

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/21761> holds various files of this Leiden University dissertation.

**Author:** Hurk, Corina van den

**Title:** Safety and effectiveness of scalp cooling in cancer patients undergoing cytotoxic treatment

**Issue Date:** 2013-09-19

# **Safety and effectiveness of scalp cooling in cancer patients undergoing cytotoxic treatment**

Corina J.G. van den Hurk

## COLOPHON

The research presented in this thesis was carried out at the department of Clinical Oncology of Leiden University Medical Centre (LUMC) and the research department of the Comprehensive Cancer Centre South (IKZ).

Printing and dissemination of this thesis was financially supported by

Leids Universitair Medisch Centrum, Leiden, The Netherlands  
Paxman Coolers Ltd, Huddersfield, UK  
Integraal Kankercentrum Zuid, Eindhoven, The Netherlands  
Incomed B.V., Laarbeek, The Netherlands  
Vierpool B.V., Maarssen, The Netherlands  
Intermélica Kliniek voor haarziekten, Geldermalsen, The Netherlands  
Sanofi-Aventis Nederland B.V., Gouda, The Netherlands  
Teva Nederland B.V., Haarlem, The Netherlands  
Merck Sharp & Dohme B.V., Haarlem, The Netherlands  
Stichting Olijf, Amsterdam, The Netherlands ([www.olijf.nl](http://www.olijf.nl))

Cover design and lay-out Marlies van Hoof, [www.madebymarlies.nl](http://www.madebymarlies.nl)  
Printed by Gildeprint Drukkerijen, Enschede

ISBN 978-94-6108-489-7

Copyright © Corina J.G. van den Hurk, 2013

All rights reserved

No part of this thesis may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, any information storage or retrieval system or otherwise without permission of the author.

# **Safety and effectiveness of scalp cooling in cancer patients undergoing cytotoxic treatment**

Proefschrift

ter verkrijging van  
de graad van Doctor aan de Universiteit Leiden,  
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,  
volgens besluit van het College voor Promoties  
te verdedigen op donderdag 19 september 2013  
klokke 15.00 uur

door

Corina Johanna Geertruida van den Hurk  
geboren te Geffen  
in 1978

## **Promotiecommissie**

- Promotores:** Prof. dr. J.W.R. Nortier  
Prof. dr. J.W.W. Coebergh (Erasmus Universiteit)  
Prof. dr. L.V. van de Poll-Franse (Universiteit van Tilburg)
- Copromotor:** Dr. W.P.M. Breed (Integraal Kankercentrum Zuid)
- Overige leden:** Prof. dr. E. van der Wall (Universitair Medisch Centrum Utrecht)  
Prof. dr. A.A. Kaptein  
Prof. dr. A.M. Stiggelbout

The research presented in this thesis was financially supported by:

- the Netherlands Organisation for Health Research and Development (ZonMW), The Hague, The Netherlands
- Sanofi Aventis, Gouda, The Netherlands
- Comprehensive Cancer Centre South, Eindhoven, The Netherlands
- Give Hair a Chance Foundation, Waalre, The Netherlands, [www.geefhaareenkans.nl](http://www.geefhaareenkans.nl)

**Het is niet een kwestie van tijd hebben, maar van tijd maken.**

Voor pap en mam, Rien en Nellie



## Contents

	<b>Page</b>
Chapter 1. Introduction	9
<b>Part I Scalp cooling in the context of developing of scalp skin metastases</b>	
Chapter 2. Unfavorable pattern of metastases in M0 breast cancer patients during 1978-2008: a population-based analysis of the Munich Cancer Registry C.J.G. van den Hurk, R. Eckel, L.V. van de Poll-Franse, J.W.W. Coebergh, J.W.R. Nortier, D. Holzels, W.P.M. Breed, J. Engel.	27
Chapter 3. Adjuvant chemotherapy with and without scalp cooling in breast cancer patients: very low incidence of scalp skin metastases in retrospective studies C.J.G. van den Hurk, M.A. van de Sande, W.P.M. Breed, J.W.R. Nortier	47
Chapter 4. Scalp cooling to prevent alopecia after chemotherapy can be considered safe in patients with breast cancer C.J.G. van den Hurk, L.V. vd Poll-Franse, W.P.M. Breed, J.W.W. Coebergh, J.W.R. Nortier	57
<b>Part II Effectiveness and the impact of scalp cooling time</b>	
Chapter 5. Scalp cooling for hair preservation and associated characteristics in 1411 patients – Results of the Dutch Scalp Cooling Registry C. J.G. van den Hurk, M. Peerbooms, L.V. van de Poll-Franse, J.W.R. Nortier, W. P.M. Breed	71
Chapter 6. Short post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia C. J.G. van den Hurk, J.W.R. Nortier, W.P.M. Breed	89
Chapter 7. Impact of scalp cooling on chemotherapy-induced alopecia, wig use and hair growth of patients with cancer C.J.G. van den Hurk, M.E. van den Akker-van Marle, W.P.M. Breed, L.V. van de Poll-Franse, J.W.R. Nortier, J.W.W. Coebergh	101
<b>Part III Impact of chemotherapy-induced alopecia and scalp cooling on quality of life</b>	
Chapter 8. Impact of alopecia and scalp cooling on the well-being of breast cancer patients C.J.G. van den Hurk, F. Mols, W.P.M. Breed, A.J.J.M. Vingerhoets	117
Chapter 9. Scalp cooling to prevent chemotherapy-induced hair loss: practical and clinical considerations F. Mols, C.J.G. van den Hurk, W.P.M. Breed, A.J.J.M. Vingerhoets	133



