Journal of Oncology Research and Therapy
Schaffrin-Nabe D, et al. Oncol Res Ther 10: 10292.
www.doi.org/10.29011/2574-710X.10292
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Research Article

Pigmentary-Hair-Follicle Unit Under Innovative Pathologic Investigation - Is There a Potential to Improve Outcome of Sensor-Controlled Scalp-Cooling?

Doerthe Schaffrin-Nabe[1*], Anke Josten-Nabe[1], Adrian Heinze[2], Andrea Tannapfel[3], Merle Schaffrin[1], Rudolf Voigtmann[1]

[1]Praxis für Hämatologie und Onkologie, Universitätsstr. 110e, 44799 Bochum, Germany.

[2]Noack Statistik GmbH, Bornheimer Straße 127, 53119 Bonn, Germany.

[3]Ruhr-Universität Bochum, Pathologie, Bürkle de la Camp-Platz 1, 44789 Bochum, Germany.

***Corresponding author:** Schaffrin-Nabe D, Praxis für Hämatologie und Onkologie, Universitätsstr. 110e, 44799 Bochum, Germany.

Citation: Schaffrin-Nabe D, Josten-Nabe A, Heinze A, Tannapfel A, Schaffrin M, et al. (2025) Pigmentary-hair-follicle unit under innovative pathologic investigation - is there a potential to improve outcome of sensor-controlled scalp-cooling?. J Oncol Res Ther 10: 10292. DOI: 10.29011/2574-710X.10292.

Received Date: 27 June, 2025; **Accepted:** 08 July, 2025; **Published Date:** 11 July, 2025.

Abstract

Introduction: Scalp cooling is an established method to reduce chemotherapy-induced alopecia (CIA), yet its efficacy remains variable. Melanosomes, as part of the follicular pigmentary unit, may serve as surrogate markers for hair follicle integrity and resistance to cytotoxic damage. This study investigates structural and ultrastructural hair parameters, focusing on melanogenesis, to identify predictors of successful hair preservation. **Methods**: Eighty-one patients with early-stage breast cancer undergoing anthracycline-taxane-based chemotherapy combined with scalp cooling were evaluated. Hair metrics were assessed pre- and post-treatment using cross-section trichometry, furthermore light microscopy, and ultrastructural analysis. Evaluated parameters encompassed morphological and ultrastructural features – including hair shaft and bulb diameter, anagen rate, shaft surface integrity, melanosome quantity and type- alongside broader trichological characteristics such as hair length, texture and natural pretreatment colour, as well as general health indicators, e.g. including comorbidities. Key outcomes included hair preservation as post-treatment hair mass index (HMI) and HMI post ≥ 50 as an indicator for avoiding visible hair loss. **Results**: Apparent alopecia was successfully prevented in 53% of patients. Multivariate analysis identified consistent melanosome quantity and reduced shaft surface contamination as key predictors of hair preservation. A greater pre-treatment hair shaft diameter, absence of comorbidities, and avoidance of known alopecia-inducing agents were significantly associated with better outcomes. Conclusion: The effectiveness of scalp cooling in preventing chemotherapy-induced alopecia is critically dependent on the preservation of the structural integrity of the follicular pigmentory unit. Structural and ultrastructural features - such as stable density of melanosomes beside hair shaft integrity - play a critical role in follicular resilience to cytotoxic injury. Enhancing overall hair health and developing strategies to protect hair follicles from chemotherapy-induced damage, particularly oxidative stress through targeted follicular protection, may significantly improve scalp cooling outcomes.

Keywords: Chemotherapy-induced hair loss; Scalp cooling; Disordered melanogenesis; Trichologic parameters; Follicular pigmentaty unit.

Introduction

Chemotherapy-induced alopecia poses a considerable psychological burden for patients impacting the quality of life during and post-treatment [1]. In response to this issue, scalp-cooling techniques have been implemented, proving to be effective in preventing visible hair loss, a benefit that has led to FDA approval.

Notably the efficacy varies among individuals rsising the question of potential influencing or even predictive factors.

Beyond clinical efficacy this trial extends to explore new pathological insights and allows for a nuanced understanding of various factors possibly influencing the efficacy of scalp-cooling. By identifying modifiable efficacy factors, it aims to contribute to the development of enhanced benefit.

The key of successful scalp-cooling is undoubtedly the reduction of cutaneous scalp temperature to below 22° C [2]. It must be noted that further lowering of temperature preclinically did not result in better efficacy in combination with CTX regimes like TAC protocol [41]. Therefore, cooling alone doesn´t appear to be an efficient-enhancing solution [3].

In this context, the improvement of hair health based on integrity of hair follicles and scalp could be considered a promising component.

The hair follicle represents a mini-organ functionally dependent on precisely coordinated interaction of keratinocytes and melanocytes, in part regulated by fibroblasts of the dermal papilla [4]. On a preclinical level,it has been demonstrated that melanogenesis in mouse hair follicles is early and predominantly impaired by cytostatic agents like cyclophosphamide [5]. Consequently, and given the capability to accurately monitor disordered melanogenesis through transmission electron microscopy over the time, the focus of this investigation was assessing of quantity and type of hair pigments, so called melanosomes, as a highly surrogate parameter of optimal hair preservation.

Preserving the pigmentory function of hair follicles and general scalp health may have therapeutic relevance in mitigating hair loss caused by chemotherapy.

Understanding the dynamics of melanogenesis could facilitate the development of targeted interventions aimed at minimizing hair follicle damage and preserving hair integrity during cytostatic treatment.

