Clinical aspects of scalp cooling in chemotherapy induced alopecia

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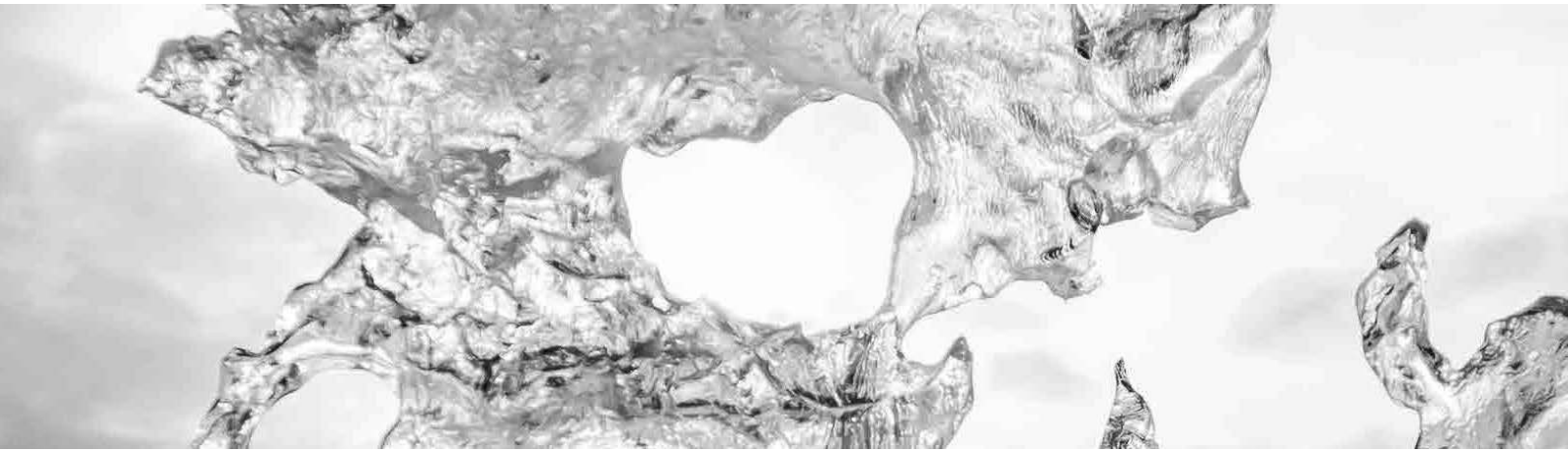
Chapter 6



Patient-reported outcome assessment and objective evaluation of chemotherapy-induced alopecia

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ABSTRACT

Purpose: Alopecia is one of the most distressing side effects of chemotherapy. Evaluating and comparing the efficacy of potential therapies to prevent chemotherapy-induced alopecia (CIA) has been complicated by the lack of a standardized measurement for hair loss. In this study we investigated the correlation between patient-reported outcome assessments and quantitative measurement with the hair check to assess CIA in clinical practice.

Method: Scalp cooling efficacy was evaluated by patients by World Health Organisation (WHO) of CIA, Visual Analogue Scale (VAS) and wig use. The Hair Check was used to determine the amount of hair (in mm^2) per unit of scalp skin area (in cm^2) (Hair Mass Index, HMI). CIA was also evaluated by doctors, nurses and hairdressers.

Results: Baseline HMI was not predictive for hair loss. HMI declined throughout all chemotherapy cycles, which was not reflected by patient-reported measures. HMI correlated with patient-reported hair quantity before the start of the therapy, but not with WHO and/or VAS during therapy. Patient's opinion correlated moderately with the opinion of doctors and nurses (ρ=0.50-0.56 respectively), but strongly with hair dressers (ρ=0.70).

Conclusions: The Hair check is suitable to quantify the amount of hair loss and could complement research on refining outcome of scalp cooling, but the patient's opinion should be considered as the best method to assess hair loss in clinical practice.