## **Part IV Cost-effectiveness**

Chapter 10.	Cost-effectiveness analysis of scalp cooling to reduce chemotherapy-induced alopecia C.J.G. van den Hurk, M.E. van den Akker-van Marle, W.P.M. Breed, L.V. van de Poll-Franse, J.W.R. Nortier, J.W.W. Coebergh	153
Chapter 11.	Discussion	169
Summary		187
Samenvatting		193
Curriculum vitae		201
List of publications		205
Dankwoord		209

# Chapter 1



**Introduction**



## Introduction

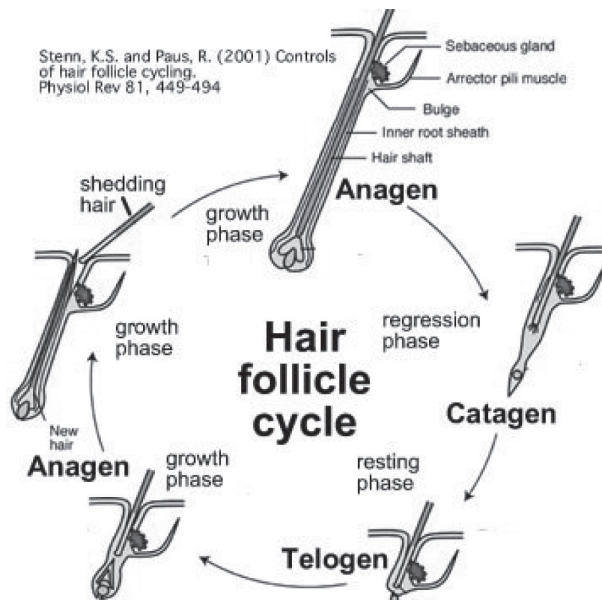
This chapter provides an overview of the mechanism, incidence and prevention of chemotherapy-induced alopecia (CIA) as well as its impact on cancer patients. Furthermore, the working-mechanism, safety, effectiveness and implementation of scalp cooling are addressed.

*(This chapter is partly derived from 'Hurk van den CJG, Breed WPM, Mols F. Chemotherapy-induced hair loss. In: Preedy Ve, editor. Handbook of Hair in Health and Disease. Wageningen, The Netherlands: Wageningen Academic Publishers; 2012. p. 403-16')*

## Mechanism of CIA

Rapidly proliferating cells, like cancer cells, are more susceptible to cytotoxic damage than most healthy cells in the human body, which are usually in a resting stage. However, certain healthy cell types multiply quickly, such as hair matrix cells, the hematopoietic cells in the bone marrow, and epithelial cells of the mouth and the gastro-intestinal tract.<sup>1</sup> These healthy cells are in a similar way affected by cytotoxic agents, resulting in side effects such as alopecia, impaired bone marrow function, mucositis, nausea and diarrhea.

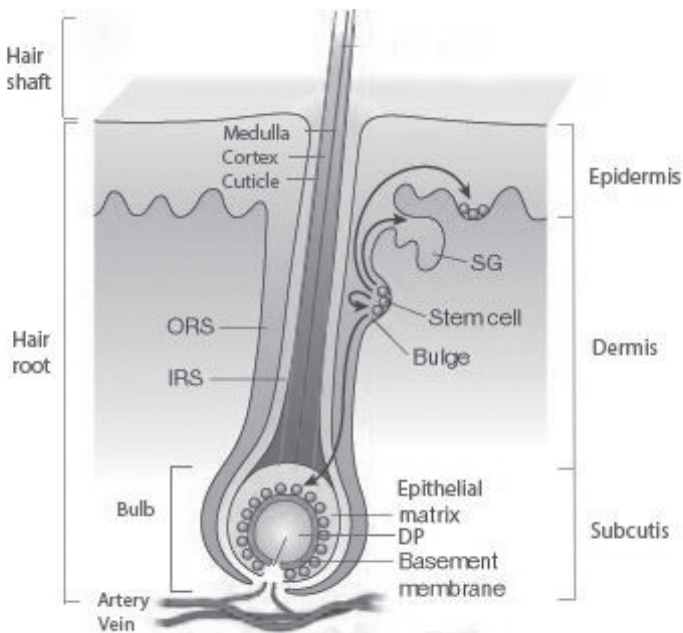
The hair follicle cycles through three distinct phases: anagen (growth), catagen (regression) and telogen (rest) (Figure 1). Scalp hair follicles are in about 90% in the anagen phase<sup>2,3</sup> and remain there for 2 to 8 years. During the catagen phase, lasting for 2 to 3 weeks, the hair follicle atrophies. The telogen phase lasts for 2 to 6 months and comprises less than 1% of the follicles. This phase ends with shedding the hair shaft from the follicle, while a new shaft is regenerated in the anagen phase.



**Figure 1.** Hair follicle cycle.

Sensitivity to chemotherapy of each part of the follicle depends on its cycling rate. Cytotoxic agents mainly affect anagen hair follicles<sup>1,4</sup>, because of their rapidly proliferating cells in the epithelial matrix of the bulb (Figure 2).<sup>5</sup> Cytotoxics suppress mitosis and initiate apoptosis of these cells. The agents also damage the follicle vasculature and the sebaceous gland, which negatively affects its health and function.<sup>6</sup> Three mechanisms have been described related to CIA: (a.) anagen effluvium (effluvium = hair loss), (b.) transition to telogen effluvium and (c.) continued anagen phase.

