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Presentation, Impact and Prevention of Chemotherapy-induced Hair Loss

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Abstract and Introduction

Abstract

Background: This article provides an overview of the incidence and severity, presentation and impact of chemotherapy-induced alopecia (CIA), one of the most common and distressing side effects of cancer therapy. Furthermore, prevention of CIA by scalp cooling is described, as well as suggestions for improvement of scalp cooling application and clinical research approaches.
Methods: This article focuses on the availability of options to treat CIA and on scalp cooling in particular. It presents an overview of 58 scalp cooling publications and three personal communications, describing its working mechanism, determinants of success rates, side effects and controversies.
Results: CIA occurs in many chemotherapy regimens and is nearly always reversible. Up to now, scalp cooling is by far the best method to reduce CIA. Concerns about the protection of malignant cells in the scalp skin by scalp cooling have been proven to be exaggerated. The majority of patients tolerate scalp cooling very well. Scalp cooling is cost-effective when compared with purchasing wigs and other head covers. A promising method for objective research on CIA is now used in studies to further improve the method of scalp cooling – that is, cooling times and temperatures.
Conclusion: Scalp cooling is effective but not for all chemotherapy patients. Further psychological, clinical and biophysical research is needed to identify the determinants of success. Scalp cooling should be available in every hospital, and every suitable patient should be given the opportunity, after being well informed by their doctor or nurse, to choose for scalp cooling.

Introduction

Alopecia, bone marrow suppression and gastrointestinal disturbances are the most important and common side effects of chemotherapy. Extensive research resulted in the development of effective drugs to prevent and manage bone marrow suppression and gastrointestinal disturbances. Considerably less attention has been given to the prevention and management of chemotherapy-induced alopecia (CIA), and up to now this has been the domain of some 'interested' oncology nurses and oncologists. In our opinion, this should be the responsibility of all treating physicians and nurses, who have daily experience of the frequency and impact of CIA.

Since the review by Grevelman and Breed,[1] the only review regarding protection against CIA is from Wang *et al.* in 2006.[2] However, Wang *et al.* focused on experimental approaches with pharmacological agents in animal models, while up to now the use of scalp cooling is nearly the only method in clinical practice to prevent CIA.

Although scalp cooling technology has been available for more than 40 years, the usage is rather low, even in chemotherapy schedules in which very good hair preservation can be achieved. We will discuss the most important reasons for this rather low usage and suggest solutions. The purpose of this review is to increase awareness of the impact of CIA, to demonstrate the possibilities of the prevention of CIA by scalp cooling and to stimulate application, registration, evaluation and clinical research to improve patient care. The three major parts of this review are: an overview of the incidence and severity, presentation and impact of CIA; prevention of CIA by scalp cooling; and suggestions for solutions of scalp cooling problems and for clinical research approaches.

The Incidence & Severity, Presentation & Impact of CIA

Incidence & Severity of CIA

The incidence of CIA is extremely high. Drugs with a high potential for inducing CIA are: anthracyclines (e.g., doxorubicin and epirubicin), cyclophosphamide, daunorubicin, etoposide, docetaxel (DT) and paclitaxel. Newer drugs, such as gemcitabine, capecitabine and vinorelbine, cause less CIA. However, as these newer agents are usually given in combination with the traditional cytostatic agents, CIA remains a major problem.

Experienced medical professionals might have a wrong impression of the actual incidence of CIA, as wide variations in incidence are mentioned by experts for certain cytostatics. Furthermore, wide variations are reported for specific chemotherapy regimens in control groups of scalp cooling studies [Geerts P, Hendriks M, van den Hurk C, Dercksen M, Breed W. Hair preservation in FEC-chemotherapy; not an exception. (2010). Manuscript submitted]. This wide variation might not only be caused by the use of various criteria for CIA, but also by the drug used and factors such as dose, administration method, number of chemotherapy courses, combination with other cytostatic agents, patient characteristics and earlier chemotherapy courses. Chemically damaged and mechanically manipulated hair and alopecia areata may also be relevant factors to consider.[3,4]

Many studies have demonstrated cytostatic dose dependency of CIA. Spreading a dose in weekly instead of 3-weekly schedules may lead to less CIA.[5] Intravenously administered chemotherapy usually leads to greater hair loss than orally administered therapies. It remains unknown whether the blood concentration of cytostatics or the exposure time of hair follicles to cytostatics is more important for the toxic effect.

Presentation of CIA

Chemotherapy-induced alopecia is known to start from areas of mechanical friction, such as the sides of the head above the ears. Hair that is formed during chemotherapy is much thinner and more brittle because of the suppression of cell production.[6] This reduced cell production may lead to localized thinning of the hair, Pohl Pinkus constriction or tapering. Sometimes those thinner parts can be seen by the naked eye and their number indicates the number of chemotherapy sessions. Whether the hair breaks or not depends on the balance between loss of tensile strength, which is a consequence of the decreased hair diameter, and external forces.[7] Traditionally, CIA has been categorized as acute diffuse hair loss – anagen effluvium.[4,8] CIA can result in hair loss from all parts of the body. Hair loss is more pronounced on the scalp because this site normally contains more hairs in the proliferating anagen phase than other sites, such as the eyebrows, eyelashes, beard, axillary and pubic hair.

Chemotherapy-induced alopecia can be diagnosed by considering the time elapsed since medication was initiated and alopecia started. Severe hair loss usually starts at 1–3 weeks after the first dose of chemotherapy[4,9] and often becomes clinically apparent within 1–2 months.[10] However, CIA can also slowly increase and becomes most clinically apparent after many chemotherapy courses. Generally, CIA can be easily diagnosed based on the story of a chemotherapy patient if time of hair loss is clearly related to time of application of chemotherapy. So blood tests, hair pull test, (photo)-trichogram or punch biopsy are only rarely needed to distinguish CIA from other forms of alopecia.

With the exception of a study in Korean cancer patients with various chemotherapy regimens by Yun and Kim, there is no accurate description on the clinical characteristics of CIA.[11] They pointed out that CIA may present as patterned hair loss, with relatively low hair loss of the hairlines, and found some difference between Korean men and women. Based on the observation of Crounse that generally in the frontal and frontoparietal area of the scalp a lower percentage of growing (anagen) hairs is present than in the occipital area,[12] one should expect that CIA is more severe occipital. However, this is not described in clinical CIA studies.

Regrowth & Hair Changes

In CIA, hair growth is usually only temporarily inhibited. The hair regrows because the stem cells of the hair follicle are protected against the effects of cytostatic agents,[13,14] presumably by their slower growth rate. Hair regrowth usually starts several weeks[4,15] to several months[9,16] after completion or cessation of chemotherapy, but can also occur during chemotherapy, especially during prolonged chemotherapy cycles.[17] We found that 71% of CIA patients used a wig or other head cover for less than 6 months [van den Hurk CJG. Cost effectiveness of scalp cooling in the prevention of chemotherapy-induced hair loss (2010). Manuscript in preparation]. When hair regrows many patients experience a change from their previous hair, but this is often transient. Alterations may occur in color, curling or straightening.[4,18]

Permanent CIA

Chemotherapy-induced alopecia is nearly always reversible, but sometimes permanent.[4,15] Permanent CIA is defined as an absence of, or incomplete hair regrowth, 6 months beyond the completion of chemotherapy. Nearly all patients with permanent CIA are patients with hematological malignancies and breast cancer patients receiving high-dose chemotherapy and bone marrow transplantation.[19] Permanent baldness has been reported with high-dose busulfan, cyclophosphamide, thiotepa, melphalan, etoposide, carboplatin, DT and paclitaxel.[19–27] Busulfan is the most commonly implicated agent. The reported incidence of permanent baldness varies from 1 to 43% in bone marrow transplantation studies.[19,22] Data regarding the relationship between dose and permanent baldness are contradictory.[19] Why some patients develop permanent CIA, rather than temporary, is unknown. Individual variation in the bioavailability of chemotherapeutic agents is well known, and may influence the occurrence of toxicity.[28]

