycles or 12 weeks of CT. Success was defined as grade 0 and 1 alopecia, and failure as grade 2 alopecia (>50% hair loss, requiring the use of a wig). Participant withdrawals after completion of one cycle of CT were deemed treatment failures. The secondary end point (SEP) comprised a hair regrowth (HR) assessment at 6 and 12 weeks (defined as attainment of grade 0/1 alopecia post completion of all CT). For further validation, independent observers from outside the study, and the subject themselves, also assessed hair loss and regrowth.

Other SEP were device related adverse events (AE) determined by patient reported symptoms and by scalp examination and tolerance to scalp cooling.

Results:

Results: 51 patients were randomised to SC (34) or control (17) in a 2:1 ratio. Twenty-five (49%) patients received A followed by T and the two arms were balanced with respect to this factor. Hair preservation rate was 56.3% with scalp cooling compared to 0% for non-cooling (control) fig 1A.

Hair regrowth at 6 weeks post chemotherapy was also higher for scalp cooling at 89% compared to 12% for control and at 12 weeks 100% of the cooling group had hair regrowth compared to 59% for control (fig 1B).

For SC patients 55% self-reported hair preservation at the end of CT compared to 18% of the control. Six weeks after treatment ended this reduced to 79% for SC and 47% for control.

Tolerability and safety: Overall, the SC device was well tolerated with no serious adverse events, and most participants perceived it as reasonably comfortable based on a comfort scale and verbal questioning. (table 1). No patient had developed scalp metastases after a median follow-up of 17.1 [inter quartile range (IQR) 13.3-21.8] months.

Limitations: The study had a relatively small sample size and the primary end point was successful hair preservation after 4 cycles of CT, which could be higher than the efficacy at the end of all the cycles. However, majority had attained grade 2 alopecia after 1-2 cycles of CT.

Table 1. Overall assessment of patients' comfort on Scalp Cooling

Sr. No.	How comfortable were you in general throughout the scalp-cooling period?	Number (%) of Patients (n=33)*
1	Very comfortable	9(27)
2	Reasonably comfortable	11(34)
3	Comfortable	9(27)
4	Uncomfortable	4(12)
5	Very uncomfortable	0

* n=33= all the patients started on scalp cooling

Drug regimen-specific hair recovery following completion of chemotherapy **FIG 1.**



A: Comparison of CIA at primary end point for scalp cooling with the Paxman Cooler System versus control.

B: Hair Regrowth Rate at Primary End Point of 6 and 12 weeks post chemotherapy after scalp cooling with the Paxman Cooler System versus control.

Scalp cooling for hair loss prevention in female Japanese breast cancer patients receiving (neo) adjuvant.

(Ohsumi et al 2020)

54%

Study shows a 54% success rate with taxane and/or anthracycline based chemotherapy in Japanese breast cancer patients.

Methods:

A prospective observational study with female Japanese breast cancer patients evaluated the effect of the Paxman scalp cooling device in preventing CIA among women undergoing SC during taxane and/or anthracycline-based chemotherapy.

The severity of hair loss was assessed by two investigators, a physician and a nurse, the grade of alopecia was judged by looking at photographs and using the WHO classification while blind to the level of scalp cooling. The primary outcomes were the rates of patients with Grade 3 alopecia (defined as hair loss of > 50%) and the rates of patients who used a wig or hat to conceal their hair loss 1 month after the last infusion of chemotherapy. The subjects were also asked to answer a questionnaire rating possible side effects on a 4-point Likert scale as none, mild, moderate, severe, after each session.

Type of Chemotherapy: anthracycline and/or taxanebased chemotherapy.

Patients:

The study included 122 Japanese female breast cancer patients 79 used scalp cooling throughout the course of treatment 43 discontinued early of these 28 stopped by day 10 of the first cycle the point when payment was required. Of the 122 patients 84 (69%) received docetaxel and cyclophosphamide (TC) and 34 (28%) an anthracycline and cyclophosphamide (AC or EC) followed by taxane (Table 1).