(a.) In general, CIA has been categorized as anagen effluvium, that is acute diffuse hair loss.<sup>1</sup> If the proliferating cells are excessively damaged, hair synthesis is impeded. It induces a sharp constriction of the hair shaft, causing a fracture in the hair.<sup>4</sup> Hair loss usually starts one to three weeks after the first chemotherapy<sup>1,7</sup> and subsequently patients become bald within several days. However, when using agents in lower dosages or with less toxicity for hair follicles, CIA may slowly occur and only becomes clinically apparent after several chemotherapy courses. Then the follicle is not able to recover between the courses and the damage is cumulative. (b.) When the hair is in its late anagen phase, with a lower mitotic activity, excessive damage by cytotoxics accelerates the hair in its normal path to telogen.<sup>4,8,9</sup> This also leads to a greater amount of shedding hairs.



**Figure 2.** Hair follicle.

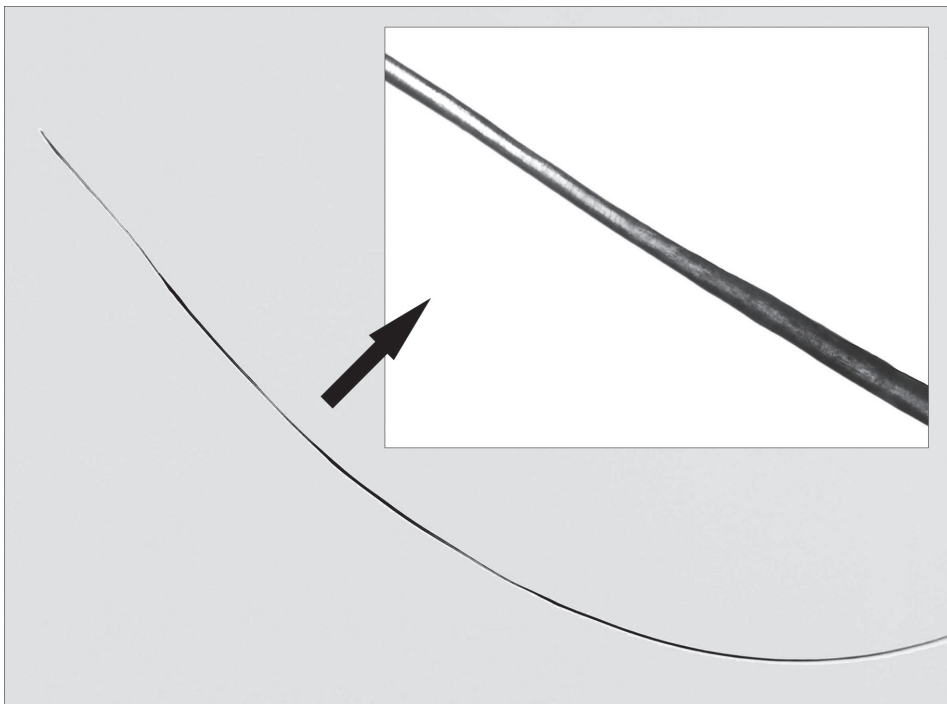
SG= Sebaceous gland  
 ORS= outer root sheath  
 IRS= inner root sheath  
 DP= dermal papilla

(c.) In case of moderate damage, hair follicles may also stay in the anagen phase. Then the follicle is able to recover and cells in the epithelial matrix continue with mitosis between the chemotherapy courses.<sup>10</sup> The hair growth rate is reduced to 0.004-0.1 mm per day as opposed to the normal rate of 0.35 mm per day. Furthermore, a weak, only partially keratinized proportion of the hair shaft is produced<sup>1,5</sup> with fewer cells per unit length<sup>11</sup> (Figure 3). Sometimes these thinner parts can be seen by the naked eye and their number accords the number of chemotherapy courses. Whether the hair breaks, even within the intra-dermal part of the hair follicle, depends on the balance between the loss of tensile strength and external forces, like combing or contact of the head with a pillow.

CIA can occur in all parts of the body. Hair loss is more pronounced on the scalp because this site normally contains more hairs in the anagen phase than other sites like eyebrows, eyelashes, beard, and axillary and pubic hair.<sup>1</sup>

### Hair growth after chemotherapy

In CIA, hair growth is usually only temporarily inhibited. The hair starts growing again because the stem cells of the hair follicle are protected against the cytotoxics<sup>5</sup>, presumably by their slower growth rate and enhanced repair mechanisms.<sup>6</sup> The normal hair growth rate usually returns within several weeks<sup>1,12</sup> to several months<sup>8</sup> after the last chemotherapy infusion. After hair has grown back, the telogen count is the same, even after repeated episodes of CIA, showing that the hair cycles have not been materially altered.<sup>1</sup> When hair grows again, about



**Figure 3.** Diminished hair shaft diameter after chemotherapy with scalp cooling (photo: H. Snijders).

65% of the patients experience a change from their previous hair color or texture (dryness, curling, straightening)<sup>7</sup>, but this is mostly transient. The altered shape of the hair shaft (curly or straight) probably results from asymmetric proliferation and differentiation during recovery of the hair follicle. Changes in color are among others caused by the melanocyt response to cytotoxics.<sup>6</sup>