Study Population

Scalp-cooling was evaluated in 81 patients (79 women and 2 men, with a median age of 56 years) undergoing curative treatment for breast carcinoma. The regimen consisted of 4 cycles of Epirubicin/Cyclophosphamide (EC) (90/600 mg/m² BSA) followed by 12 cycles of Paclitaxel weekly (80 mg/m2, BSA) to exert a comparable cell biologic effect. Due to predictable and uniform severity of alopecia associated with this treatment protocol, a control group without scalp cooling was not included. Patients were excluded from scalp cooling in cases of clinically manifest skull metastases, generalized hematologic malignancies such as leukemia, skull injuries, or the presence of cryoglobulinemia [42].

Objectives: The primary outcomes included hair preservation (measured by Hair Mass Index [HMI]), avoidance of visible hair loss (HMI ≥50), and hair loss as measured by the HMI difference (HMI post – HMI pre-therapeutical) over the course using the Cross Section Trichometer. To account for interindividual differences in baseline hair density, the analysis incorporated relative HMI changes. This allowed a more nuanced assessment of hair preservation efficacy, particularly in patients with pre-existing low hair density, for whom even modest additional loss may lead to disproportionate impact on quality of life. Additional parameters assessed before and after treatment included density (HMI), trichological parameters such as hair shaft and bulb diameter, anagen rate, and shaft surface damage, determined through (ultra-) structural microscopy. Particularly it is focused on characterization of melanosomes and melanosomal density via transmission-electron microscopy. The study included an evaluation of potential factors influencing or even predictive in hair preservation, encompassing general health parameters such as age, internal comorbidities, alopecia inducing medication like antihypertensives, nicotine use, menopausal status and hair treatment.

Individual hair characteristics (colour, length, structure) parameters were additionally evaluated. Neutrophil nadirs serving as indicators of individual hematologic toxicity during cytostatic treatment were also investigated. Further laboratory assessments included evaluation of liver and kidney function, as well as thyroid parameters. In addition, endocrine profiling was performed exclusively in female participants to assess gonadal status based on FSH, LH, and estradiol levels.

.Methodology

Hair density was assessed in the anterior vertex region before and after therapy using the Cross Section Trichometer (Cohen Hair Mass Index Trichometer), a reproducible method for quantitative

scalp hair mass assessment from a 4 cm2 scalp section. The measurement protocol was sufficiently standardized to allow for highly reproducible single-timepoint assessments, provided that the investigator performing the evaluations had received appropriate training. Repeated measurements on individual patients were therefore not necessary, as intraobserver consistency was ensured through standardized methodology. Measurements require a minimum hair length of 2.5 cm, with results displayed as the Hair Mass Index (HMI) value, calculated as mm² of hair per cm² of scalp, multiplied by 100. Normal HMI values range from 75 to 100, with visible alopecia beginning below HMI 50, and complete alopecia indicated by HMI values below 20 [6]. For pre-analytic preparation, approximately 50 hair follicles were epilated from the marked 4 cm² area and placed between two microscope slides with roots exposed.

Light microscopy was used to photograph native hair at 10x and 40x magnifications under a Leica DM 3000 microscope. Bulb diameter (normal: 150-200 µm) and shaft diameter (normal for frontal vertex: 75-85 µm) were measured [7]. The proportion of anagen phase follicles was determined by the onion bulb shape, with catagen phase follicles showing reduced bulb diameter and telogen phase follicles featuring club shaped ends. Criteria for dystrophy included irregularities in the hair shaft, breakage, and distortions.

Transmission electron microscopy (TEM) was employed to analyze the quantity and type of melanosomes in hair shaft slices from 52 patients before and after treatment. Pheomelanosomes, round and granular, are smaller than eumelanosomes, being elliptic and fibrillar. Quantitatively, blond hair has relatively low melanosome content (9.2 ±1.6/100 µm²), while brown and black hair show higher concentrations (66.3 ±14 and 70.5 ±4.78/100 µm², respectively [9]. Hair follicles were fixed in 2.5% glutaraldehyde, dehydrated through multiple steps, and embedded in Epon resin. Ultra-thin sections (50 nm) were prepared and contrasted using uranyl acetate and lead citrate. Imaging was performed at magnifications between 1.5K and 15K.