Method of scalp cooling: Paxman Scalp Cooler (Orbis) 30 min prior to, during and 90 min after each chemotherapy infusion. SC was free for 1st cycle after which a charge of about US\$ 1130 was incurred. At this point and before hair loss occurs 28 patients discontinued SC and this group was used as the control.

Results:

Of the 79 patients who used the Paxman scalp cooling system throughout the chemotherapy, 36 patients (45.6%) experienced Grade 3 alopecia 1 month after the last infusion of chemotherapy. In contrast of the 28 patients who decided to discontinue the cooling by Day 10 of the first cycle of chemotherapy (when payment was required) 25 (89.3%) experienced Grade 3 alopecia this group was used to exclude the patients who discontinued SC because of a lower effect on alopecia prevention than they expected because it is before the point when hair loss normally occurs (Fig. 1).

Figure 1 Grades of hair loss 1 month after the last infusion of chemotherapy in the evaluable patients who completed the chemotherapy. Comparison between the patients who completed the scalp cooling for the entire cycles (n=79) and those who discontinued it by Day 10 of the first cycle (n=28)

Comparison of chemotherapy regimes: For those that completed the chemotherapy and SC the rate of Grade 3 hair loss after TC was 55.4% (n=56) significantly lower than that after AC or EC followed by taxane 19.0% (n=21) (Fig. 2). There was no difference in the completion of cooling in between the 2 regimes.

Figure 2 Grades of hair loss 1 month after the last infusion of chemotherapy in the evaluable patients who completed both chemotherapy and the scalp cooling throughout the chemotherapy in TC x 4 (n=56) and AC or EC x 4 followed by taxane x 4 (n=21) groups.

In the whole study group all but one answered the question regarding head covering of these 3 were "not at all", 13, "sometimes" and 105, "almost always". It is thought that the high level of head covering was likely to be due to a cultural sensitivity which results in even a little hair loss being covered.

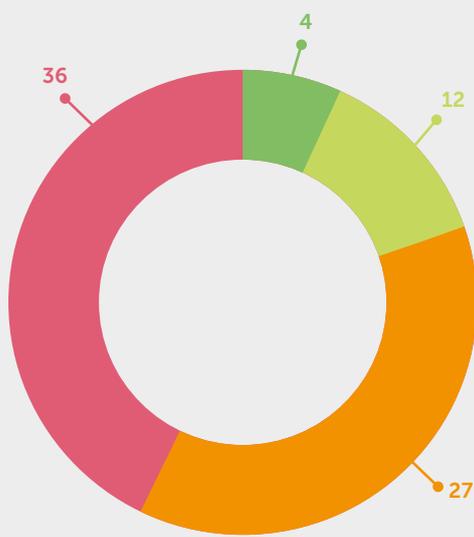
Tolerability: Most patients complained of some headaches, bad mood, fatigue, and chills (figure 3), but these symptoms were relatively mild, except for chills, and self-limited. Fifty-four patients had pain of the jaw, mainly due to the strap around the jaw which was used to make the cooling cap fit the scalp more tightly.

Limitations: The trial involved a cohort without patient randomisation and studied taxane based chemotherapy regimens known to cause alopecia in women with breast cancer. Hair loss was graded by medical professionals (blinded to the treatment use) but this removed the patient's own assessment. A relatively large proportion (43) of the participants discontinued the use of SC 28 of these did so by Day 10 of the 1st cycle, before a charge was incurred and this group was used as the control and thus this might introduce some bias. However, it was thought that most made this decision for financial reasons rather than due to efficacy, since this is before hair loss is known to occur.