### Incidence of CIA

CIA occurs during cytotoxic treatment for a variety of tumors. Of the ±95,000 patients newly diagnosed with solid tumors in the Netherlands in 2010<sup>13</sup>, about 30% received (i.e. ±28,500) chemotherapy as part of their *primary treatment* (Netherlands Cancer Registry, personal communication). The proportion of patients without metastases at diagnosis (MO) who subsequently receive chemotherapy as *palliative treatment* for distant metastases is unknown, but an estimation for two common tumor types can be made:

In the Netherlands, each year approximately 3200 patients die because of metastasized (M1) breast cancer.<sup>13</sup> With a median survival of two years, it can be estimated that there are about 6400 M1 patients. About 1200 of them already had M1 disease at diagnosis. It is estimated that within two years about two third of the remaining 5200 patients receive chemotherapy during the course of M1 disease, resulting in about 1700 patients per year.<sup>14</sup>

Each year approximately 5000 patients die because of M1 colorectal cancer. Median survival at present after optimal chemotherapy is approximately 20 months, probably less if this is not feasible.<sup>15</sup> So there are about 8300 M1 patients, of whom about 1000 had metastases at diagnosis.<sup>13</sup> Approximately 60% of the remaining 7300 patients will receive palliative chemotherapy within 20 months<sup>16</sup>, thus contributing about 2600 patients per year.

From 2000 to 2008, the proportion of breast cancer patients who received chemotherapy as part of their primary treatment increased by 40%.<sup>17</sup> This proportion even doubled for patients with gastro-intestinal cancer (oesophagus, stomach, small intestine, colorectal) and lung cancer (Eindhoven Cancer Registry, personal communication) and in the period from 2007 to 2010 also for endometrial cancer.<sup>18</sup> The use of chemotherapy is still increasing, as well as the use of targeted therapies.

The incidence and severity of CIA depends on many factors, especially the type, dose, method of administration and frequency of infusion of cytotoxic agents. CIA is more common after intravenously administered than after orally administered chemotherapy and the incidence varies after intravenous administration of liposome-entrapped cytotoxic drugs.<sup>19-21</sup> Whether the toxic effect for epithelial matrix cells is mainly caused by the peak concentration of cytotoxics in these cells or the exposure time to cytotoxics is unknown. Other possible factors related to the severity of CIA are the patient's age, comorbidities, nutritional and hormonal aspects, psycho-emotional stress and multiple other factors within the individual patient.<sup>6</sup>

At present, commonly administered drugs with a high potential for inducing alopecia in solid tumors are: anthracyclines (doxorubicin and epirubicin), taxanes (docetaxel, paclitaxel, cabazitaxel), cyclophosphamide, irinotecan, etoposide and nonpegylated liposomal

doxorubicin.<sup>1,19,22</sup> Cisplatin, 5-fluorouracil, methotrexate, mitoxantrone, vinorelbine, gemcitabine, carboplatin,<sup>1,22</sup> and pegylated liposomal doxorubicin<sup>20,21</sup> cause less CIA. However, these latter agents are often administered in combination with other alopecia-inducing agents, and therefore CIA remains a frequently occurring side-effect. The exact percentages of CIA for each chemotherapy regimen are unknown and show a large variation in the literature.<sup>1,7</sup> It is estimated that at least half of the patients who receive chemotherapy are facing severe CIA.

Many chemotherapeutic agents share pro-apoptotic pathways that have crucial roles in CIA, especially P53-mediated signaling.<sup>6</sup> The chemotherapeutic agents most frequently associated with alopecia have however distinct mechanisms of action and differ substantially according to an individual's genetically determined susceptibility to chemotherapy-induced cytotoxic effects. CIA can therefore not be perceived as one entity.<sup>6</sup>

CIA is rarely permanent, which is defined as an absence of, or incomplete, hair growth six months after the last chemotherapy cycle. Nearly all patients with permanent CIA are patients with haematological malignancies or breast cancer patients receiving high dose chemotherapy and bone marrow transplantation. Reported incidences vary between 1% and 43%.<sup>12</sup> Busulphan is the most commonly implicated agent, but it has also been described following cyclophosphamide, thiotepa, melphalan, etoposide, carboplatin, docetaxel, paclitaxel<sup>12</sup>, and in the sequential scheme of 5-fluorouracil, epirubicin, cyclophosphamide (FEC) followed by docetaxel.<sup>23</sup>

### Impact of CIA on cancer patients

CIA is a constant reminder of the disease and it stigmatizes the cancer patient, not only for him- or herself, but also for others.<sup>24</sup> It has been repeatedly reported that for a majority of patients the experience of alopecia is distressing.<sup>25-29</sup> Surprisingly, the burden of CIA and its impact on Quality of Life (QoL) has hardly systematically been investigated in quantitative studies and CIA is rarely a primary outcome.<sup>30,31</sup> When ranking side effects of cancer treatment, patients indicate CIA as one of the most feared sequelae of chemotherapy<sup>32-34</sup> and rank it among the five most troublesome.<sup>35-38</sup> The impact of CIA on body image is the most often studied QoL aspect, but outcomes are inconclusive.<sup>7</sup>

Cancer patients cope differently with CIA. Coping comprises realizing an altered sense of self because of the changed appearance, trying to look normal, being reminded of the disease, using wigs or head covers and/or sharing being bald.<sup>39</sup> It is known that many patients purchase a wig and/or another head cover, but it has hardly been reported whether patients were satisfied with it and felt the need to wear it.<sup>25,39,40</sup> Wigs and head covers are a cost to health insurance companies and in some countries as well to patients. Cost aspects for the Dutch society are unknown.