INTRODUCTION

Alopecia is one of the most distressing side effects of chemotherapy and may have an impact on treatment decisions. (Batchelor, 2001, Rosman, 2004, Hesketh et al., 2004, Mols et al., 2009) Scalp cooling is a treatment option to prevent chemotherapy-induced alopecia (CIA)[1]. (Nangia et al., 2017, Rugo et al., 2017) It is assumed that scalp cooling works by inducing vasoconstriction and reduction of metabolism. Vasoconstriction leads to reduced blood flow to the hair follicles during the time period of peak plasma concentrations of the relevant chemotherapeutic agent. In addition, reduced metabolic activity could make hair follicles less vulnerable to the damage of cytotoxic agents. Both randomized and nonrandomized studies proof that scalp cooling can prevent CIA. (Breed et al., 2011, Grevelman and Breed, 2005, Rugo et al., 2017, Nangia et al., 2017) However, comparing or pooling data on the efficacy of scalp cooling between studies has been complicated by the lack of a standardized methodology to evaluate hair loss. (Van Neste, 1999, Van Neste, 2002, Chamberlain and Dawber, 2003, van den Hurk et al., 2015)

Methods to measure the severity of chemotherapy-induced hair loss can be categorised as invasive, semi-invasive and non-invasive. Invasive and semi-invasive measurements like scalp skin-biopsies and hair root analysis are objective, but can be unpleasant for patients and are costly and time consuming. (Chamberlain and Dawber, 2003, Van Neste, 2002, Van Neste, 1999, Canfield, 1996, Donati et al., 2011) Non-invasive techniques like photography or counting shed hairs could also be useful in assessing the severity of hair loss. (Chamberlain and Dawber, 2003, Van Neste, 2002, Donati et al., 2011, Massey, 2004, Peck et al., 2000, Ridderheim et al., 2003) Photography may be used to compare the difference in visible hair loss during treatment, but it is subjective and does not generate a reliable estimation for hair loss on a localized area of the scalp. Hair counts do generate a quantitative value, although they also do not provide information about hair loss on a localized area of the scalp. (Cohen, 2008) In scalp cooling studies, several widely accepted subjective scales have been used to assess hair loss, such as the World Health Organisation (WHO) classification of chemotherapy-induced alopecia (World Health Organisation, 1979), the Common Terminology Criteria for Adverse Events (CTC-AE) (U.S.Department of Health and Human Services, 2009) or Visual Analogue Scale (VAS) (Ridderheim et al., 2003) In addition, other measurements like Dean's alopecia scale (grade 1: <25% hair loss; grade 2: 25%-50% hair loss; grade 3: 50%-75% hair loss, grade 4: >75% hair loss), various Likert scales (rating scales) and pictorial assessments have been described in literature on scalp cooling. (van den Hurk et al., 2015) For study purposes, there is a need for an operator- and patient friendly, inexpensive, and validated method for measuring hair quantity. Until recently

[1] CIA chemotherapy-induced alopecia

there was no reliable, simple method available to measure hair quantity in an objective way, but in recent years the Hair Check method has become available. (Cohen, 2008) The Hair Check is a mechanical device that compresses a bundle of hair in a disposable cartridge from a delineated area of the scalp and measures its cross-sectional area. In this way, the amount of hair (in mm^2) per unit of scalp skin area (in cm^2) (Hair Mass Index, HMI)[2] can be defined. (Hendriks et al., 2012) In a study to test the clinical utility of the Hair Check in healthy volunteers it was concluded that measurements were simple to perform, and data showed high reproducibility. (Hendriks et al., 2012) We therefore decided to investigate the correlation between patient reported outcome assessments and the quantitative method of HMI measurement to assess the amount of hair loss in patients treated with chemotherapy. In addition, we studied the correlation between the opinion of patients, doctors, nurses and hairdressers assessed with subjective methods.