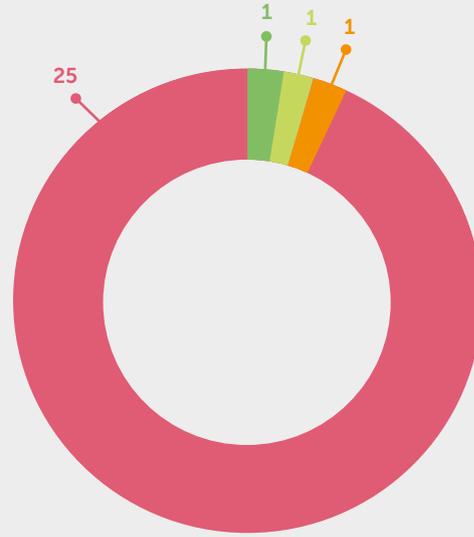
Conclusion:

Scalp cooling mitigates CIA in (neo)adjuvant chemotherapy for Japanese breast cancer patients with a success rate comparable to that in Caucasian patients.

FIG 1.

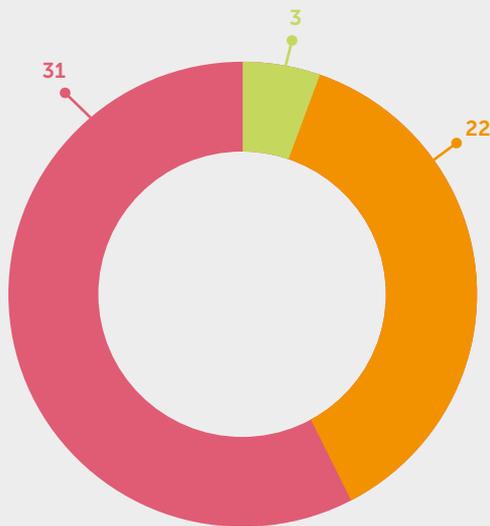


Completed (n = 79)

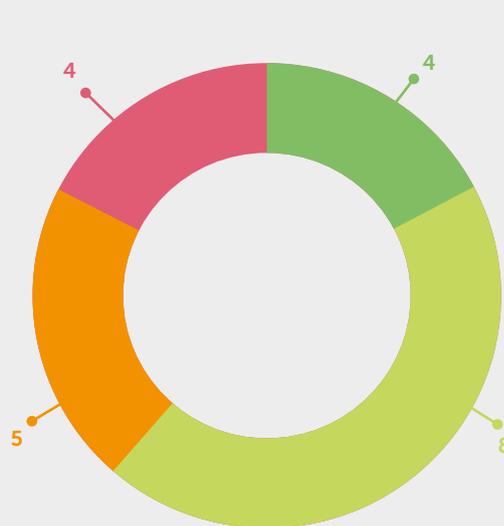


Discontinued (n = 28)

P < 0.001 Comparison of the G3 rates

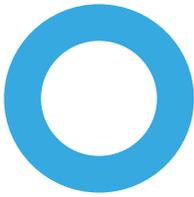


TC x 4 (n = 56)



AC or EC x 4 followed by taxane x4 (n = 21)