Impact

Chemotherapy-induced alopecia is still one of the most common and most emotionally distressing side effects of cancer therapy.[29–31] We found that this negative feeling about hair loss was still present, even 6 months after completing chemotherapy.[32] This is in accordance with the observation of Auvinen *et al.*.[33]

Chemotherapy-induced alopecia may lead to a negative body image, depression and anxiety.[5,34,35] In a literature review about the effects of CIA on quality of life (QoL), Lemieux *et al.* reported that patients described hair loss as distressing and that it affected their body image.[36] Very little quantitative data was found on other aspects of QoL.[5,34–38] Therefore, the true extent to which CIA adds to the stress of having cancer or undergoing chemotherapy is unknown. CIA constantly reminds the patient of the disease,[33] has an impact on various daily-life activities [van den Hurk CJG. Cost effectiveness of scalp cooling in the prevention of chemotherapy-induced hair loss (2010). Manuscript in preparation] and is a burden to approximately half of breast cancer patients.[34] It stigmatizes by making cancer visible. CIA also has an impact on family and loved ones; children of cancer patients felt that their mother's hair loss was the worst aspect of the treatment.[39] One study found that some patients considered the loss of hair to be more difficult to cope with than the loss of their breast,[17] and another study found that 13% believed that they would be rejected by their partner once CIA occurred.

For some patients, CIA is a reason to refuse chemotherapy, and as much as 8% of patients may choose chemotherapy regimens with possibly less favorable tumor outcomes as long as these regimens do not cause severe hair loss.[3,40,41] The impact of CIA is also shown by the high number of patients that want to camouflage their baldness and purchase a wig or other head covering [van den Hurk CJG. Cost effectiveness of scalp cooling in the prevention of chemotherapy-induced hair loss (2010). Manuscript in preparation].

Dougherty reported that 38% of patients with unsuccessful scalp cooling would want the scalp cooling again if they needed another chemotherapy.[29] Williams *et al.* also described that most patients have some difficulty coping with CIA.[42] However, some patients perceive CIA in a positive way – they interpret it as a sign of effective cancer therapy.

Women find hair loss more troublesome than men and require more information about it.[3] For women, hair is linked symbolically to their femininity and hair loss is especially problematic in breast cancer patients if there is also a visual impact of breast surgery.[43]

Medical oncologists and nurses underestimate the impact for their patients considerably.[44] Other side effects of chemotherapy, such as nausea, vomiting and fatigue, and their prevention are much more frequently and better investigated than CIA. This has led to improvement of these symptoms through, for example, new antinauseous drugs and erythropoietin, and as a result these side effects were ranked lower by patients over time. By contrast, CIA remained highly ranked among the side effects of chemotherapy. A reason for the lack of CIA prevention research may be an underestimation of the impact of hair loss by medical professionals and little interest from the pharmaceutical industry.

Prevention of CIA

Since approximately 1970, attempts to prevent CIA have been made through the development of pharmacological and nonpharmacological measures such as mechanical strategies and scalp cooling. Currently, preventive measures mainly focus on scalp cooling.

Non-scalp Cooling Prevention

Research has been carried out in different ways:

- Pharmacological agents: Wang *et al.* published an expert review on many pharmacological agents in 2006.[2] With the exception of folic acid and a liposomal alternative of conventional doxorubicin, up to now the results of many agents under evaluation are disappointing in patients for the prevention of CIA.[2,17,45–49] Minoxidil is one of the agents that stimulates hair growth, but the results of topical application of minoxidil solutions in animal models and chemotherapy patients are very inconsistent;[50–52]
- Tourniquets: a mechanical strategy is a scalp tourniquet, designed to reduce blood flow to scalp hair follicles during peak cytostatic agent levels in intravenous chemotherapy.[53,54] Pesce's tourniquet method resulted in a significant reduction of doxorubicin-induced CIA.[54] Side effects, such as nerve compression and headaches, are reported, and there are no recent reports of tourniquet use;
- Electrotrichogenesis: a pilot study of the use of a specific pulsed electrostatic field has demonstrated promising results in preventing CIA caused by cyclophosphamide, methotrexate and fluorouracil (CMF) in 13 pregnant women.[55] However, no other studies have been published since this pilot study in 2002.

Scalp Cooling Prevention

Working Mechanism

Scalp cooling works by inducing vasoconstriction and reduction of metabolism. Vasoconstriction leads to reduced blood flow to the hair follicles in the period of peak plasma concentration of the relevant chemotherapy agent. This blood flow reduction was demonstrated by Bulow *et al.*.[56] Reduced biochemical activity makes hair follicles less vulnerable to the damage of chemotherapy agents (). The latter may be more important than vasoconstriction.[56]

Table 1. Working mechanisms of scalp cooling.

Hypothermia	
Perfusion ↓ ▾	Metabolism ↓ ▾
Concentration of cytostatics in hair follicle cells ↓	**Cell membrane** if active transport: cytostatic influx ↓ cytostatic outflow ↓ **Intracellular** cell mitosis ↓ toxic reactions ↓ repair mechanisms ↓

▾ Hair † ↓	▾ Hair † ↓ = ↑
▾ Hair loss ↓	▾ Hair loss ↓ = ↑

▾: Leads to/causes; †: Severe damage of hair-forming cells; ↓: Decrease; ↑: Increase.

Methods

In the past decades, scalp cooling has been practised with several methods, such as simple bags with crushed ice, frozen cryogel packs and packs with an endothermic cooling reaction. Examples of precooled caps are ChemoCap™ (ChemoCap, Canada), Elasto-Gel™ Cold Caps (Southwest Technologies, Akromed Inc.) and Penguin Cold Caps (Medical Specialities Of California). These methods require frequent cap changes due to thaw-effects and are labor-intensive for the nursing staff. It can also be very uncomfortable for patients due to the cap's heavy weight. In previous years, cooling systems have been adopted that cool continuously. Caps are cooled by fluid or chilled air. These continuously cooling machines are more convenient for the nursing staff because no cap changes are needed. Cooling machines that use liquid circulation are the systems of Paxman (PCS-1 and 2, Orbis) and Dignitana (DigniCap™), while Amit Technology (SCSII™) uses chilled air. The advantage of a system with air cooling is that it is a one-size-fits-all system. Thus, there are no problems fitting the cap to the scalp. However, for unknown reasons only one clinical study of SCSII is published, and the system is hardly used or promoted.[57] The few studies performed to find out which scalp cooling method is the most effective are not conclusive.[29,57,58]

Criteria for Success of Scalp Cooling

Patient-view The use of a wig or head cover is often rightly used as a parameter for success. However, this use is less in male patients, and so this parameter seems to be gender dependent. Regularly, there is a discrepancy between patients' hair loss scoring by graded scales and the use of wigs or head covers.

Investigators View So far, grading scales of hair loss, such as the WHO and common toxicity criteria scales, photographs or counting shed hairs are methods used to document the results of scalp cooling. Hair loss becomes noticeably visible after the loss of 50% or more of the scalp hair. Recently, an objective method has become available to measure hair quantity by use of the cross-section trichometer.[59] This trichometer is a very promising technology for hair quantity measurements in the field of research [Hendriks MAE, Geerts PAF, Dercksen MW, van den Hurk CJG, Breed WPM. The usefulness of Cohen's cross-section trichometer for measuring hair quantity (2010). Manuscript submitted]. However, the use of a wig or head cover as a parameter for patients satisfaction concerning hair preservation should remain the most important clinical criterion for the success of scalp cooling.

Not only the quantity, but also the quality of remaining hair is important. Some patients and hairdressers report that when hair is preserved thanks to scalp cooling, the quality is not always optimal. However, up to now this has not been investigated properly.