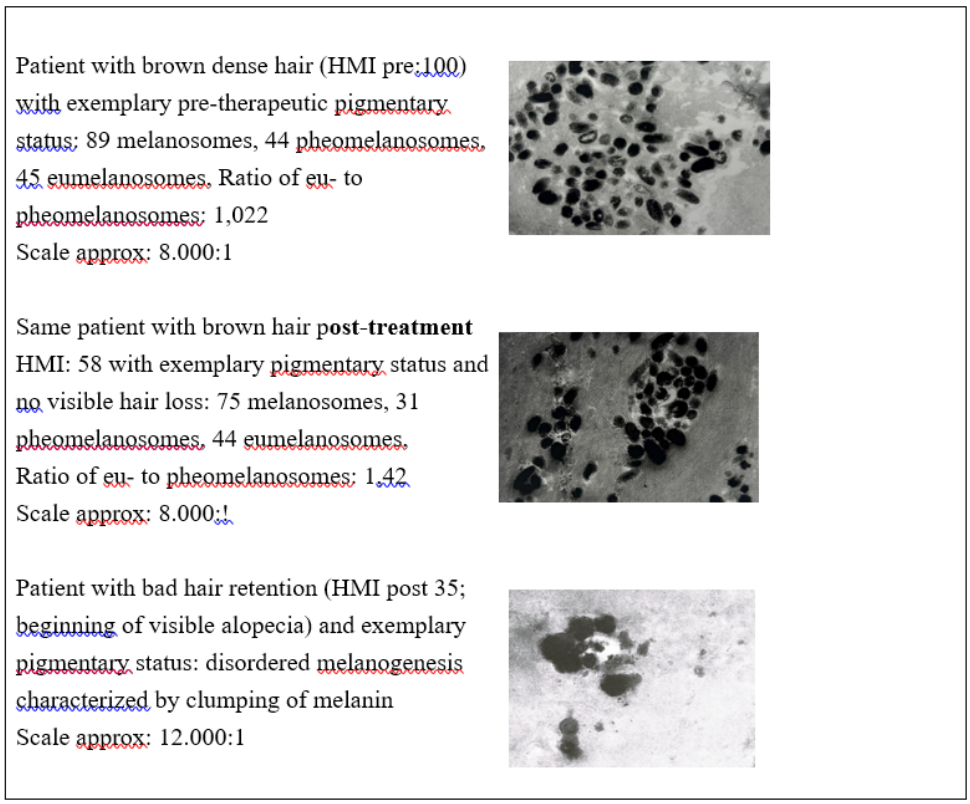

Figure 1: Exemplary TEM photos.

Scanning electron microscopy (SEM) was utilized to assess hair shaft surface damage in native hairs before and after therapy. Using a Zeiss Gemini 982 FESEM at 200-2000x magnification, hairs were sputter-coated with gold and later imaged.

The assessment of the degree of damage to the hair shaft surface is based on criteria established analogously to the Kim's Scale for extrinsically induced hair damage [8].

By analogy, examples of our recruited patients exhibiting different patterns and grades of hair shaft surface damage are presented in the following photographs in figure 2:

Kim scale: Grade 0: Virgin intact hair with regular overlay of the cuticle

Grade 1: Irregular overlay of the cuticle, slight dents without cracks or holes, lift ups of cuticle

Grade 2: Severe lift up of the cuticle with cracks or holes but without exposure of the cortex

Grade 3: Partial exposure of cortex

Grade 4: Complete disappearance of cuticle.

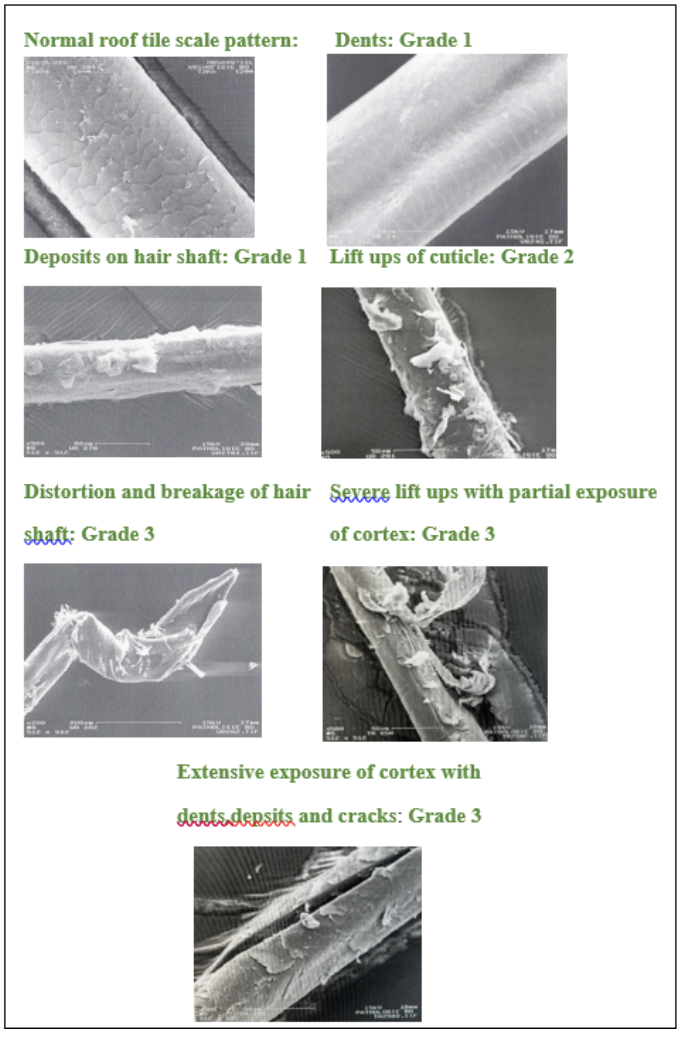

Figure 2: Different patterns and grades of hair shaft surface damage.

Multiple sections of hair shafts from a cohort of 52 patients were scanned to ensure uniformity of observed changes. The focus was on evaluating the degree 0 to 4 of intrinsic damage to the hair shaft surface as a result of the therapeutic intervention.

Results

Objectives – descriptive aspects:

Hair Retention (HMI post) and Avoidance of visible Alopecia (HMI post ≥50): The study evaluated 81 patients with a median pre-treatment HMI-score of 75 (IQR 58-92), which decreased to a median of 51 (IQR 17-58) post-treatment. Following treatment, 53% of patients retained an HMI-score of 50 or higher, indicating no visible hair loss.

Hair Loss During Therapy (HMI difference post-pre): In individuals with low baseline hair density, stabilization of the HMI proved to be of particular clinical relevance, underscoring the importance of relative HMI preservation as a meaningful success criterion. The median reduction in HMI-score from pre- to post-treatment was -27, IQR (-45,-10). For patients with an initial HMI-score below 50, the median change was -20.