Case reports: Different coping strategies in two young women with CIA.

Chantal, 25 years old women with a primitive neuroectodermal tumor for which combination chemotherapy was indicated with a curative intent

*“My friend and I were both in tears when shaving my head, it was horrible, but a solution for the ongoing confrontation with the hairs everywhere in the house. I couldn’t get used to my bald head. No matter how loud I over and over sang together with Christina Aguilera ‘I am beautiful, in every single way’, my altered appearance made me feel ugly, unattractive and I felt not like my usual self at all. I tried to do things young people normally do, but at crowded places I was always very aware of my wig, scared that it would fall off if someone passed too close. How embarrassing would that be?! When I used my scarves, shopping people in town turned behind my back and stared at me. Everyone saw I was fighting cancer, and I received their ‘cruel’ compassion.”*

Judith, 23 years old women with rhabdomyosarcoma for which combination chemotherapy was indicated with a curative intent

*“I wanted to be in control of hair loss, being able to decide when it would happen. Especially because everything about cancer and its treatments felt so outside of my personal control. I kind of joked about the hair loss by inviting my naturally bald dad to be my role model during shaving and got a temporary tattoo on the back of my scalp. I was not ashamed of my baldness and wore solely head covers. I more or less compared myself with GI Jane: a tough bald woman fighting to survive a grueling ‘selection program’. I solely wore my wig for the sake of other people, for example during a wedding, just to attract as less attention as possible during that day. I felt more like myself with my bald head than when I wore my wig, and my boyfriend felt the same about that. After chemotherapy I never got my hair grown long again, because that was me before cancer.”*

Case report: Expected impact of CIA.

Christ, 67 years old man with prostate cancer, undergoing scalp cooling during docetaxel chemotherapy with a palliative intent

*“I really wanted to keep my hair. I had no sense in going out into the world with a bald head, I wanted to act in my life as I always used to do. I feared hair loss, because I have a truly full head of hair that even would have made Beethoven jealous. Besides I have a heavy mustache, which is my figurehead. Hair loss was a highly undesirable coincidence of chemotherapy, despite it is quite normal for males to have a shaved bald head today. A wig was surely no solution for me and then I found information about scalp cooling on the internet. I thought: this is meant to achieve results, so let’s give it a try. The other extreme was a bald head. If it would fail, I would have attached to the former line of expectations. I saw it as a chance, two sides of the same coin, I just had to wait and see. It has worked wonderfully well. Hairs elsewhere on my body have mainly disappeared, unfortunately also my mustache. But my scalp hair has hardly changed, even after eight cycles of chemotherapy.”*

## Prevention of CIA

Since about 1970, attempts have been made to prevent CIA by the development of pharmacological agents, mechanical strategies, and scalp cooling. Currently, prevention mainly focuses on scalp cooling.

### Pharmacological agents

A review on many pharmacological agents showed that at present there is no approved agent to prevent CIA in humans.<sup>3</sup> Although some agents might be promising, it will take a long time before effective medicaments for humans will have been developed, and their safety and adverse effects have been studied. Besides, because of combined chemotherapy regimens, pharmacological interventions to prevent CIA will likely require various agents with different mechanisms of action.

Several cosmetics are on the market, which pretend to reduce hair loss or to stimulate hair growth, also during and after chemotherapy. However, no studies have been published about the effectiveness of these products against CIA.

### Tourniquets and electrotrichogenesis

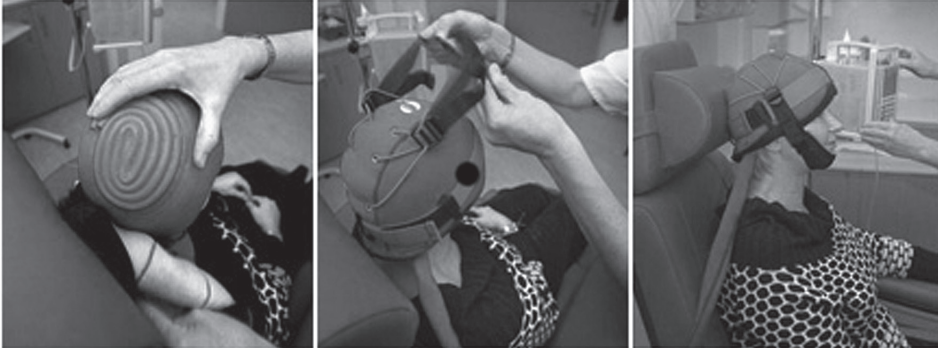
Scalp tourniquets have been placed around the hair line in order to put pressure on the blood vessels in the scalp skin, higher than the systolic blood pressure. They were designed to reduce blood flow to hair follicles during peak plasma concentrations of the cytotoxic agents.<sup>41,42</sup> It resulted in a reduction of CIA, but side effects as nerve compression and headaches have been reported and for this reason they have not been further developed and used.

Electrotrichogenesis (electric fields applied on the scalp) had a positive biological effect on hair growth in men with androgenetic alopecia. It also showed promising results in preventing CIA in a limited number of patients (n=13).<sup>43</sup> However, no other studies have been published since this preliminary report in 2002.

### Scalp cooling

Scalp cooling was originally practiced by simple ice or cryogel packs that were applied to the head.<sup>44-46</sup> Then cool caps were used, which had to be stored in the refrigerator and had to be changed every half an hour. Nowadays, continuous cooling systems with caps cooled by liquid are most often used (Figure 4).