Results/Success Rates

We gathered the results of 60 scalp cooling studies: seven randomized studies, with and without scalp cooling; six nonrandomized studies with statistical analysis; 11 nonrandomized studies with control groups, without statistical analysis; and 36 studies without controls ( ) [van den Hurk CJG, Peerbooms M, Breed WPM. Results of scalp cooling in the Netherlands from 2006 up to 2010 (2010). Manuscript in preparation; van den Hurk CJG. Cost effectiveness of scalp cooling in the prevention of chemotherapy-induced hair loss (2010). Manuscript in preparation;.[29,30,33,41,57,58,60–107]] In six out of the seven randomized studies, significantly better hair preservation was seen when scalp cooling was used.[57,60–65] Although the number of patients in these studies were small, the differences in hair preservation between scalp-cooled and non-scalp-cooled patients were often highly significant. Statistical analysis of results of the six nonrandomized studies also demonstrated a clear advantage of scalp cooling in all studies. In the 47 studies without statistical analysis, the authors concluded positive results for certain indications in all but one study. In the 11 nonrandomized studies with control groups without statistical analysis, the percentage of patients with good hair preservation varied from 0 to 100%, with a mean of 67%. The median value for good hair presentation in the 36 studies without controls was approximately 80%.

Table 2. Results of scalp cooling studies.

Study (year)	Cooled patients (n)	Controls (n)	Cytostatic agents and doses (mg/m^2)	Hair loss scoring	% patients with good hair preservation (controls)†	p-value	Ref.
Randomized studies with & without scalp cooling							
Edelstyn *et al.* (1977)	40	37	D50, Vc2‡, F500, 4× p.o.: M20 + Ch40	Graded scale	50% (19%)	$p < 0.05$	[60]
Giaccone *et al.* (1988)	19	16	Combinations including D30–70	Graded scale	37% (0%)	$p < 0.025$	[61]

Ron *et al.* (1997)	19	16	C600, M40, F600	Graded scale	85% (63%)	p = 0.014§	[57]
Macduff *et al.* (2003)	15	15	E75, DT75	Graded scale plus photos	25% (0%)	p = 0.001–0.012¶	[63]
Satterwhite and Zimm (1984)	12	13	D20–60 multiple combinations	Graded scale	75% (8%)	p = 0.0009	[65]
Kennedy *et al.* (1983)	10	9	D31–125 ‡, C300–800 ‡	Graded scale and no wig required	10% (0%)	NS	[62]
Parker (1987)	6	6	C600, M40, F600	Hair loss counts	100% (17%)	p < 0.01	[64]
Nonrandomized studies with control groups with statistical analysis							
Spaeth *et al.* (2008)	770	141	Multiple combinations	No head cover required	46% (31%)	p < 0.0018	[66]
Van den Hurk (2010)	–	86	Multiple combinations	No head cover required Graded scale	(9%) (9%)	#	[Manuscript in preparation]
▫	160	–	Multiple combinations	No head cover required Graded scale	49% 70%	#	[Manuscript in preparation]
Lemenager *et al.* (1997)	98	–	DT100	Graded scale	97% (5%)	▫	[67]
Belpomme *et al.* (1982)	72	77	Multiple combinations	No wig required	72% (38%)	2 out of 5 schedules p < 0.001	[68]
van den Hurk *et al.* (2010)	62	149	D60, C100; F500, E90, C500; DT75, D50, C500	Graded scales	52% (0%)	WHO: p < 0.001 VAS: p < 0.0001	[69]
Protiere *et al.* (2002)	27	109	Mi12, C600	Graded scale	41% (16%)	p < 0.05	[70]
Villani *et al.* (1986)	18	18	Combinations including D	Graded scale	67% (17%)	Significant	[71]
Nonrandomized studies with control groups without statistical analysis							
Lemenager *et al.* (1995)	39	H	DT100	Graded scale	97% (5%)	▫	[72]
Dean *et al.* (1979)	33	H: 120	D30, C150 × 4 p.o.	Graded scale plus photos	60% (5%)	▫	[41]
Lenaerts *et al.* (2001)	29	H	C E (min50) F	No wig required	50% (0%)	▫	[30]
Dean *et al.* (1981)	25	H: 150	D30–40, C150–200 × 4 p.o.	Graded scale plus photos	75% (5%)	▫	[73]
Gregory *et al.* (1982)	24	H	D40, Vc2‡, Pr p.o.	Graded scale plus photos	42%	▫	[74]
Robinson *et al.* (1987)	22	10	E40–80	Graded scale	73% (20%)	▫	[75]
Guy *et al.* (1982)	12	H: 100	D50, Vc1.4,	Graded	100% (2%)	▫	[76]

			C1000, M40	scale plus photos			
Luce *et al.* (1973)	12	16	Combinations including D	Maximum % of hair loss	††	▫	[77]
Peck *et al.* (2000)	10	7	F600, E50, C600	No wig required	70% (0%)	▫	[78]
Lundgren-Eriksson *et al.* (1999)	9	2	P135–175/DT100 and multiple combinations	Graded scale	100% (0%)	▫	[79]
Dugan (1983)	6	5	D40, C1000, Vc1	Graded scale	0% (0%)	▫	[80]
Studies without controls							
van den Hurk *et al.* (2010)	1415	–	Multiple combinations	No head cover required	50%	▫	[Manuscript in preparation]
Kato *et al.* (2010)	225	–	Multiple combinations	Graded scale plus photos	82%	▫	[81]
David and Speechley (1987)	180	–	Multiple combinations	Graded scale	54%	▫	[82]
Kiser *et al.* (1982)	176	–	Combinations including D	No wig required	58%	▫	[83]
Stein *et al.* (2000)	138	–	Multiple combinations	Graded scale	CMF: 100%, D: 54%, E: 95%, Tx: 81%	▫	[84]
van den Hurk *et al.* (2009)	129	–	3-weekly DT (mono and combinations) Randomization study between 90 and 45 PICT	No head cover required	84%‡‡	▫	[85]
ElGenidi (2001)	127	–	P180, DT80, D60, C500, M50 in multiple combinations	Graded scale	87%	▫	[86]
Lemenager *et al.* (1997)	98	–	DT100	Graded scale	86%	▫	[67]
Massey (2004)	94	–	FEC60–75 and multiple combinations	Graded scale	89%	▫	[87]
Benglia *et al.* (1986)	91	–	D ± C	Graded scale plus photos	61%	▫	[88]
Barzo *et al.* (1992)	88	–	C800–1000, M40–60 F200–250 and multiple combinations	Graded scale	90%	▫	[89]
C Christododoulou, Athens Medical Centre, Greece	83	–	D50–60 or E60–110 or P175–200 or ET and combinations	Graded scale	65%	▫	[Pers. Comm.]
Goldhirsch *et al.* (1982)	82	–	D30–70 alone or in multiple combinations	No wig required	57%	▫	[90]
Ridderheim *et al.* (2003)	74	–	Multiple combinations	No wig required	78%	▫	[91]
						▫	