Possible influencing or even predictive factors: Factors potentially influencing outcomes comprise general health conditions such as age, comorbidities, alopecia-inducing medications e.g. hypertensives, smoking status, and menopausal condition, also individual hair characteristics, such as original color, structure, and length and hair treatment. Additional variables include neutrophil nadirs and specific trichologic parameters, encompassing bulb and shaft diameter, anagen rate, shaft surface condition and hair pigment density.

In the category of general health, neutrophil nadirs and hair treatment, comorbidity tends to be associated with poorer hair retention HMI post (p= 0.060, ß= -0,55). This trend is also observed in the prevention of visible alopecia by comorbidity (p= 0.053, OR -0,27) and elevated nadir neutrophil count (p=0,055, OR 1,97).

The use of alopecia-inducing medications predictably leads to greater hair loss during therapy (p=0,033, ß=-0,54). Other mentioned potential influencing factors, including hair treatment do not affect hair loss over the time.

Light Microscopy Results: Correlational analysis demonstrated that pre- and post-therapeutic factors significantly impacted hair retention. Post-treatment factors had a stronger influence, with a stable anagen rate showing a strong correlation with hair retention (HMI post) ($r = 0.41$, $p = 0.007$). A stable shaft diameter was also significantly linked to better hair retention ($r = 0.41$, $p = 0.008$). Post-treatment shaft diameter had the strongest association with hair retention ($r = 0.62$, $p < 0.001$), followed by post-treatment anagen rate ($r = 0.59$, $p < 0.001$) and bulb diameter ($r = 0.40$, $p = 0.016$) demonstrating a more substantial impact on hair retention.

Therapeutic Effects on Melanosomes

Multivariate analysis indicates a link between stable melanosome density during therapy and reduced hair loss. A smaller decrease in pheomelanosomes correlates with less hair loss (p=0.013, ß=+0,35), while less pronounced changes in eumelanosomes show a positive, though borderline significant, effect (p=0.061, ß= +0,26) (Table 1).

Predictor	β	95 % CI		*p*
		LL	*UL*	
Intercept	0.1	-0.15	0.36	0.414
Age	0.36	0.07	0.64	0.017
Medication	-0.31	-0.57	-0.06	0.017
Nicotin abuse	0.06	-0.21	0.32	0.673
Bulb diameter pre	0.05	-0.2	0.31	0.68
Pheo difference	0.35	0.08	0.62	0.013
Eu difference	0.26	-0.01	0.53	0.061
Note. CI = Confidence interval, LL = Lower limit, UL = Upper limit, Pheo = Pheomelanosomes, Eu = Eumelanosomes.				

Table 1: Hair loss during treatment and influencing factors as every significant one from all categories as BEST of BEST.

A Fisher test was carried out and no relationship between original hair color and prevention of visible hair loss (HMI 50) was shown.

Melanosome clustering defined as more than five touching pigments exhibits a consistent pattern across all hair colors, showing no correlation with hair retention or the avoidance of visible hair loss (see table 2).

• Clustering Pre with HMI-Post: r = -0,05, p = 0.730
• Clustering Post with HMI-Post: r = -0.03, p = 0.827
• Clustering Pre with HMI-Post ≥50: r = -0.04, p = 0.795
• Clustering Post with HMI-Post ≥50: r = -0.10, p = 0.497

Table 2: Statistical analysis reveals the following correlation coefficients (r) and p-values.

Results SEM:

Descriptive analyses: pre-treatment evaluation exhibits a low median shaft surface damage of grade 1, post-treatment median shaft surface damage shows grade 2

In the univariate analysis the pre-treatment damage grade of the hair shaft significantly influences hair preservation (p= 0.012, correlation coefficient = -0.37); though it is surpassed by the impact of the post-therapeutic damage grade (p = 0.0006, correlation coefficient = -0.50)

Specifically, the greater the degree of damage to the shaft surface post-treatment, the lower the probability of avoiding visible hair loss (p=0,007, cc=-0,41).

The two highly meaningful surrogate parameters like melanosome density and low shaft surface damage, do not exhibit a statistically important context among themselves (r = -0.10, p = 0.564).

Surrogate Parameters for Hair Preservation as BEST of BEST

From all parameters previously tested with each HMI outcome variable, we included every significant one in overall regression analyses. We used linear regression to predict HMI post and difference and logistic regression to predict HMI ≥ 50.

When predicting HMI difference (Table 1), the difference of Pheomelanosomes (β = 0.35, p = 0.019) and the difference of Eumelanosomes (β = 0.25, p = 0.061) showed an effect. The less melanosomes were lost the more hair could be preserved. No medication results in better hair preservation (p=0,017, ß= -0,31). The model explained 32% variance (adj. $R^2 = 0.32$) and contained 46 patients with complete data.

When predicting HMI post (Table 3), less post-therapeutic damage degree of shaft surface led to better hair preservation (β = -0.30, p = 0.034). Having no comorbidities (β = -0.28, p = 0.073) and elevated nadir neutrophil count (β = 0.21, p = 0.083) were related to better hair preservation. The model explained 33% variance (adj. $R^2 = 0.33$) and contained 51 patients with complete data.

Predictor	β	95 % CI		*p*
		LL	*UL*	
Intercept	0.1	-0.17	0.36	0.465
Comorbidity	-0.28	-0.58	0.03	0.073
Neutrophil Nadir	0.21	-0.03	0.45	0.083
Anagen post	0.22	-0.09	0.54	0.163
Damage degree post	-0.3	-0.58	-0.02	0.034
Age	-0.07	-0.37	0.23	0.654
Medication	-0.14	-0.39	0.12	0.285
Note. CI = Confidence interval, LL = Lower limit, UL = Upper limit.				