PATIENTS AND METHODS

Patients

The study enrolled patients with primary invasive breast cancer without distant metastasis planned for treatment with three to six cycles of combination chemotherapy at 3-weekly intervals with FEC (5-fluorouracil, epirubicin, cyclophosphamide) or AC (adriamycin, cyclophosphamide). Subsequent chemotherapy cycles consisting of docetaxel monotherapy were allowed after 3 FEC cycles. Patients were excluded if they lacked basic proficiency in Dutch, if they were unable to understand the patient information brochure or if they suffered from cold sensitivity, cold agglutinin disease, cryoglobulinemia, cryofibrinogenemia or cold posttraumatic dystrophy.

Study design

We conducted an explorative prospective single-centre study between August 2010 and January 2014 at the department of Internal Medicine of the Medical Centre Alkmaar, the Netherlands. At baseline, patient characteristics were collected. Before the start of the chemotherapy, patients were asked to rate their hair quantity (much, moderate, little hair).

Objective hair quantity was measured with a Hair Check before each chemotherapy cycle (table 1). The mechanical device compresses a bundle of hair in a disposable cartridge from a delineated area of the scalp and measures its cross-sectional area. HMI incorporates both density and diameter and was measured at both temporal sides. (Cohen, 2008) The validity of the device was tested using bundles of hair and surgical silk fibres. It showed a high degree of precision and it was concluded that the device could be used as a reliable substitute for the methods that are presently used to

[2] HMI Hair Mass Index

measure hair loss.(Cohen, 2008) Hendriks et al. designed a study to test the clinical utility and reproducibility of the Hair Check. Data in this study showed high reproducibility. For intra-observer reproducibility, the mean difference was .2 (95% confidence interval (CI)= -4.7-5.1, correlation coefficient (*r*) =.99). For interobserver reproducibility, the mean difference was -.4, 95% CI = -8.0-7.2, *r*=.97. (Hendriks et al., 2012) To define the measuring location, a location strip was used and marked using a four-legged marking template moistened with red ink (figure 1). The hair bundle within this marked area was measured using the Hair Check.

Table 1. Methods to evaluate the amount of hair loss after scalp cooling to prevent CIA

Grading scale	Subjective/ objective	Scale	Measuring timepoints
HMI* 100 much hair 1 little hair	Objective	Scale:Continuous	Cycle 1-6
VAS** 0 → 10 No hair loss total hair loss	Subjective	Ordinal: 0-10	Cycle 2-6
WHO classification [19] 0 No change 1 minimal hair loss 2 moderate, patchy alopecia 3 complete alopecia, but reversible	Subjective	Ordinal: 0-3	Cycle 2-6
Head covering Yes/ no	Subjective	Nominal: Yes/ no	Cycle 2-6

*HMI: Hair Mass Index

**VAS: Visual Analogue Scale

Figure 1. The use of the hair check

Before cycle 2, patients evaluated the severity of alopecia on the 4-point scale (range 0-3) for alopecia of the World Health Organisation (WHO) (World Health Organisation, 1979) and by using a VAS for hair loss (range 0-10, 0 = 'No hair loss', 10 = 'Total hair loss'). The success of scalp cooling was defined in terms of the patient's self-determined need to wear a wig or other head covering to mask visible hair loss after chemotherapy treatment (table 1). To assess hair loss by photography, a protocol was designed to standardise camera settings to depict various degrees of hair loss. Five digital images at standard views from frontal, vertex, occipital and both temporal sides were made before start of chemotherapy and before the 4th and 6th or last chemotherapy cycle. Images were kept in the medical records. Doctors, nurses and hairdressers were asked to rate the visible hair loss as depicted on pictures of the patients according to the WHO and VAS scores. They assessed the same images twice. Mean scores of the two assessments were used and the mean scores of the doctors, nurses and hair dressers were calculated. End points were the mean VAS scores of cycle 4 and cycle 6.