Auvinen *et al.* (2010)	64	–	D60; DT80; F600, E60, C600; 3 × DT 80 + 3 × F600, E60, C600	Graded scale	80%		[33]
Kato *et al.* (2008)	64	–	Multiple combinations	Graded scale	94%	▫	[92]
Middleton *et al.* (1985)	60	–	D40, Vc1.4, C200 × 4 p.o.	Graded scale	0%	▫	[93]
Byachov (2006)	59	–	Multiple combinations	Graded scale	85%	▫	[94]
Katsimbri *et al.* (2000)	57	–	Multiple combinations	Graded scale	Tx: 88%, ET: 100%, Tx + ANR: 36%, ANR: 100%	▫	[95]
B Kolen, Elisabeth Hospital, Tilburg, Holland	55	–	D60, C600 or multiple combinations	No wig required	47%	▫	[Pers. Comm.]
Ciambellotti (1993)	50	–	E30–50 (weekly)	Graded scale	100%	▫	[96]
Hillen *et al.* (1990) (cold air)	48	–	Multiple combinations	Graded scale	CMFP: 95%; CMFPCAP: 30%; EC: 0%	▫	[58]
Semsek (2000)	45	–	D or E > 50 and multiple combinations	Graded scale	82%	▫	[97]
Howard and Stenner (1983)	35	–	Combinations including D	Graded scale	100%	▫	[98]
Kolen *et al.* (2002)	31	–	D60, C600 or DT100 or multiple combinations	No wig required	52%	▫	[99]
Anderson *et al.* (1981)	31	–	D40, Vc2 or Vd5	Graded scale	90%	▫	[100]
Dougherty (1996)	30	–	D or E or in multiple combinations	Graded scale	50%	▫	[29]
Wills *et al.* (2009)	28	–	Multiple combinations	Graded scale	47%	▫	[101]
Hunt *et al.* (1982)	28	–	D40, Vc2, Vd5 or D80	Graded scale plus photos	79%	▫	[102]
Adams *et al.* (1992)	24	–	E100, E50	Graded scale	E100: 0%; E50: 86%	▫	[103]
AD Klaren, Albert Schweitzer Hospital, Dordrecht, Holland	23	–	D60, C600	No wig required	76%	▫	[Pers. Comm.]
Fiebig *et al.* (1997)	23	–	D > 50, C with multiple combinations	Graded scale	90%	▫	[104]
Alexopoulos *et al.* (1999)	15	–	ANR, Tx, CMF	Graded scale	80%	▫	[105]
Dixon-Hughes (1984)	13	–	D, Vc	ns	76%	▫	[106]
Hillen *et al.* (1990) (cryo gel)	13	–	Multiple combinations	Graded scale	CMFP: 89%; CMFPCAP: 0%	▫	[58]
Cooke *et al.* (1981)	ns	–	D40	ns	55%	▫	[107]

†WHO grade 0,1,2 unless in the opinion of the authors the hair preservation in a part of the patients with grade 2 is not good or if the authors mention 'good hair preservation' or 'no wig required'.
‡Doses not per m^2.
§p-value calculated for the incidence of alopecia of any grade.
¶Depending on who rated hair loss: patients, nurses or experts.
#Among patients who purchased a wig, it was significantly less used in the scalp-cooled group ($p < 0.0001$).
†† The noncooled patients lost an average of 80% of their hair, the cooled patients 30%.
‡‡No significant difference between 90 and 45 min PICT.
ANR: Anthracyclines; C: Cyclophosphamide; Ch: Chlorambucil; Cp: Cisplatin; Ct: Cytarabine; D: Doxorubicin; DT: Docetaxel; E: Epirubicin; ET: Etoposide; F: 5-fluorouracil; H: Historical control; M: Methotrexate; Mi: Mitoxantrone; NS: Not significant; ns: Not specified; P: Paclitaxel; PICT: Post-infusion cooling time; p.o.: Per orem; Pr: Prednisolone; Tx: Taxanes; VAS: Visual analogue scale; Vc: Vincristine; Vd: Vindesine.

By far the largest study is an observational nonrandomized multicenter study in The Netherlands, in which 1415 patients were included and which ran from 2006 until 2009 in 27 hospitals using the Paxman scalp cooling systems (PCS1 and PCS2). In this study, overall 50% of the patients with scalp cooling had good hair preservation ( ). Together, these studies show that there is clear evidence that scalp cooling can prevent CIA. In general, more recent studies contain much more patients and are of better quality than older studies. In our earlier review, a tendency towards better results was seen from 1995 onwards.[1] This tendency also seems to be present in more recent studies, but it cannot be excluded that this is due to publication bias. The influence of dosage and type of chemotherapy on success rates is discussed in the next section 'Factors that influence success rate'. Often, these factors are hardly described in articles.

Table 3. Overview of scalp cooling results in The Netherlands 2006–2009.

Chemotherapy†	Patients with good hair preservation (%)
F500E100C500-D100	47 (n = 45)
F500E100C500	33 (n = 123)
F500E90C500	52 (n = 552)
F500D50C500	55 (n = 38)
P175Carbo5/6	37 (n = 49)
P70–90 (mono/combinations)‡	82 (n = 39)
DT100 (mono/combinations§)	59 (n = 42)
DT75 (mono/combinations§)	79 (n = 58)
DT75D50C500¶	8 (n = 66)
D60C600DT100H#	63 (n = 16)
D60C600P175H	29 (n = 21)
D60C600P80H	48 (n = 29)
D60C600	39 (n = 74)
Irinotecan350	29 (n = 41)

†Numbers represent the dosage in mg/m^2.
‡Administered at weekly schemes; dosages range from 70 to 90 mg/m^2.
§Docetaxel combinations with exception of docetaxel, doxorubicin, cyclophosphamide (DTAC).
¶DT, D and C are administered simultaneously.
#Sequential scheme: DC followed by DT and H.
C: Cyclophosphamide; Carbo: Carboplatin; D: Doxorubicin; DT: Docetaxel; E: Epirubicin; F: 5-fluorouracil; H: Herceptin (trastuzumab); P: Paclitaxel.

One has to realize that even without scalp cooling good hair preservation may occur, even in schedules containing high-dose 5-fluorouracil–epirubicin–cyclophosphamide (FEC), doxorubicin and cyclophosphamide and taxanes [Geerts PAF, Hendriks MAE, Dercksen MW, van den Hurk CJG, Breed WPM. Hair preservation in FEC-chemotherapy; not an exception (2010). Manuscript in preparation], and may vary considerably; for example 17 and 63% in the CMF studies of Parker and Ron, respectively.[57,64]

Factors that Influence Success Rate*Dosage & Type of Chemotherapy* It is generally accepted that the number of chemotherapy courses, the admission method and the doses have an influence on the result of scalp cooling.[65,82,103,108] Better results at a lower dosage is demonstrated by the differences between F500E100C500 and F500E90C500 and between DT100 and DT75 in our study (see).

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P175Carbo5/6	37 (n = 49)
P70–90 (mono/combinations)‡	82 (n = 39)
DT100 (mono/combinations§)	59 (n = 42)
DT75 (mono/combinations§)	79 (n = 58)
DT75D50C500¶	8 (n = 66)
D60C600DT100H#	63 (n = 16)
D60C600P175H	29 (n = 21)
D60C600P80H	48 (n = 29)
D60C600	39 (n = 74)
Irinotecan350	29 (n = 41)

†Numbers represent the dosage in mg/m^2.
‡Administered at weekly schemes; dosages range from 70 to 90 mg/m^2.
§Docetaxel combinations with exception of docetaxel, doxorubicin, cyclophosphamide (DTAC).
¶DT, D and C are administered simultaneously.
#Sequential scheme: DC followed by DT and H.
C: Cyclophosphamide; Carbo: Carboplatin; D: Doxorubicin; DT: Docetaxel; E: Epirubicin; F: 5-fluorouracil; H: Herceptin (trastuzumab); P: Paclitaxel.

In our studies, specifically the results achieved with taxanes were excellent (& . This is in accordance with other studies that demonstrated most positive results achieved in taxanes or anthracyclines schedules.[1,33,65,67,79,102] However, when anthracyclines and taxanes are combined and given together (simultaneously) with cyclophosphamide (a schedule that is often called TAC; taxotere, adriamycin, cyclophosphamide), the results are very poor ( ).[101] This is remarkable because the results of scalp cooling in schedules containing doxorubicin and cyclophosphamide are not so bad. We have the impression that when these three cytostatic agents are administered simultaneously the results are less than when they are administered in a sequential scheme (four-times of 3-weekly doxorubicin–cyclophosphamide followed by four-times of 3-weekly DT) ( ).

Table 2. Results of scalp cooling studies.