Table 3: Hair retention post treatment and influencing factors as every significant one from all categories in overall regression analysis as BEST of BEST.

When predicting HMI ≥ 50 (Table 4), an increased pre-treatment shaft diameter (OR = 1.11, p = 0.012), presenting no comorbidities (OR = 0.12, p = 0.024) and to be medication free were related to prevention of alopecia. The model explained a high amount of variance (Nagelkerke $R^2 = 0.47$) and contained 52 patients with complete data.

Predictor	*OR*	95 % CI		*p*
		LL	*UL*	
Intercept	0.13	0	15.24	0.408
Comorbidity	0.12	0.02	0.68	0.024
Neutrophilennadir	2.03	0.81	7.73	0.199
Bulb size pre	0.99	0.96	1.01	0.222
Shaft diameter pre	1.11	1.04	1.22	0.012
Pheo difference	1.04	0.97	1.13	0.295
Eu difference	1	0.84	1.18	0.984
Note. OR = Odds ratio, CI = Confidence interval, LL = Lower limit, UL = Upper limit, Pheo = Pheomelanosomes, Eu = Eumelanosomes.				

Table 4: Avoiding visible hair loss and identifying the most significant influencing factors across all categories in overall regression analysis to determine BEST of BEST.

Pragmatic approach to evaluate the efficacy of scalp-cooling:

For prediction purposes we conducted a logistic regression with HMI≥50 as outcome and pre-HMI alongside comorbidity and medication as predictors. The model fit was moderately strong (Nagelkerke $R^2 = 0.22$). The analysis found that in the absence of comorbidities and medication a pre-HMI-score of 69 was a critical threshold for a significant prediction of hair loss prevention (OR = 6.98, 95% CI [1.01; 48.33]).

In a similar prediction-focused regression we entered post-therapeutic shaft surface damage and total melanosome difference as binary median-split variables (cut-off 2 and -12.9) alongside comorbidity and medication. The model contained only 37 patients due to missing data but showed a strong model fit (Nagelkerke $R^2 = 0.37$). Using favourable values for all predictors indicated at least a two-fold increased chance of preventing alopecia (OR = 137.50, 95% CI [2.12; 8911.32]) and effectively even much higher though wide confidence intervals reflecting small sample size.

Discussion

Visible hair loss (HMI < 50) was avoided in 53% of patients, though the median HMI dropped significantly from 75 pre-treatment to 51 post-treatment, indicating varied scalp-cooling effectiveness. Beside pre-treatment reduced hair density, this decline requires an analysis of the underlying factors contributing to this outcome in this patient cohort. Individual scalp temperature differences of up to 11.7 °C [10] may alter chemotherapy exposure at hair follicles, affecting cell biologic activity in the pigmentary unit influencing alopecia prevention. Pharmacodynamic responses to residual cytostatics in follicular cells may contribute to these variations. Firstly, this evaluation aimed at investigating significant effects on hair preservation across various parameters concerning general health, hair characteristics based on light and electron microscopy.

High and stable anagen rates and increased pre-therapeutic shaft diameter emerge as a red flag in statistical efficiency evaluation, exerting substantial influence on hair preservation assessed by light microscopy. Scanning electron microscopy show that better initial hair conditions including shaft surface integrity and stable pigment density correlate strongly with effective scalp-cooling. This points to the follicular unit as central determinant for the success of scalp cooling. The pigmentary unit, comprising fibroblasts, melanocytes, and keratinocytes, produces and transfers pigments during the anagen phase, influenced by both intrinsic factors (released by fibroblasts of the dermal papilla, melanocytes, keratinocytes, inflammatory and endocrine cells) and extrinsic (as UV radiation or drugs), being critical for hair retention under chemotherapy and cooling [11-14].

Alongside the anagen rate, bulb and shaft diameter and shaft surface condition, the components of the follicular pigmentary unit, particularly melanosomes, significantly impact hair preservation. Electron microscopy identified pheomelanosomes and eumelanosomes, with hair color diversity based on their ratio [15-19]. The role of melanosomes in hair retention under scalp-cooling and chemotherapy warrants further exploration.

Preclinical studies show that cyclophosphamide induces changes in mouse hair follicles besides the apoptosis of proliferating matrix keratinocytes, especially affecting melanocytes and potentially causing premature disordered or even disrupted melanogenesis. These pigment changes including quantity and type of

melanosomes may act as surrogate markers for chemotherapy-induced follicular alterations, aligning with the study's focus on efficiency parameters [5,14 20].

In the context of hair pigment alterations, functional aspects of the follicular pigmentary unit's function must be considered, going beyond pigment transfer. Melanosomes are positioned around keratinocyte nuclei providing photoprotection and reducing oxidative stress, subsequently stabilizing keratinocyte proliferation which forms the hair shaft [21-23]. Stable melanosome density, as shown in electron microscopy, strongly correlates with reduced hair loss. Despite scalp-cooling, disordered melanogenesis may occur due to chemotherapy-induced oxidative stress, leading to melanin clumping and disrupted pigment production, particularly affecting pheomelanin. This is likely due to increased antioxidant defence mechanism by incorporation of cysteine into glutathione, thereby leading to decreased availability of cysteine for the formation of cysteinyldopa indispensible for pheomelanogenesis, shifting melanin synthesis toward eumelanogenesis. Post-treatment, a reduced pheomelanosome density and a higher eumelanin-to-pheomelanin ratio were observed [24-28].