Scalp cooling is continuously applied before, during and about 90 minutes after chemotherapy infusion. The cooling times are arbitrarily chosen and its impact on the hair preservative effect in relation to the various cytotoxic agents is unknown. Tolerance of scalp cooling has only been systematically studied using overall comfort and acceptability scores.<sup>47,48</sup> The majority of patients tolerate scalp cooling very well, head aches and coldness are the most frequent complaints<sup>49</sup>, but are rarely quantified. For the medical profession, the main limitation for application of scalp cooling on a broad scale is the risk for the emergence of scalp skin metastases. These metastases have been described in the literature following



**Figure 4.** Scalp cooling (photo: M. Molle, Volkskrant).

scalp cooling<sup>49</sup>, but a relation was never likely for patients with solid tumors. The incidence without scalp cooling is in general low, but not precisely known.

Scalp cooling probably works by inducing vasoconstriction and reducing the metabolism in hair producing matrix cells. Vasoconstriction causes a decreased blood flow to the hair follicles and therefore a considerable reduction of cytotoxic concentration in the cells (Figure 2). Moreover, the reduced metabolism may make hair matrix cells less vulnerable to the damaging effect of cytotoxic agents. After scalp cooling, diminished hair shaft diameters have been observed, indicating only moderate damage and recovery of the hair follicle: the continued anagen phase (Figure 3).

Scalp cooling can be applied to all patients receiving chemotherapy for solid tumors. Contraindications for scalp cooling are haematological malignancies with generalised metastases, cold sensitivity, cold agglutinin disease, cryoglobulinaemia, cryofibrinogenaemia and cold post-traumatic dystrophy. Assuming that half of the estimated 28,500 Dutch patients receiving chemotherapy as primary treatment (as described above) are facing CIA and are treated in approximately 100 out-patients' departments, each hospital has on average minimally 140 patients per year who could possibly benefit from scalp cooling.

Effectiveness of scalp cooling has been proven in six out of seven randomized trials<sup>50-56</sup>, supported by studies with historical controls.<sup>57</sup> However, scalp cooling is not effective for each patient and it is known to depend on the type and dose of chemotherapy. Other factors determining the effectiveness of scalp cooling remain controversial and knowledge on biological factors is lacking. Furthermore, there are hardly data on the dose-effect relation, e.g. optimal temperature and post-infusion cooling times for each type of chemotherapy. Although scalp cooling has been practiced for more than 40 years<sup>57</sup>, still remarkably little research has been conducted on preventing hair loss, in particular in comparison with prevention of other side-effects of cancer treatment. Up to now, most scalp cooling studies only evaluated the effectiveness of often outdated types of chemotherapy. Therefore patients can not be well informed on their chance of hair preservation by scalp cooling, as data are lacking for the more modern chemotherapy schedules.

Effectiveness of scalp cooling is in general assessed by wig and head cover use, Likert scales or Visual Analogue Scales (VAS). It is unknown to what extent these measures correspond to objective preservation of hair or which method is most suitable.

In the Netherlands, scalp cooling is part of the intramural care, there is no insight in cost-effectiveness.

### Implementation of scalp cooling in the Netherlands, initiated by the Dutch Scalp Cooling Network.

Although it was already known that CIA could sometimes be prevented by scalp cooling, the number of Dutch hospitals offering this supportive care modality decreased before the year 2000. One reason was time investment, mainly due to changing the cool cap from the refrigerator every half hour to 45 minutes. Another reason was the lack of knowledge about the effectiveness of scalp cooling amongst medical professionals and nurses. Therefore, they easily stopped scalp cooling after several experiences of failure of hair preservation.

In 2001 a group of oncological professionals started a scalp cooling program in the Netherlands. A scalp cooling registry was set up in four Dutch hospitals.<sup>58,59</sup> Besides, a study was initiated to compare the perceived impact of CIA between patients, nurses and medical oncologists. It showed that the impact was underestimated by the professionals, which formed an explanation for the minimal scalp cooling application at that time.<sup>35</sup> In 2005 a review was published, underscoring the effectiveness of scalp cooling.<sup>49</sup> In order to increase the knowledge on CIA and scalp cooling, researchers/epidemiologists of the Comprehensive Cancer Centre South (IKZ, Eindhoven), and nurses and clinicians from several hospitals decided to start studies, facilitated by IKZ. A foundation was established to promote knowledge on (the effectiveness of) scalp cooling and a website was developed to provide information for patients and their relatives (Give Hair a Chance Foundation, [www.geefhaareenkans.nl](http://www.geefhaareenkans.nl)). Furthermore, attention was drawn on scalp cooling through several media, in cooperation with ex-patients. The main goal was to inform (future) patients about the existence of scalp cooling.

### Objectives and outline of this thesis

The aim of this thesis is to approach the problem of CIA in patients with cancer in several ways:

- Is hair loss a problem?
- And if so, how effective is scalp cooling to prevent CIA?
- If results of scalp cooling on prevention of CIA are insufficient, how can they be improved?
- Is there a risk for development of scalp skin metastases after scalp cooling?
- What is the impact of CIA on quality of life (QoL) and does scalp cooling contribute -positive or negative- to QoL?
- Finally, how does the cost of scalp cooling relate to the cost of a wig, is it cost-effective?

The focus of this thesis is on breast cancer patients, because scalp cooling is mainly applied in that group.