Study (year)	Cooled patients (n)	Controls (n)	Cytostatic agents and doses (mg/m^2)	Hair loss scoring	% patients with good hair preservation (controls)†	p-value	Ref.
Randomized studies with & without scalp cooling							
Edelstyn *et al.* (1977)	40	37	D50, Vc2‡, F500, 4× p.o.: M20 + Ch40	Graded scale	50% (19%)	$p < 0.05$	[60]
Giaccone *et al.* (1988)	19	16	Combinations including D30–70	Graded scale	37% (0%)	$p < 0.025$	[61]
Ron *et al.* (1997)	19	16	C600, M40, F600	Graded scale	85% (63%)	$p = 0.014$§	[57]
Macduff *et al.* (2003)	15	15	E75, DT75	Graded scale plus photos	25% (0%)	$p = 0.001–0.012$¶	[63]
Satterwhite and Zimm (1984)	12	13	D20–60 multiple combinations	Graded scale	75% (8%)	$p = 0.0009$	[65]
Kennedy *et al.* (1983)	10	9	D31–125 ‡, C300–800 ‡	Graded scale and no wig required	10% (0%)	NS	[62]

Parker (1987)	6	6	C600, M40, F600	Hair loss counts	100% (17%)	p < 0.01	[64]
Nonrandomized studies with control groups with statistical analysis							
Spaeth *et al.* (2008)	770	141	Multiple combinations	No head cover required	46% (31%)	p < 0.0018	[66]
Van den Hurk (2010)	–	86	Multiple combinations	No head cover required Graded scale	(9%) (9%)	#	[Manuscript in preparation]
▫	160	–	Multiple combinations	No head cover required Graded scale	49% 70%	#	[Manuscript in preparation]
Lemenager *et al.* (1997)	98	–	DT100	Graded scale	97% (5%)	▫	[67]
Belpomme *et al.* (1982)	72	77	Multiple combinations	No wig required	72% (38%)	2 out of 5 schedules p < 0.001	[68]
van den Hurk *et al.* (2010)	62	149	D60, C100; F500, E90, C500; DT75, D50, C500	Graded scales	52% (0%)	WHO: p < 0.001 VAS: p < 0.0001	[69]
Protiere *et al.* (2002)	27	109	Mi12, C600	Graded scale	41% (16%)	p < 0.05	[70]
Villani *et al.* (1986)	18	18	Combinations including D	Graded scale	67% (17%)	Significant	[71]
Nonrandomized studies with control groups without statistical analysis							
Lemenager *et al.* (1995)	39	H	DT100	Graded scale	97% (5%)	▫	[72]
Dean *et al.* (1979)	33	H: 120	D30, C150 × 4 p.o.	Graded scale plus photos	60% (5%)	▫	[41]
Lenaerts *et al.* (2001)	29	H	C E (min50) F	No wig required	50% (0%)	▫	[30]
Dean *et al.* (1981)	25	H: 150	D30–40, C150–200 × 4 p.o.	Graded scale plus photos	75% (5%)	▫	[73]
Gregory *et al.* (1982)	24	H	D40, Vc2‡, Pr p.o.	Graded scale plus photos	42%	▫	[74]
Robinson *et al.* (1987)	22	10	E40–80	Graded scale	73% (20%)	▫	[75]
Guy *et al.* (1982)	12	H: 100	D50, Vc1.4, C1000, M40	Graded scale plus photos	100% (2%)	▫	[76]
Luce *et al.* (1973)	12	16	Combinations including D	Maximum % of hair loss	††	▫	[77]
Peck *et al.* (2000)	10	7	F600, E50, C600	No wig required	70% (0%)	▫	[78]
Lundgren-Eriksson *et al.* (1999)	9	2	P135–175/DT100 and multiple combinations	Graded scale	100% (0%)	▫	[79]
Dugan (1983)	6	5	D40, C1000, Vc1	Graded	0% (0%)	▫	[80]

				scale			
Studies without controls							
van den Hurk *et al.* (2010)	1415	–	Multiple combinations	No head cover required	50%	▫	[Manuscript in preparation]
Kato *et al.* (2010)	225	–	Multiple combinations	Graded scale plus photos	82%	▫	[81]
David and Speechley (1987)	180	–	Multiple combinations	Graded scale	54%	▫	[82]
Kiser *et al.* (1982)	176	–	Combinations including D	No wig required	58%	▫	[83]
Stein *et al.* (2000)	138	–	Multiple combinations	Graded scale	CMF: 100%, D: 54%, E: 95%, Tx: 81%	▫	[84]
van den Hurk *et al.* (2009)	129	–	3-weekly DT (mono and combinations) Randomization study between 90 and 45 PICT	No head cover required	84%‡‡	▫	[85]
ElGenidi (2001)	127	–	P180, DT80, D60, C500, M50 in multiple combinations	Graded scale	87%	▫	[86]
Lemenager *et al.* (1997)	98	–	DT100	Graded scale	86%	▫	[67]
Massey (2004)	94	–	FEC60–75 and multiple combinations	Graded scale	89%	▫	[87]
Benglia *et al.* (1986)	91	–	D ± C	Graded scale plus photos	61%	▫	[88]
Barzo *et al.* (1992)	88	–	C800–1000, M40–60 F200–250 and multiple combinations	Graded scale	90%	▫	[89]
C Christododoulou, Athens Medical Centre, Greece	83	–	D50–60 or E60–110 or P175–200 or ET and combinations	Graded scale	65%	▫	[Pers. Comm.]
Goldhirsch *et al.* (1982)	82	–	D30–70 alone or in multiple combinations	No wig required	57%	▫	[90]
Ridderheim *et al.* (2003)	74	–	Multiple combinations	No wig required	78%	▫	[91]
Auvinen *et al.* (2010)	64	–	D60; DT80; F600, E60, C600; 3 × DT 80 + 3 × F600, E60, C600	Graded scale	80%	▫	[33]
Kato *et al.* (2008)	64	–	Multiple combinations	Graded scale	94%	▫	[92]
Middleton *et al.* (1985)	60	–	D40, Vc1.4, C200 × 4 p.o.	Graded scale	0%	▫	[93]
Byachov (2006)	59	–	Multiple combinations	Graded scale	85%	▫	[94]
Katsimbri *et al.*	57	–	Multiple	Graded	Tx: 88%, ET:	▫	[95]

(2000)			combinations	scale	100%, Tx + ANR: 36%, ANR: 100%		
B Kolen, Elisabeth Hospital, Tilburg, Holland	55	–	D60, C600 or multiple combinations	No wig required	47%	▫	[Pers. Comm.]
Ciambellotti (1993)	50	–	E30–50 (weekly)	Graded scale	100%	▫	[96]
Hillen *et al.* (1990) (cold air)	48	–	Multiple combinations	Graded scale	CMFP: 95%; CMFPCAP: 30%; EC: 0%	▫	[58]
Semsek (2000)	45	–	D or E > 50 and multiple combinations	Graded scale	82%	▫	[97]
Howard and Stenner (1983)	35	–	Combinations including D	Graded scale	100%	▫	[98]
Kolen *et al.* (2002)	31	–	D60, C600 or DT100 or multiple combinations	No wig required	52%	▫	[99]
Anderson *et al.* (1981)	31	–	D40, Vc2 or Vd5	Graded scale	90%	▫	[100]
Dougherty (1996)	30	–	D or E or in multiple combinations	Graded scale	50%	▫	[29]
Wills *et al.* (2009)	28	–	Multiple combinations	Graded scale	47%	▫	[101]
Hunt *et al.* (1982)	28	–	D40, Vc2, Vd5 or D80	Graded scale plus photos	79%	▫	[102]
Adams *et al.* (1992)	24	–	E100, E50	Graded scale	E100: 0%; E50: 86%	▫	[103]
AD Klaren, Albert Schweitzer Hospital, Dordrecht, Holland	23	–	D60, C600	No wig required	76%	▫	[Pers. Comm.]
Fiebig *et al.* (1997)	23	–	D > 50, C with multiple combinations	Graded scale	90%	▫	[104]
Alexopoulos *et al.* (1999)	15	–	ANR, Tx, CMF	Graded scale	80%	▫	[105]
Dixon-Hughes (1984)	13	–	D, Vc	ns	76%	▫	[106]
Hillen *et al.* (1990) (cryo gel)	13	–	Multiple combinations	Graded scale	CMFP: 89%; CMFPCAP: 0%	▫	[58]
Cooke *et al.* (1981)	ns	–	D40	ns	55%	▫	[107]

†WHO grade 0,1,2 unless in the opinion of the authors the hair preservation in a part of the patients with grade 2 is not good or if the authors mention 'good hair preservation' or 'no wig required'.
‡Doses not per m^2.
§p-value calculated for the incidence of alopecia of any grade.
¶Depending on who rated hair loss: patients, nurses or experts.
#Among patients who purchased a wig, it was significantly less used in the scalp-cooled group ($p < 0.0001$).
†† The noncooled patients lost an average of 80% of their hair, the cooled patients 30%.
‡‡No significant difference between 90 and 45 min PICT.
ANR: Anthracyclines; C: Cyclophosphamide; Ch: Chlorambucil; Cp: Cisplatin; Ct: Cytarabine; D: Doxorubicin; DT: Docetaxel; E: Epirubicin; ET: Etoposide; F: 5-fluorouracil; H: Historical control; M: Methotrexate; Mi: Mitoxantrone; NS: Not significant; ns: Not specified; P: Paclitaxel; PICT: Post-infusion cooling time; p.o.: Per orem; Pr: Prednisolone; Tx: Taxanes; VAS: Visual analogue scale; Vc: Vincristine; Vd: Vindesine.