Tolerance of scalp cooling was measured during all visits by a Visual Analogue Scale (VAS) of 0-10, in which 0 represented 'Not tolerable' and 10 meant 'Very well tolerable'. Patients were considered evaluable for hair preservation if they were treated with at least three cycles of chemotherapy or if they discontinued scalp cooling due to severe hair loss.

The study was approved by an independent ethics committee and institution review board. All procedures were conducted in accordance with the 1964 Helsinki declaration and its later amendments. Specialised oncology nurses informed patients about the study. Written informed consent was obtained from all individual participants included in the study.

Scalp cooling

All patients used the one-person cooling machine (PSC-1) of Paxman. The cap was applied according to the instructions for use in the nursing protocol. The temperature of the coolant in the refrigeration tank was -10°C. This temperature is a standard set up performed by the manufacturer. The pre-cooling time was 30 minutes before the start of

the chemotherapy infusion. The cool cap remained on the scalp during the infusion period, being 60 minutes as a standard, and during 90 minutes afterwards. Scalp cooling was applied during all planned cycles of chemotherapy, unless the patient decided to stop the cooling procedure based on hair loss, side-effects or for other reasons.

Statistical analysis

All tests of significance were two-sided, and differences were considered statistically significant when $p<0.05$. All tests were performed using SPSS software (version 20.0) for Windows XP. Data was collected using standard forms, which were compiled into a SPSS database. The analyses were carried out on all evaluable patients. Descriptive statistics were performed to describe the socio-demographic and clinical-related characteristics of the study sample. Spearman's rho rank correlation was used for measuring the association between the objective and subjective measurements and between the patients, doctors, nurses and hairdressers opinion.

RESULTS

Patient and treatment characteristics

Sixty-two female Caucasian patients with breast cancer were included in this study. Patient characteristics are listed in table 2. The median age of the patients was 60 years. All patients were treated conform the study protocol, for a median of three cycles of chemotherapy and scalp cooling (range 1-6). The median duration of scalp cooling was 195 minutes per cycle. All patients were evaluable for hair preservation and tolerance. At the time of data cut-off (January 1, 2016), the median follow-up of patients was 51 months.

Table 2. Patient characteristics (n=62)

	N (%)	No head covering *N* (%)	Head covering *N* (%)
Patients included	62	13 (21%)	49 (79%)
Median age, years (range)	60 (32-74)		
Epirubicin	50 (81%)	8 (16%)	42 (84%)
6x F500/E100/C500	28 (45%)	5 (18%)	23 (82%)
3x F500/E100/C500 followed by 3xT100	22 (36%)		
Overall 3xFEC, 3xT		3 (14%)	19 (86%)
Result after 3xFEC		8 (36%)	14 (64%)
Adriamycin	12 (19%)	5 (42%)	7 (58%)
4x A60/C600	10 (16%)	4 (40%)	6 (60%)
6x A60/C600dd	2 (3%)	1 (50%)	1 (50%)
Median number of cycles with scalp cooling (range)	3 (1-6)		