In part I the safety of scalp cooling is addressed for breast cancer patients. To gain insight in the risk for scalp skin metastases amongst non scalp-cooled patients, the incidence of and survival after various distant metastases were studied using the Munich Cancer Registry (**chapter 2**). Besides, the incidence of scalp skin metastases was investigated in a cohort of non scalp-cooled high risk patients who received chemotherapy and a diverse group of scalp-cooled patients (**chapter 3**). Furthermore, the current perspective of the risk of scalp skin metastases following scalp cooling was described (**chapter 4**).

In part II the effectiveness of scalp cooling for currently used chemotherapy schedules is described. A multivariate analysis of data collected in a nationwide registry shows characteristics which are possibly associated with the scalp cooling results (**chapter 5**). One of these characteristics, post-infusion cooling time (PICT), has been studied in a randomized trial (**chapter 6**). PICTs of 90 and 45 minutes were compared in patients receiving docetaxel chemotherapy. Besides, effectiveness was evaluated by comparing severity of CIA, and wig and head cover purchase and use between scalp-cooled and non scalp-cooled patients (**chapter 7**).

In part III the impact of CIA and scalp cooling on breast cancer patients is described. The impact of CIA on QoL and body image was compared for scalp-cooled and non scalp-cooled patients, with or without CIA (**chapter 8**). The same dataset was used to more extensively investigate the severity and burden of CIA, patients' satisfaction with wigs and the burden of scalp cooling (**chapter 9**).

In part IV cost-effectiveness of scalp cooling was assessed by comparing costs and QoL between scalp-cooled and non scalp-cooled patients (**chapter 10**). Scalp cooling was compared to standard care, i.e. the purchase of a wig or other head cover.

## References

1. Trueb RM. Chemotherapy-induced alopecia. *Sem Cut Med Surg.* 2009; 28: 11-4.
2. van Scott EJ, Reinerton, R.P., Steinmuller, R. The growing hair roots of the human scalp and morphological changes therein following amethoperin therapy. *J Invest Dermatol.* 1957; 29: 197-204.
3. Wang J, Lu Z, Au JL. Protection against chemotherapy-induced alopecia. *Pharma Res.* 2006; 23: 2505-14.
4. Rebora A. Telogen effluvium. *Dermatology.* 1997; 195: 209-12.
5. Cotsarelis G, Millar SE. Towards a molecular understanding of hair loss and its treatment. *Trends Molec Med.* 2001; 7: 293-301.
6. Paus R, Haslam IS, Sharov AA, Botchkarev VA. Pathobiology of chemotherapy-induced hair loss. *Lancet Oncol.* 2013; 14: e50-9.
7. Batchelor D. Hair and cancer chemotherapy: consequences and nursing care-a literature study. *Eur J Cancer Care.* 2001; 10: 147-63.
8. Karakunnel JJ, Berger AM. Hair loss. In: DeVita V, Lawrence W, Rosenberg S, eds. *Cancer Princ Pract Oncol.* 8 ed 2008:2688-91.
9. Bleiker TO, Nicolaou N, Traulsen J, Hutchinson PE. 'Atrophic telogen effluvium' from cytotoxic drugs and a randomized controlled trial to investigate the possible protective effect of pretreatment with a topical vitamin D analogue in humans. *Br J Dermatol.* 2005; 153: 103-12.
10. Kligman AM. Pathologic dynamics of human hair loss. I. Telogen effluvium. *Arch Dermatol.* 1961; 83: 175-98.
11. Hussein AM. Chemotherapy-induced alopecia: new developments. *South Med J.* 1993; 86: 489-96.
12. Tallon B, Blanchard E, Goldberg LJ. Permanent chemotherapy-induced alopecia: case report and review of the literature. *J Am Ac Dermatol.* 2009; 63: 333-6.
13. Dutch Cancer Registry: <http://cijfersoverkanker.nl>. 2012.
14. Manders K, van de Poll-Franse LV, Creemers GJ, Vreugdenhil G, van der Sangen MJ, Nieuwenhuijzen GA, et al. Clinical management of women with metastatic breast cancer: a descriptive study according to age group. *BMC Cancer.* 2006; 6: 179.
15. Meulenbeld HJ, van Steenberghe LN, Janssen-Heijnen ML, Lemmens VE, Creemers GJ. Significant improvement in survival of patients presenting with metastatic colon cancer in the south of The Netherlands from 1990 to 2004. *Ann Oncol.* 2008; 19: 1600-4.
16. Gestel van YRBM, Herk-Sukel van MPP, Hingh de IHJT, Rutten HJT, Creemers GJ, Lemmens VEPP. Distant recurrences of colorectal cancer: incidence, systemic treatment, and survival in daily practice ASCO 2013.
17. Sukel MP, van de Poll-Franse LV, Nieuwenhuijzen GA, Vreugdenhil G, Herings RM, Coebergh JW, et al. Substantial increase in the use of adjuvant systemic treatment for early stage breast cancer reflects changes in guidelines in the period 1990-2006 in the southeastern Netherlands. *Eur J Cancer.* 2008; 44: 1846-54.
18. Pijnenborg H, Vos C, Ezendam N, Poll van de-Franse LV, Lemmens VEPP. Factsheet gynaecological malignancies. IKZ Eindhoven; 2012.
19. Stavridi F, Palmieri C. Efficacy and toxicity of nonpegylated liposomal doxorubicin in breast cancer. *Exp Rev Anticancer Th.* 2008; 8: 1859-69.
20. Vici P, Colucci G, Giotta F, Sergi D, Filippelli G, Perri P, et al. A multicenter prospective phase II randomized trial of epirubicin/vinorelbine versus pegylated liposomal doxorubicin/vinorelbine as first-line treatment in advanced breast cancer. A GOIM study. *J Exp Clin Cancer Res.* 2011; 30: 39.
21. Fiegl M, Mlineritsch B, Hubalek M, Bartsch R, Pluschnig U, Steger GG. Single-agent pegylated liposomal doxorubicin (PLD) in the treatment of metastatic breast cancer: results of an Austrian observational trial. *BMC cancer.* 2011; 11: 373.
22. Reeves DM. Alopecia. In: Henke Yarbro C, Hansen Frogge M, Goodman M, eds. *Cancer Sympt Managem.* 3th ed. Sudbury, Massachusetts, USA: Jones&Barlett Publishers International 2004:561-70.