Table 3. Overview of scalp cooling results in The Netherlands 2006–2009.

Chemotherapy†	Patients with good hair preservation (%)
F500E100C500-D100	47 (n = 45)
F500E100C500	33 (n = 123)
F500E90C500	52 (n = 552)
F500D50C500	55 (n = 38)
P175Carbo5/6	37 (n = 49)
P70–90 (mono/combinations)‡	82 (n = 39)
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Irinotecan350	29 (n = 41)

†Numbers represent the dosage in mg/m^2.
‡Administered at weekly schemes; dosages range from 70 to 90 mg/m^2.
§Docetaxel combinations with exception of docetaxel, doxorubicin, cyclophosphamide (DTAC).
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Temperature In 1982, Gregory *et al.* found a clear relation between the degree of decrease in scalp temperature and the protective effect against hair loss in patients treated with doxorubicin ( ).[74] In this very important study, the difference between the mean temperature of patients with good and bad results was only 4 °C. Therefore, the relationship between the degree of scalp cooling and success rate seems to be rather critical. However, no further studies have been conducted to confirm this finding, for doxorubicin or other forms of chemotherapy. Scalp temperature measurements during scalp cooling are rarely carried out and are difficult to compare.[56,58,109] Thus, after more than 40 years of scalp cooling application, optimal scalp hypothermia for various chemotherapy schemes is unknown. A nonclinical study conducted by Janssen was based on a heat transfer model.[109] He concluded that for doxorubicin the superficial scalp skin temperature should be less than 19 °C. Van de Sande *et al.* reported a decrease of scalp skin temperature from 19.5 to 16.8 °C by use of conditioner [van de Sande M, van den Hurk CJG, Nortier JWR, Breed WPM. Scalp cooling influence on core temperature and the temperature decreasing effect of hair conditioner. (2011). Manuscript in preparation]. Comparing this obtained mean skin temperature without conditioner (19.5 °C) with Gregory's findings raises the question of whether more intensive cooling is needed in a subset of the patients.

Table 4. Comparison of studies regarding scalp temperature during scalp cooling.

Temperature (°C)	Gregory 1982 [74]	Van de Sande [Manuscript in preparation]	Janssen 2007 [109]
	Patients hair preservation	Volunteers	Heat transfer model
23	▫	▫	▫
22	Bad	▫	▫
21	▫	▫	▫
20	▫	Without conditioner	▫
19	▫	▫	▫
18	Good	▫	Optimal
17	▫	With conditioner	Optimal
16	▫	▫	▫

Mean superficial skin temperatures during scalp cooling obtained versus desired according to Gregory [74].

It is diffcult to carry out scalp temperature measurements during cooling, and the degree of scalp hypothermia cannot be predicted from the decrease of the temperature of cooling fluid or heat extraction of the cooling device. The reason is that the heat gradient from cold cap to scalp skin varies considerably between individuals.[109] Moreover, cold-induced heat production of the body may play a role.[110–113] Theoretically, a lower core temperature may diminish the effect of some types of chemotherapy. Therefore, we measured core temperature during long-term scalp cooling. Up to now, there is no evidence that scalp cooling decreases one's core temperature [van de Sande M, van den Hurk CJG, Nortier JWR, Breed WPM. Scalp cooling influence on core temperature and the temperature decreasing effect of hair conditioner. (2011). Manuscript in preparation].

Wetting of the Hair Wetting of the hair is often used in the UK, and is strongly advised by Hunt *et al.*[102] However, there are no comparative studies regarding the influence of wetting on scalp temperature and scalp cooling success rates.

Cap Application/Fitting of the Cap Contact between the cold cap and the scalp skin is decisive for scalp temperature. It is evident that optimal fitting of the cap is an important factor for success. Often, bald areas are seen where the cap did not fit properly.

Scalp Cooling Times & Half-life Time Theoretically, the cooling time after infusion of chemotherapy (the postinfusion cooling time [PICT]) should be related to the half-life time of the used cytostatics, their active metabolites and the duration of infusion. However, research on PICT is very scarce. In a review, Grevelman *et al.* reported a median success rate of 76 and 71% when the PICT was 90 or more and 90 or less minutes, respectively, in 47 studies.[1,114] A wide range in PITCs is still seen today, for example, Wills and colleagues used 3 h[101] and Auvinen used 15–20 min.[33]

We are investigating whether good results of scalp cooling can lead to a shortened PICT and whether a longer PICT might improve the less satisfying results. To date, we found no difference in results when patients treated with DT (monotherapy or combinations) were randomized between 45- and 90-min PICT (n = 180).[85] Therefore, we started a new DT study in which patients are randomized between 45- and 20-min PICT. In patients treated with FEC chemotherapy, we investigate whether a PICT of 150 min is more favorable than a PICT of 90 min.

The manufacturers of cooling systems, Paxman and Dignitana, recommend very different cytostatic-specific PICTs. Both manufacturers do not mention that the duration of cooling during the actual administration of chemotherapy is also important. In daily practice, these administration times of specific schedules differ greatly.

Previous Chemotherapy As hair loss induced by paclitaxel is considerably increased if patients have undergone previous chemotherapy, it seems likely that the results of cooling will also be influenced by previous chemotherapy.[115] Therefore, previous chemotherapy treatments should always be taken into consideration when analyzing results of scalp cooling.[1,101]

Hair Characteristics In cases of Afro–American hair, scalp cooling is less successful. It is unknown whether the sometimes advised increase of PICT, wetting the hair or lowering the temperature of liquid coolant are useful to improve these results. A lower temperature of liquid coolant seems more reasonable to improve hair preservation in these situations because thickness of the hair layer is one of the most important variable factors for scalp temperature.[109]

Liver Function & Liver Metastases The influence of liver function and liver metastases on the success of scalp cooling is controversial. In 13 studies, liver function or the presence of liver metastasis were taken into consideration for the hair-protective effect of scalp cooling. In six out of these 13 studies, impaired liver function seemed to be related to less benefit from cooling.[62,75,82,100,116,117]

Device Only very few, small studies have been carried out to find out which method of scalp cooling is the most effective,[29,57,58] and these studies are not conclusive. Therefore, our results with Paxman devices can not be generalized to other cooling devices.

Haircare All issues regarding haircare remain to be clarified. Recently, both Wills *et al.*[101] and Auvinen *et al.*[33] described their attention to haircare in periods before, during and after scalp cooling (washing, coloring, drying and the use of hot rollers or curling irons and products containing alcohol or peroxide, avoiding hot air and hot water and hard brushing, and using gentle products). However, none of this advice is evidence based. Nevertheless, since exposure to heat affects the strength of the hair, it seems logical to avoid the use of extreme heat applicators.[118] It also seems logical to advise the use of a wide-toothed comb or soft bristle and avoid excessive combing and brushing because breakage of thinned hair is an important factor in CIA.