F: 5-fluorouracil; E: Epirubicin; C: Cyclofosfamide; A: Adriamycin; T: Docetaxel

dd: every two weeks

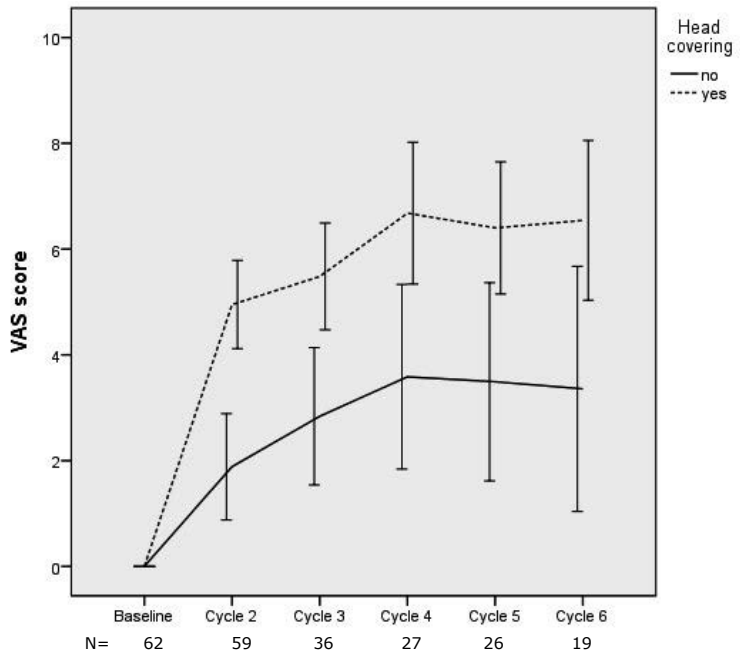
Baseline hair quantity

Forty-one percent of the patients reported their hair quantity prior to chemotherapy as moderate (scale: much, moderate, little).

Patient-reported success of scalp cooling

- Head covering yes/no
  Thirteen out of 62 patients (21%) did not wear a wig or head cover at the end of anthracycline chemotherapy, despite some slight hair loss.
- VAS
  Median VAS scores for hair loss increased from 4.1 (range 0-10) after the 1st cycle to 5.8 (range 0-10) at the 6th cycle. Patients who did not need a head covering had a significantly lower median VAS score for hair loss (VAS: 2.3 versus 5.8; $p<0.0001$) (Figure 2).

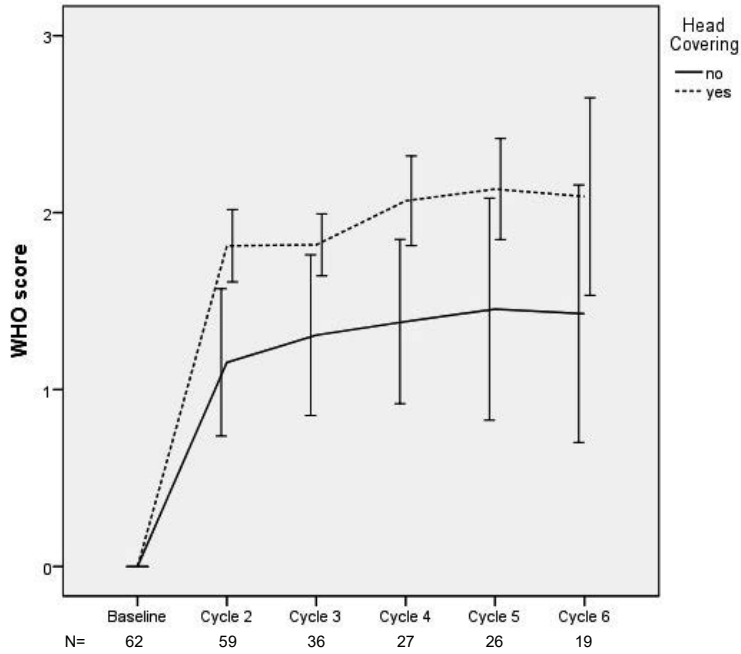
Figure 2. Visual Analogue Scale (VAS) scores for patients with and without head covering during 6 cycles chemotherapy (P<0,0001)



- WHO

  Median WHO scores for hair loss were 2 (range 0-3) after cycle 1 and at cycle 6. Overall, the median WHO score in patients who did not need a head covering was significantly lower than in patients who needed a head covering (WHO: 1 versus 2; p<0.0001) (figure 3). Hair loss assessed with VAS and WHO demonstrated a strong correlation (ρ= 0.7).