Scale: appr. 6.000:1

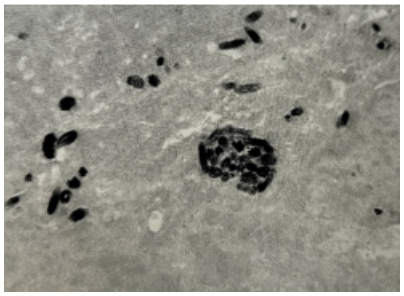

Photo 1: Example for clustering (more than five touching pigments).

Similar to cutaneous keratinocytes in light-skinned individuals, pigment clustering in light-colored hair may serve as a UV-protective mechanism [29, 30], though its occurrence during treatment is rare and does not significantly correlate with hair retention.

Chemotherapy-induced alterations in melanogenesis, along with other changes in the follicular pigmentary unit, are critical for evaluating scalp-cooling efficacy.

Light microscopy identifies stable anagen rate, consistent shaft diameter, and bulb diameter as key factors for hair preservation.

Ultrastructural analysis reveals increased shaft surface damage following treatment, exacerbating the hair´s susceptibility to breakage, primarilary due to its limited antioxidant defenses. Multivariate analysis confirms that minimal post-treatment shaft surface damage and stable melanogenesis are independently significant for hair preservation, marking them as essential parameters for scalp-cooling success confirmed as Best of Best.

Despite extensive research on chemotherapy's damaging effects on hair follicles and the protective role of scalp-cooling, additional measures are being considered to enhance efficacy. Follicular targeting could support scalp-cooling by providing localized protection to the follicular pigmentary unit without systemic side effects. Topical melatonin and vitamin C nanovesicles, which have shown antioxidant benefits in androgenetic alopecia, a protypical ROS-related follicular pathology may improve hair shaft integrity and hair density [35].

Cytostatic agents such as anthracyclines also target sebocytes by increasing ROS levels thereby impairing their function. This can lead to hindered shaft protrusion, hair breakage and glandular apoptosis and follicular cornification while also reducing UV protection and weakening antimicrobial properties [31,39, 40].

Additionally, Paclitaxel as the final component of this CTX regime contributes to hair loss by targeting mitotically active matrix keratinocytes and potentially impacting non-dividing melanocytes and fibroblasts by increased oxidative cell stress, both crucial for melanosome transfer and follicle health [25].

Stem and progenitor cells residing in the bulge of the hair follicle's outer root sheath, vital for hair growth and cycling, are vulnerable to chemotherapy-induced damage, potentially leading to permanent alopecia in case of prolonged retention of taxanes [32,33].

Paclitaxel primarily impacts actively proliferating cells like matrix keratinocytes. This raises the possibility that temporary G1 cell cycle arrest could shield these cells. Topical Palbociclib, a CDK 4/6 inhibitor, has shown promise in preclinical studies by inducing a brief G1 arrest in hair follicle cultures followed by activation of anagen phase without promoting hair shedding. This approach may allow hair growth to resume post-treatment, offering a way to protect hair follicles without safeguarding tumor cells from chemotherapy effects by topical application [34].

Remarkably, in the discussion of elevated ROS levels as chemotherapy-induced damaging factors to the cellular structures of the follicular pigmentary unit, it is crucial to consider the aspect that the dose makes the poison. Elevated ROS levels, indicative of oxidative stress, have been proven to cause damage to hair follicles [36].

Interestingly, Zhang and colleagues demonstrated at the preclinical level that mild oxidative stress may confer protection against chemotherapy-induced hair loss [37]. Subcutaneous application of peroxide induces cell cycle arrest through p53 activation, thereby shielding hair follicles from the cytotoxic effects of chemotherapy on actively dividing cells.

This is underscored at clinical level by Chen and colleagues revealing that cooling mitigates chemotherapy-induced alopecia by decelerating the cell cycle in hair follicles, thereby making them more resistant to chemoterapy's cytotoxic effects. This provides further evidence that cell cycle arrest enhances the resistance of hair follicles to cytotoxic chemotherapy [38].

In light of these findings, it might be advantageous to combine scalp-cooling with pre-treatment-induced mild oxidative stress for example via topical peroxid application.

Discussing red flags of efficacy, alongside hair health as a key factor but also broader health parameters, such as comorbidity and medication use, has proven to be statistically significant.

After identifying significant variables from each parameter domain, joint regression models are created for hair mass index outcome as a prognostic approach. For patients with a pre-treatment Hair Mass Index (HMI) of 69, no comorbidities, and no alopecia-inducing medications, the odds of avoiding alopecia increases 6.98-fold. With additional favourable factors like no post-treatment shaft damage and minimal melanosome difference (<20 units), the odds of hair preservation increased up to 137 fold under anthracycline-taxane chemotherapy.

These findings suggest that, while baseline parameters such as a high pre-treatment Hair Mass Index and the absence of comorbidities or alopecia-inducing medications contribute to hair retention, the most pronounced effect is observed when post-treatment shaft integrity and stable melanosome density are present. The substantial increase in predictive power—reflected in an odds ratio rising from 6.98 to 137—highlights melanogenic stability together with intact hair shaft surface as a key determinant of follicular resilience. This underscores the importance of preserving the structural and functional integrity of the pigmentary follicular unit as a central target in mitigating chemotherapy-induced hair loss.

Limitations include the study's single-center design, a small cohort of 81, and only 52 patients with REM-analyzed follicles, which could introduce bias.