Side Effects & Tolerance In general, scalp cooling is well tolerated. Tolerance can be graded by a Visual Analogue Scale of 0–10, in which 0 represents 'not tolerable' and 10 means 'really well tolerable'. Mean scores vary between 6.9 and 8.0.[85,99,119] No serious side effects have been reported. The most common reported side effects are headaches, unpleasant feelings due to the heaviness of the cap and coldness, dizziness and transient lightheadedness. Headaches are mostly not severe and can usually be prevented by paracetamol. Freezing has never been reported. Side effects in more than 10% of the patients were the reason to stop scalp cooling in only four of all studies.[59,68,88,95] Dougherty reported that in the group of patients in which cooling had been ineffective, 38% felt that they would want the scalp-cooling procedure again if they needed another chemotherapeutic treatment.[29]

Scalp Skin Metastases Scalp cooling has been somewhat controversial in the curative chemotherapy setting. The concern is regarding the risk of scalp metastases, which may have a negative influence on the course of the disease, as a result of the decreased drug exposure by the decrease of scalp blood perfusion. However, a negative influence on the course of the

disease by scalp cooling has only been reported in one patient with mycosis fungoides and one patient with leukemia (which is a contraindication for scalp cooling). It has never been reported in patients with solid tumors.[29]

In a review of 2005, scalp skin metastases were found in nine patients out of a total of approximately 2500 patients in 56 scalp cooling studies.[1,65,78,83,93,117,120,121] In all these cases, it was very unlikely that scalp metastases were a result of scalp cooling. Lemenager *et al.* and Ridderheim *et al.* looked systematically for the incidence of scalp skin metastases after scalp cooling and did not find an increased incidence in scalp metastases.[67,91] Christodoulou *et al.* reported in 442 patients an incidence of scalp metastases of 0.45% across all tumor types and 0.88% (two out of 227) for breast cancer patients.[122] Lemieux *et al.* were the first who specifically designed a study to assess the incidence of scalp metastases in early breast cancer patients who received neoadjuvant or adjuvant chemotherapy.[123] They studied 553 patients with scalp cooling and 87 without scalp cooling, with a median follow-up of more than 5 years. The incidence of scalp metastases was low in both groups, 1.1% (six out of 553) in women who did get scalp cooling and 1.2% (one out of 87) without scalp cooling. Scalp metastases were never the first single site of recurrence, but were diagnosed at the same time, or after previous diagnosis of metastases at other sites. Spaeth *et al.* found no increase in incidence of scalp or brain metastases in a multicenter study of 911 scalp-cooled patients.[66] Auvinen *et al.* encountered a couple of breast cancer patients with scalp metastases, but none of these patients used scalp cooling ( ).[33]

Table 5. Summary of the most important studies regarding the incidence of scalp metastases in patients with and without scalp cooling.

Study (year)	Study design	Patients (n)	Breast cancer	Other types of cancer	Scalp-cooled patients	Non-scalp-cooled patients	Scalp metastases		Ref.
							%	Number	
Spaeth *et al.* (2008)	Prospective	911	▫	+	770	141	No excess	▫	[66]
Grevelman and Breed (2005)	Review	Approximately 2500	▫	+	+	▫	0.4	9 out of 2500	[1]
Christodoulou *et al.* (2006)	Retrospective	442	▫	+	+	▫	0.9†	2 out of 227‡	[122]
Lemieux *et al.* (2009)	Retrospective	553 87	+ +	▫	+	-	1.1 1.2	6 out of 553 1 out of 87	[123]
van de Sande *et al.* (2010)	Retrospective	885	+	▫	▫	+	0.5	4 out of 885	[124]
van den Hurk *et al.* (2010)	Retrospective	33,771	+	▫	▫	+	1.8	616 out of 33,771	[Manuscript in preparation]

†0.9% among breast cancer patients; 0.5% among all patients; ‡2 out of 227; 227 breast cancer patients.

In non-scalp-cooled patients, van de Sande *et al.* found a scalp skin metastases incidence of 0.5% in 885 high-risk breast cancer patients, after a median follow up of 110 months.[124] van den Hurk *et al.* studied the incidence of cutaneous metastases in 33,771 breast cancer patients without metastases at diagnosis [van den Hurk CJG, Eckel R, van de Poll-Franse LV *et al.* Unfavourable pattern of metastases in M0 breast cancer patients during 1978–2008: a population based analysis of the Munich Cancer Registry (2010). Manuscript submitted]. Within 5 years following initial diagnosis, 1.8% of these patients developed a distant skin metastasis.

A meta analysis of Krathen *et al.* showed that, compared with other malignancies, skin metastases are most common in breast cancer.[125] A total of 24% of the breast cancer patients had skin metastases, and the face and scalp were the least common sites (5 and 7%, respectively).

In conclusion, for breast cancer patients the theoretical risk of scalp cooling during adjuvant chemotherapy seems to be minimal. In visceral malignancies other than breast cancer, the risk associated with scalp cooling will be even lower, because the incidence of cutaneous metastases is lower.

Requests to investigate the influence of scalp cooling on survival or on the incidence of scalp skin metastases are rather senseless. First, a very large number of patients and a very long follow-up are needed and second, it will have minimal consequences since methods of scalp cooling and chemotherapy will have changed by the time the study is finished.

Brain Metastases Fear of undoing the effect of chemotherapy on (micro-) brain metastases by cooling is rarely seen. It seems unrealistic as the current cooling techniques do not cause a significant decrease in brain temperature.[126]

Spaeth *et al.* reported no excess of brain metastases in a multicenter prospective study of 911 mainly breast cancer patients; 770 patients with scalp cooling, 141 patients without scalp cooling and a median follow-up of 36 months.[66]

Contraindications

Scalp cooling should not be applied in cases of:

- Hematological malignancies: leukemia, multiple myeloma, non-Hodgkins and other generalized lymphomas
- Cold sensitivity, cold agglutinin disease, cryoglobulinemia, cryofibrinogenemia and cold traumatic dystrophy
- Melanoma patients with adjuvant or curative chemotherapy

Impact of Scalp Cooling on QoL A trend to better well-being was found in successfully scalp-cooled patients, as evidenced by a generally improved QoL and an improved body image.[32] These findings correspond to another study of van den Hurk *et al.*, a cost–effectiveness study [van den Hurk CJG. Cost effectiveness of scalp cooling in the prevention of chemotherapy-induced hair loss (2010). Manuscript in preparation].

Scalp cooling contributes to the well-being of successfully scalp-cooled patients, but seems to cause additional distress and less well-being when patients lose their hair despite scalp cooling. From a psychological point of view, the uncertainty regarding hair preservation in scalp-cooled patients may cause additional distress, and severe alopecia despite scalp cooling may lead to extra disappointment [van den Hurk CJG. Cost effectiveness of scalp cooling in the prevention of chemotherapy-induced hair loss (2010). Manuscript in preparation; 127]. However, an alternative or concomitant explanation for the differences in well-being is physiological in nature; maybe unsuccessfully scalp-cooled patients have a greater biological availability of cytostatics. This hypothesis is supported by the additional report of more hot flashes, more fatigue, more nausea and less appetite in unsuccessfully scalp-cooled patients in comparison with successfully and non-scalp-cooled patients. Moreover, it could explain their alopecia despite scalp cooling.[32] Another argument for this physiological hypothesis is the observation of a relationship between the occurrence of CIA and bone marrow suppression.[12]

Cost–Effectiveness of Scalp Cooling In The Netherlands, van den Hurk *et al.* conducted a study on the cost–effectiveness of scalp cooling with Paxman coolers (PCS) in 15 hospitals, with a total of 160 scalp-cooled patients and a control group of 86 patients without scalp cooling [van den Hurk CJG. Cost effectiveness of scalp cooling in the prevention of chemotherapy-induced hair loss (2010). Manuscript in preparation]. A considerable difference was observed between hospitals with regard to the type of patient groups that were offered scalp cooling (gender, type of cancer and type of chemotherapy) and the number of cooling sessions per machine. A total of 30% of scalp-cooled patients reported severe hair loss, versus 91% in the non-scalp-cooled group. In total, 52 of the scalp-cooled patients purchased a wig and 62% of these patients used it. In non-scalp-cooled patients, 77% purchased a wig and nearly all used it (89%). In The Netherlands, most patients are fully or partly compensated by health insurance companies for one wig a year, but up to now hospitals are not compensated for scalp cooling.