Figure 3. World Health Organisation (WHO) scores for patients with and without head covering during 6 cycles chemotherapy (P<0,0001)



HMI

Hair Check measurements at the left and right side of the head did not show significant differences, except for cycle 4. Since there is no rationale for these differences, they were reported as the mean of the two temporal measures. The mean baseline HMI was 64 (range 24-100) and decreased to 25 (range 6-53) in the 17 patients who were evaluable after 6 cycles (table 3). HMI decreased throughout all cycles of chemotherapy, but the highest decrease was seen after the second cycle (figure 4). Baseline HMI correlated with patient-reported baseline hair quantity, but was not predictive for hair loss (HMI no head covering 61; HMI head covering 64; p=0.7). HMI did not correlate with VAS and WHO during therapy (HMI-WHO: ρ= -0.4; HMI-VAS: ρ= -0.4). Patients who did not need a head covering had a higher median HMI score (HMI: 51 versus 43; p=0.034) (Figure 5).

Table 3. Mean HMI before each chemotherapy cycle

Cycle of chemotherapy	No. of patients	Mean HMI	SEM	Range of HMI
1	59	64	2.5	24-100
2	41	54	3.2	13-95
3	28	44	4.0	15-84
4	26	39	3.9	9-73
5	25	35	4.0	10-80
6	17	25	3.7	6-53

Figure 4 Hair Mass Index (HMI) during six cycles chemotherapy

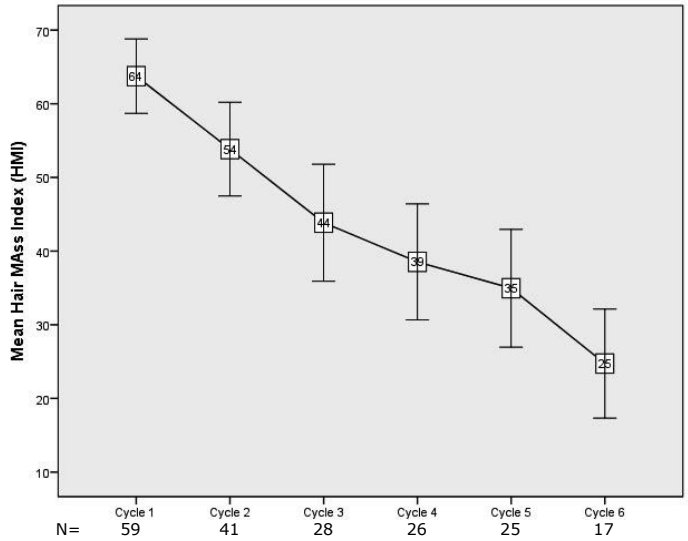
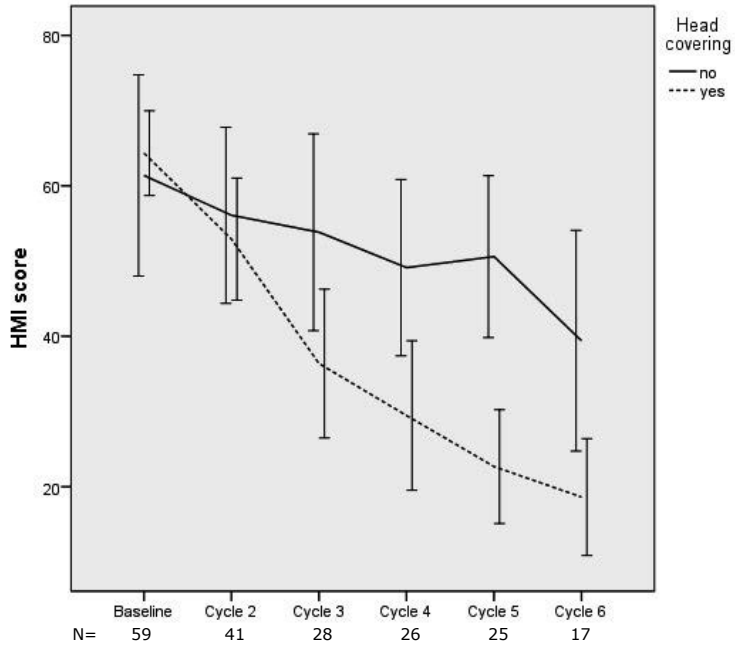