Gonadal profiling was performed exclusively in female participants through assessment of menopausal status based on serum levels of FSH, LH, and estradiol. As no significant association was found between menopausal status and hair retention, further sex-specific hormonal analyses were not extended to the male cohort. This approach was guided by both biological relevance and observed data patterns.

Crucially, no increased risk of scalp metastases supports scalp-cooling as a safe option in cancer treatment.

Conclusion

Scalp-cooling has demonstrated efficacy in preventing visible hair loss in 53% of patients undergoing chemotherapy. Assuming optimal application of scalp-cooling beyond considerations of comorbidity and medications, its effectiveness is constrained by the integrity of the follicular pigmentary unit. Chemotherapy primarily induces hair loss by causing apoptosis in rapidly dividing matrix keratinocytes and by damaging hair follicle components through elevated oxidative stress. Achieving optimal hair health in combination with scalp-cooling could significantly improve hair retention.

Due to the multifaceted damage inflicted on hair follicles by reactive oxygen species, follicular targeting emerges as a promising approach to counteract these significant damaging factors. For example, topical applications of melatonin and vitamin C encapsulated in nanovesicles could provide targeted protection. Research represents an unmet need to establish protocols integrating follicular targeting within the existing framework of scalp-cooling systems. Optimizing these aspects is essential to maximize patients' comfort and satisfaction, holistically addressing the multidimensional challenges of managing chemotherapy-induced alopecia as one of the most distressing periods of patients´ lives.

Statements and Declarations

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Author contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dörthe Schaffrin-Nabe, Anke Josten-Nabe, Andrea Tannapfel, Merle Schaffrin, Adrian Heinze and Rudolf Voigtmann. The first draft of the manuscript was written by Dörthe Schaffrin-Nabe and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval:This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University Münster, Germany, Northrhine-Westfalia on April 15, 2024 under code 2016-011-f-s.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent to publish: The authors affirm that human research participants provided informed consent for publication of all fotos and figures.

Citation: Schaffrin-Nabe D, Josten-Nabe A, Heinze A, Tannapfel A, Schaffrin M, et al. (2025) Pigmentary-hair-follicle unit under innovative pathologic investigation - is there a potential to improve outcome of sensor-controlled scalp-cooling?. J Oncol Res Ther 10: 10292. DOI: 10.29011/2574-710X.10292.