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Glossary of abbreviations

FEC: 5-fluorouracil, epirubicin and cyclophosphamide

FAC: 5-fluorouracil, Adriamycin and cyclophosphamide

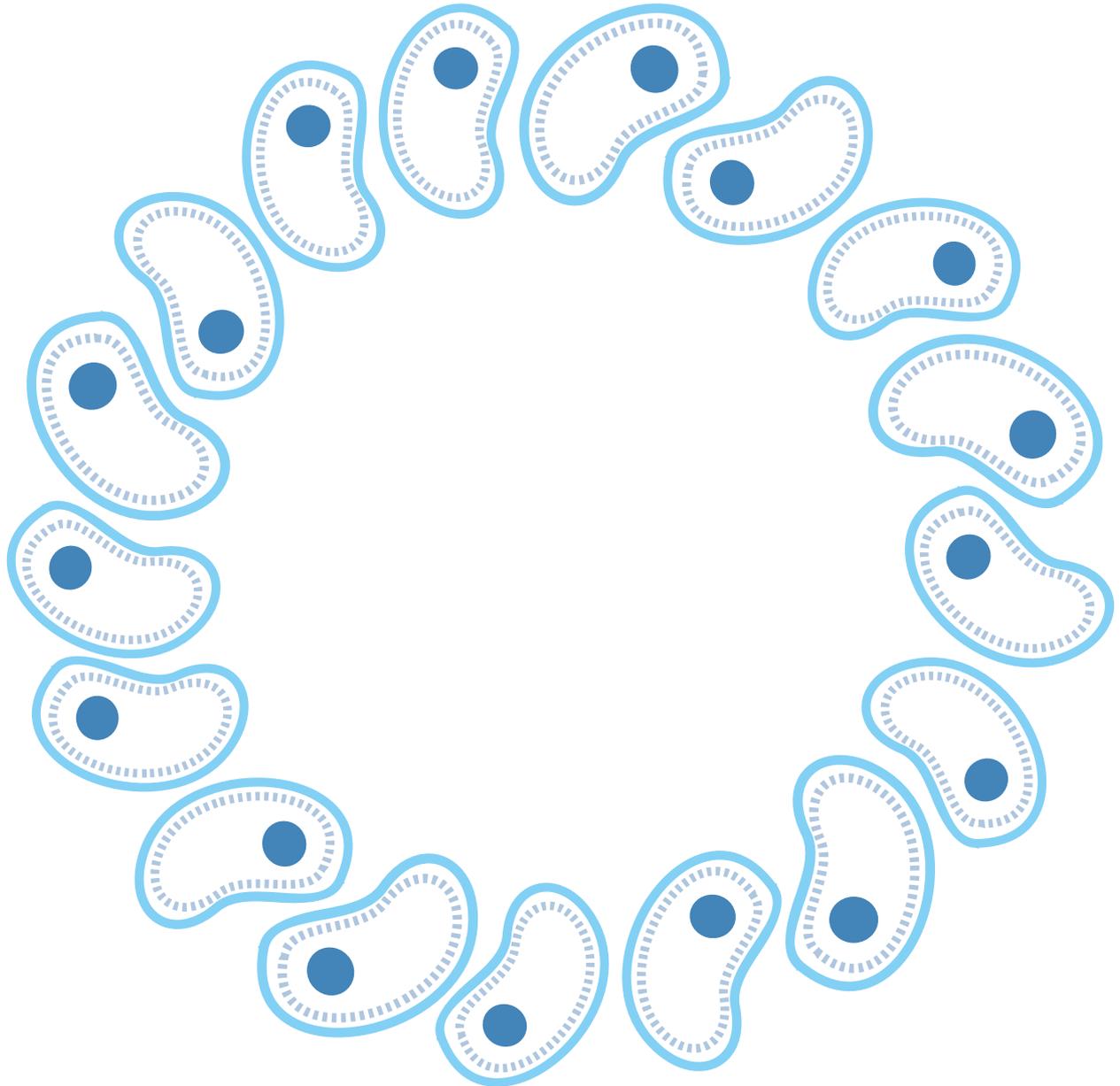
CMF: Cyclophosphamide, methotrexate and 5-fluorouracil

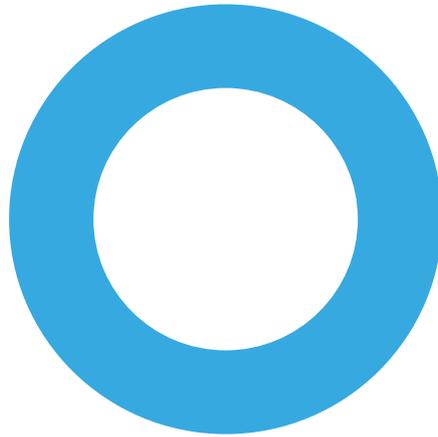
TAC: Docetaxel, doxorubicin and cyclophosphamide

AC: Doxorubicin, Endoxan4

CIA: Chemotherapy-Induced Alopecia.

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