Figure 5. Hair Mass Index (HMI) scores for patients with and without head covering during 6 cycles chemotherapy (P=0,034)



Healthcare professional evaluation of hair loss-photography

There was a strong correlation of the VAS scores of hair loss, as measured by doctors and nurses (ρ=0.84). The correlation between the opinion of health care professionals (doctors and nurses) and the opinion of the patients was moderate (VAS: ρ=0.50-0.56 respectively). However, the opinion of the hair dressers matched strongly with the opinion of the patients with respect to hair loss measured with VAS (ρ=0.70) (table 4).

Table 4. The association between the VAS-scores of patients and professionals

	Nurse	Doctor	Hair dresser	Patient
Nurse	-	0.84**	0.83**	0.56**
Doctor	-	-	0.80**	0.50**
Hair dresser	-	-	-	0.70**
Patient	-	-	-	-

** = sig. at 0.01 level

Tolerance and safety analysis

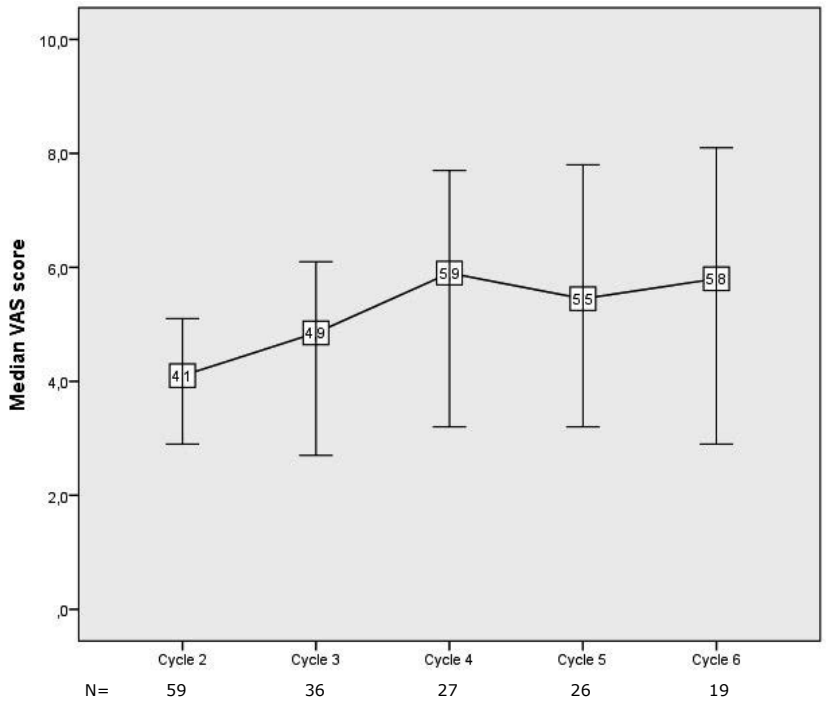
Scalp cooling was very well tolerated. The VAS score for the tolerance of scalp cooling was performed over 192 cooling sessions, resulting in a mean score of 8 (SD: 1.9). Only one patient stopped scalp cooling because of intolerance after cycle 4. No scalp metastases were reported during follow up.

DISCUSSION

This study investigated the value of the Hair Check to measure chemotherapy-induced hair loss in patients treated with anthracycline-containing combination chemotherapy. Initial hair mass as measured by the Hair Check correlated with patient-reported hair quantity before the start of the chemotherapy, but was not predictive for the severity of hair loss during scalp cooling. Thus, it seems that the efficacy of scalp cooling in preventing CIA is independent of having either thin or thick hair. This adds to our knowledge that the efficacy of scalp cooling mainly depends on the type and dose of chemotherapy, and the degree and duration of scalp cooling. (Komen et al., 2013) Unfortunately, we do not have data on the Hair Check during scalp cooling in Asian or Afro-hair patients.