It appeared that the total costs (costs of scalp cooling, wigs and other head covers and hair dressers) were considerably lower when scalp cooling was applied. In the Dutch situation, scalp cooling saved €252 per patient. The hospital spent a mean of €200 per scalp-cooled patient. Health insurance companies saved a mean of €292 per scalp-cooled patient and the patient saved €160.

Considerable improvement of cost–effectiveness will be possible by means of:

- Reducing costs. These can be reduced:
    - If purchase of machines is better tuned into the number of cooling sessions. A hospital that owns one cooling machine can treat at least one patient a day, but, in van den Hurk's study, overall less than three patients a week were cooled
    - Advising patients only to purchase wigs when hair loss really occurs. Both in this study and in the study of Auvinen, many patients purchased a wig and never used it[33]
- Increasing the proportion of patients that are satisfied with the result. This can be obtained by better selection of patients for scalp cooling and improved scalp cooling methods

We are neither aware of any other study on the cost–effectiveness of scalp cooling compared with standard care, nor of studies comparing the costs of different cooling systems.

Only one nurse manager who had used Elastogel™ caps for many years reported to have switched to a cooling machine for cost–effectiveness and time-investment reasons. First of all, Elastogel-caps had to be replaced regularly due to a rising temperature during wearing the cap. Moreover, the time invested by the nurse in each cooling session was much less if a cooling machine was used than when caps had to be changed regularly. One can expect that the use of cooling machines is cheaper unless there are only a few cooling sessions in a hospital. Although scalp cooling requires an extra time investment, most nurses report that they offer it with pleasure [Peerbooms M, van den Hurk CJG, Breed WPM. Inquiry on scalp cooling among Dutch oncologists, nurses and patients (2010). Manuscript in preparation].

Management of CIA

Although scalp cooling may prevent CIA in a considerable number of chemotherapy patients, CIA is still unavoidable for some patients. Patients have to be prepared for potential hair loss to minimize its impact on QoL.[3,128] Information regarding side effects of cancer increases understanding, satisfaction and treatment compliance and decreases emotional distress, anxiety and depression.[42,129,130] Adaptive self-care strategies to prepare for and cope with CIA should be introduced, based on individual discussions with patients. Intervention strategies should be developed for the anticipation of hair loss, actual hair loss, coping with CIA and hair regrowth.[5,131] The hair program described by McGarvey *et al.* is a promising program for supportive care in CIA.[43] In a study of Mols *et al.,* 82% (n = 126) of the patients who used a wig or head cover were satisfied with it.[34] In another study, satisfaction with wigs and head covers was reported in 87% of the patients who had hair loss, during and within 6 months after completing chemotherapy [van den Hurk CJG. Cost effectiveness of scalp cooling in the prevention of chemotherapy-induced hair loss (2010). Manuscript in preparation].

Suggestions for Solutions of Scalp Cooling Problems

The increasing influence in healthcare of assertive patient organizations and client counsels of hospitals should be used to improve the underestimation of the impact of hair loss by medical professionals and to stimulate the use of scalp cooling and research. Drawing up protocols and guidelines for CIA prevention by scalp cooling will have many advantages: these will not only be a guideline for the many uncertain oncology nurses and oncologists, but will also lead to discussion, increased interest, a better knowledge of scalp cooling possibilities and limitations, an increase of scalp cooling application and stimulation of research to prevent CIA. We are preparing a working group to draw up a protocol as a first step to an official guideline for international oncology nurses and oncologist organizations. To improve knowledge of results of present applications of scalp cooling, success rates should always be registered in every hospital. To limit the nursing time, patients should have a major role in hair loss registration; preferably online. Per region or country data should be sampled and evaluated. In this manner, it is possible to gain an idea of whether scalp cooling in a specific (new) chemotherapy schedule is useful or not. Moreover it will give insight into the quality of nursing care of scalp cooling and allows for the possibility to recognize less optimal care and the need for improvement.

This registration and evaluation of results in daily practice in general hospitals proved to be very effective in The Netherlands; in a rather short time a lot of success rates became available for many, also new, chemotherapy schedules. This is very useful for patient information and decisions regarding management and research priorities.

Research to improve scalp cooling results, for example to establish the optimal skin scalp temperature and optimal post-infusion cooling time, will be much more effective if new possibilities and ideas are applied, such as, first, a rather simple objective method to measure hair loss – the trichometer developed by Cohen[59] – and second, our idea to compare the hair preservation of different cooling intensity (or no cooling at all) and duration of small parts on the left and right side of the scalp.

Expert Commentary

In spite of the use of newer chemotherapy, the incidence of CIA is very high. The ongoing underestimation by medical professionals of the great impact of CIA for patients and their relatives has led to minimal research to prevent CIA, even though it is by far the most applied intervention to prevent CIA. It is evidence-based that scalp cooling is a moderate to very effective method of preventing CIA, which is in general well tolerated and without severe side effects. Patients' satisfaction regarding hair preservation has to be the most important criterion for success of scalp cooling. Up to now, the use of wigs or head covers is the best parameter for this satisfaction. The success rate of scalp cooling depends on many factors. The quantitative influence of these factors is not well known. Concerns regarding the protection of malignant cells in the scalp skin by scalp cooling have been proven to be exaggerated, with an exception in cases of chemotherapy with curative intention in patients with hematological malignancies or melanoma. Healthcare professionals have to offer the possibility of scalp cooling to all potential patients and have to explain the theoretical risk (although very small) of a disadvantageous disease course to adjuvant treated patients. The cost–effectiveness of scalp cooling is favorable. Scalp cooling should be available in all hospitals where cancer patients are treated with chemotherapy. More attention focused on the development and application of strategies to cope with CIA is needed.

Five-year View

Currently, there are no alternative strategies to prevent CIA other than scalp cooling. It is very unlikely that other strategies, such as pharmacological agents, electrotrichogenesis or laser therapy, will be an alternative for scalp cooling within 5 years. Results of scalp cooling will be improved by clinical research, improvements of scalp cooling devices and more intensive multicenter registration of scalp cooling results and central analysis of those registration data. The optimal scalp hypothermia and the optimal PICT to reduce CIA will be investigated for various chemotherapy schedules. This will be facilitated by the availability of a new rather simple objective method to measure hair quantity, the cross-section trichometer of Cohen and a new human research model. In this model, the influence of variation in the intensity and duration of cooling of small parts of the left and right side of the scalp on CIA can be studied. This research will contribute to the improvement of scalp cooling results and, together with the application of new psychosocial strategies to cope with all problems related with CIA, will result in a better quality of life for chemotherapy patients

Sidebar

Key Issues

- There is a very high incidence of chemotherapy-induced alopecia (CIA).
- Generally, CIA presents as acute temporary diffuse hair loss.
- CIA is one of the most common and emotionally distressing side effects of chemotherapy.
- The impact of CIA on patients and their relatives is considerably underestimated by medical professionals.
- To date, scalp cooling is by far the best method to reduce CIA.
- It is evidence-based that scalp cooling is moderate to very effective to prevent or reduce CIA. Success rates vary considerably in different chemotherapy regimens.
- Generally, scalp cooling is well tolerated.
- Concerns regarding the protection of malignant cells in the scalp skin by scalp cooling have been proven to be exaggerated.
- Scalp cooling is contraindicated in chemotherapy with curative intention for most patients with hematological malignancies or melanoma.
- Research conducted to prevent CIA is very minimal. There are promising facilities for research.
- Central evaluation of hospital's scalp cooling results gives much insight into the many factors influencing these results.
- Generally, the cost–effectiveness of scalp cooling is favorable compared to the purchase of wigs or head covers.
- Scalp cooling should be available in every hospital, and every suitable patient should be given the opportunity, after being well-informed by their doctor or nurse, to choose for scalp cooling.
- New individual psychosocial strategies to cope with CIA and scalp cooling are promising.

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