References

1. Dua P, Heiland MF, Kracen, AC, Deshields T L (2017) Cancer-related hair loss: a selective review of the alopecia research literature. Psycho-Oncology 26: 438–443.
2. Gregory RP, Cooke T, Middleton J, Buchanan RB, Williams CJ (1982) Prevention of doxorubicin-induced alopedia by scalp hypothermia: relation to degree of cooling. Br Med J 5:284-1674.
3. Al-Tameemi W, Dunnill C, Hussain O, Komen MM, Hurk CJVD, et al. (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.
4. Tobin DJ (2011) Ex Vivo Organ Culture of Human Hair Follicles: A Model Epithelial–Neuroectodermal–Mesenchymal Interaction System. Methods in Molecular Biology 695:213-27.
5. Hendrix S, Handjiski B, Peters EMJ, Paus R (2005) A guide to assessing damage response pathways of the hair follicle: lessons from cyclophosphamide-induced alopecia in mice. J Invest Dermatol 125:42-51.
6. Wikramanayake TC, Mauro LM, Tabas IA, Chen AL, Llanes IC, et al. (2012) Cross-section Trichometry: A Clinical Tool for Assessing the Progression and Treatment Response of Alopecia. International Journal of Trichology 4:259-264.
7. Whiting D (2008). Histology of the Human Hair Follicle. Hair Growth and Disorders 107-123.
8. Kim YD, Jeon SY, Ji JH, Lee WS (2010) Development of a classification system for extrinsic hair damage: standard grading of electron microscopic findings of damaged hairs. The American Journal of Dermatopathology 32:432-438.
9. Roldan-Kalil J, Zueva L, Alves J, Tsytsarev V, Sanabria P, et al. (2023) Amount of Melanin Granules in Human Hair Defines the Absorption and Conversion to Heat of Light Energy in the Visible Spectrum. Photochem Photobiol 99:1092-1096.
10. Janssen FEM, Leeuwen GMJV, Steenhoven AAV (2005) Modelling of temperature and perfusion during scalp cooling. Phys Med Biol 50:4065-73.
11. D'Mello SAN, Finlay GJ, Baguley BC, Askarian-Amiri ME, (2016) Signaling Pathways in Melanogenesis. Int J Mol Sci 17:1144.
12. Ortonne JP, Prota G (1993) Hair melanins and hair color: ultrastructural and biochemical aspects. J Invest Dermatol 101:82S-89S.
13. Benito-Martínez S, Salavessa L, Raposo G, Marks MS, Delevoye C (2021) Melanin Transfer and Fate within Keratinocytes in Human Skin Pigmentation. Integr Comp Biol 61:1546-1555.
14. Videira IFDS, Moura DFL, Magina S (2013) Mechanisms regulating melanogenesis. An Bras Dermatol 88:76-83.
15. Slominski A, Wortsman J, Plonka PM, Schallreuter KU, Paus R, et al. (2005) Hair follicle pigmentation. J Invest Dermatol 124:13-21.
16. Qiu W, Chuong CM, Lei M (2019) Regulation of melanocyte stem cells in the pigmentation of skin and its appendages: Biological patterning and therapeutic potentials. Exp Dermatol 28:395-405.
17. Koch SL, Shriver MD, Jablonski NG (2019) Variation in human hair ultrastructure among three biogeographic populations. J Struct Biol 205:60-66.
18. D'Alba L, Shawkey MD (2019) Melanosomes: Biogenesis, Properties, and Evolution of an Ancient Organelle. Physiol Rev 99:1-19.
19. Wakamatsu K, Ito S (2023) Recent Advances in Characterization of Melanin Pigments in Biological Samples. Int J Mol Sci 24:8305.
20. Slominski A, Paus R, Plonka P, Handjiski B, Maurer M, et al. (1996) Pharmacological disruption of hair follicle pigmentation by cyclophosphamide as a model for studying the melanocyte response to and recovery from cytotoxic drug damage in situ. J Invest Dermatol 106:1203-11.
21. Kobayashi N, Nakagawa A, Muramatsu T, Yamashina Y, Shirai T, et al. (1998) Supranuclear melanin caps reduce ultraviolet induced DNA photoproducts in human epidermis. J Invest Dermatol 110:806-10.
22. You J, Yusupova M, Zippin JH (2022) The potential impact of melanosomal pH and metabolism on melanoma. Front Oncol 12:887770.
23. Hurbain I, Romao M, Sextius P, Bourreau E, Marchal C, et al. (2018) Melanosome Distribution in Keratinocytes in Different Skin Types: Melanosome Clusters Are Not Degradative Organelles. J Invest Dermatol 138:647-656.
24. Marmol VD, Ito S, Bouchard B, Libert A, Wakamatsu K, et al. (1996) Cysteine deprivation promotes eumelanogenesis in human melanoma cells. J Invest Dermatol 107:698-702.
25. Kim E, Panzella L, Micillo R, Bentley WE, Napolitano A, et al. (2015) Reverse Engineering Applied to Red Human Hair Pheomelanin Reveals Redox-Buffering as a Pro-Oxidant Mechanism. Sci Rep 5:18447.
26. Villarama CD, Maibach HI (2005) Glutathione as a depigmenting agent: an overview. Int J Cosmet Sci 27:147-53.
27. Dröge W (2005) Oxidative stress and ageing: is ageing a cysteine deficiency syndrome?. Philos Trans R Soc Lond B Biol Sci 360:2355-72.
28. Yu X, Long YC (2016) Crosstalk between cystine and glutathione is critical for the regulation of amino acid signaling pathways and ferroptosis. Scientific Reports 6:30033.
29. Hurbain I, Romao M, Sextius P, Bourreau E, Marchal C, et al. (2017) Melanosome Distribution in Keratinocytes in Different Skin Types: Melanosome Clusters Are Not Degradative Organelles. J Invest Dermatol 138:647-656.
30. Bento-Lopes L, Cabaço LC, Charneca J, Neto MV, Seabra MC, et al. (2023) Melanin's Journey from Melanocytes to Keratinocytes: Uncovering the Molecular Mechanisms of Melanin Transfer and Processing. Int J Mol Sci 24:11289.
31. Lim J, Joy KNg, Clave Cl (2019) Chapter Four - Dermal papilla regulation of hair growth and pigmentation. Advances in Stem Cells and their Niches 3:p115-138.
32. Huang WY, Lin ET, Hsu YC, Lin SJ (2019) Anagen hair follicle repair: Timely regenerative attempts from plastic extra-bulge epithelial cells. Experimental dermatology 28:406-412.
33. Purba TS, Haslam IS, Poblet E, Jiménez F, Gandarillas A, et al. (2014) Human epithelial hair follicle stem cells and their progeny: current state of knowledge, the widening gap in translational research and future challenges. Bioessays 36:513-25.
34. Purba TS, Ng'andu K, Brunken L, Smart E, Mitchell E, et al. (2019) CDK4/6 inhibition mitigates stem cell damage in a novel model for taxane-induced alopecia. EMBO Mol Med 11:e11031.
35. Hatem S, Nasr M,. Moftah NH, Ragai MH, Geneidi AS, et al. (2018) Melatonin vitamin C-based nanovesicles for treatment of androgenic alopecia: Design, characterization and clinical appraisal. European Journal of Pharmaceutical Sciences 122:246-253.

36. Trüeb RM (2015) The impact of oxidative stress on hair. Int J Cosmet Sci 2:25-30.

37. Zhang Y, Jimenez JJ (2023) Mild oxidative stress protects against chemotherapy-induced hair loss. Front Oncol 12:1078916.

38. Chen L, Xu Y, Ye X (2022) Low temperature mitigating the paclitaxel-induced damages in mouse cell and hair follicle model. Biochem Biophys Res Commun 603:94-101.

39. Dunnill C, Ibraheem K, Peake M, Ioannou M, Palmer M, et al. (2020) Cooling-mediated protection from chemotherapy drug-induced cytotoxicity in human keratinocytes by inhibition of cellular drug uptake. PLoS One 15:e0240454.

40. Selleri S, Seltmann H, Gariboldi S, Shirai YF, Balsari A, et al. (2006) Doxorubicin-induced alopecia is associated with sebaceous gland degeneration. J Invest Dermatol 126:711-20.

41. Komen MMC, Smorenburg CH, van den Hurk CJG, Nortier JWR (2013) Factors Influencing the Effectiveness of Scalp Cooling in the Prevention of Chemotherapy-Induced Alopecia. The Oncologist 18:885-891.

42. Freites-Martinez A, Shapiro J, Goldfarb S, Nangia J, Jimenez JJ, et al. (2019) Hair disorders in patients with cancer. J Am Acad Dermatol 80:1179-1196.