It is noteworthy that, according to the Hair Check, hair loss continued throughout six chemotherapy cycles, although patients themselves did not report any increase in hair loss (as measured with VAS for hair loss) after cycle 4 (figure 6). Obviously, HMI is more sensitive for detecting subtle changes in hair loss than subjective measurements. Therefore, to improve the efficacy of scalp cooling, efforts should be made to increase its efficacy throughout the complete time span in which all cycles of chemotherapy are administered. Hair mass as measured by the Hair Check did not correlate with patient-reported outcome assessments such as WHO and VAS score. Therefore, it is not useful as a clinically relevant endpoint for hair loss, while it is time consuming in daily practice as well (about 15 minutes per measurement).

Figure 6 Visual Analogue Scale (VAS) score during six cycles chemotherapy



The opinions of hair loss of health care professionals correlated only moderately with those of patients, but the opinion of hair dressers was more in line with the patients. Apparently, due to their professional experience hairdressers are better capable to estimate hair loss than healthcare professionals are. The weak correlation between patients and health care professionals demonstrates that the patients' opinion of hair loss should be considered as the best subjective method to assess the efficacy of scalp cooling. In some clinical studies on CIA hair loss is measured by clinicians (Nangia et al., 2017) or nurses (Lemenager et al., 1997, Massey, 2004), but our study confirms the findings of Mulders et al. (Mulders et al., 2008) that healthcare professionals underestimate the severity of hair loss.

This study has some limitations. Firstly, the sample size was limited. The study may have been underpowered to detect differences between the methods of evaluation. Secondly, we did not prescribe a standardized hair care at the day of measuring HMI. Possibly, the use of styling products could have slightly influenced HMI, but before standardized hair care might be prescribed, the exact influence has to be examined. Thirdly, we delineated the measured location by using a location strip. The use of this strip can cause slight deviations in retrieving the exact measuring location every cycle. However, Vleut et al. (Vleut et al., 2013) showed that a slight deviation of the measurement area caused no significant deviations in HMI.

In a large registry study on scalp cooling 33% and 39% of patients treated with FEC or AC chemotherapy, respectively, did not need a head covering. (van den Hurk et al., 2012) In this study, only 21% of patients was successfully treated with scalp cooling to prevent CIA. The low efficacy in the present study might be explained by the fact that patients decided to stop scalp cooling because they were more aware of the continuous hair loss during chemotherapy as measured by the Hair Check and subjective registries.

We measured HMI at both sides of the head, because the gradation of hair loss in a balding individual was found to be much higher along the sagittal axis than the coronal axis. (Cohen, 2008) According to our results, HMI measurements at the left and right side of the head did not show significant differences; therefore we recommend HMI measurement at one side for future research. However, in daily practice we advise to preferably use a generally accepted and practical subjective scale for hair loss such as WHO or VAS.

Although it was confirmed that WHO and VAS correlated strongly ($\rho = 0.7$), the latter is more sensitive for small changes in hair loss and therefore more valuable to use when comparing different groups of patients. In addition, to evaluate hair loss in clinical practice, the use of a wig or head cover can be considered as a parameter for patient satisfaction. (Breed et al., 2011)

CONCLUSIONS

Initial hair mass index (HMI) as measured by the Hair Check correlated with patient-reported hair quantity before the start of the chemotherapy, but was not predictive for the severity of hair loss during scalp cooling. It seems that the efficacy of scalp cooling in preventing CIA is independent of having either thin or thick hair. According to the Hair Check, hair loss continued during all chemotherapy cycles. Therefore, to improve the efficacy of scalp cooling, efforts should be made to increase its efficacy throughout the complete time span in which all cycles of chemotherapy are administered. The weak correlation between patients and health care professionals demonstrates that the patients' opinion of hair loss should be considered as the best method to assess the efficacy of scalp cooling.

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