23. Kluger N, Jacot W, Frouin E, Rigau V, Poujol S, Dereure O, et al. Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients. *Ann Oncol.* 2012; 23: 2879-84.
24. Freedman TG. Social and cultural dimensions of hair loss in women treated for breast cancer. *Cancer Nurs.* 1994; 17: 334-41.
25. Rosman S. Cancer and stigma: experience of patients with chemotherapy-induced alopecia. *Pat Educ Couns.* 2004; 52: 333-9.
26. Hilton S, Hunt K, Emslie C, Salinas M, Ziebland S. Have men been overlooked? A comparison of young men and women's experiences of chemotherapy-induced alopecia. *Psych Oncol.* 2008; 17: 577-83.
27. Boehmke MM, Dickerson SS. Symptom, symptom experiences, and symptom distress encountered by women with breast cancer undergoing current treatment modalities. *Cancer Nurs.* 2005; 28: 382-9.
28. Browall M, Gaston-Johansson F, Danielson E. Postmenopausal women with breast cancer: their experiences of the chemotherapy treatment period. *Cancer Nurs.* 2006; 29: 34-42.
29. Atay S. Symptom characteristics and clustering in children and adolescents undergoing or being off cancer chemotherapy. *J Buon.* 2011; 16: 751-8.
30. Lemieux J, Maunsell E, Provencher L. Chemotherapy-induced alopecia and effects on quality of life among women with breast cancer: a literature review. *Psych Oncol.* 2008; 17: 317-28.
31. Reilly CM, Bruner DW, Mitchell SA, Minasian LM, Basch E, Dueck AC, et al. A literature synthesis of symptom prevalence and severity in persons receiving active cancer treatment. *Supp Care Cancer.* 2013; 21: 1525-50.
32. Tierney A, Taylor J, Closs SJ, Chetty U, Rodger A, Leonard RCF. Hair Loss Due to Cytotoxic Chemotherapy - a Prospective Descriptive Study. *Brit J Cancer.* 1990; 62: 527-28.
33. McGarvey EL, Baum LD, Pinkerton RC, Rogers LM. Psychological sequelae and alopecia among women with cancer. *Cancer Pract.* 2001; 9: 283-93.
34. Hofman M, Morrow GR, Roscoe JA, Hickok JT, Mustian KM, Moore DF, et al. Cancer patients' expectations of experiencing treatment-related side effects: a University of Rochester Cancer Center-Community Clinical Oncology Program study of 938 patients from community practices. *Cancer.* 2004; 101: 851-7.
35. Mulders M, Vingerhoets A, Breed W. The impact of cancer and chemotherapy: perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nurs.* 2008; 12: 97-102.
36. Duric VM, Stockler MR, Heritier S, Boyle F, Beith J, Sullivan A, et al. Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes AC and CMF worthwhile now? *Ann Oncol.* 2005; 16: 1786-94.
37. Carelle N, Piotto E, Bellanger A, Germanaud J, Thuillier A, Khayat D. Changing patient perceptions of the side effects of cancer chemotherapy. *Cancer.* 2002; 95: 155-63.
38. de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, v Beurden V, Stoter G, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. *Br J Cancer.* 1997; 76: 1055-61.
39. Williams J, Wood C, Cunningham-Warburton P. A narrative study of chemotherapy-induced alopecia. *Oncol Nurs Forum.* 1999; 26: 1463-8.
40. Zannini L, Verderame F, Cucchiara G, Zinna B, Alba A, Ferrara M. 'My wig has been my journey's companion': perceived effects of an aesthetic care programme for Italian women suffering from chemotherapy-induced alopecia. *Eur J Cancer Care.* 2012; 21: 650-60.
41. Lovejoy NC. Preventing hair loss during adriamycin therapy. *Cancer nursing.* 1979; 2: 117-21.
42. Pesce A, Cassuto JP, Joyner MV, DuJardin P, Audoly P. Scalp tourniquet in the prevention of chemotherapy-induced alopecia. *NEJM.* 1978; 298: 1204-5.
43. Benjamin B, Ziginaskas D, Harman J, Meakin T. Pulsed electrostatic fields (ETG) to reduce hair loss in women undergoing chemotherapy for breast carcinoma: a pilot study. *Psych Oncol.* 2002; 11: 244-8.
44. Timothy AR, Bates TD, Hoy AM. Influence of scalp hypothermia on doxorubicin related alopecia. *Lancet.* 1980; 1: 663.

45. Hillen HF, Breed WP, Botman CJ. Scalp cooling by cold air for the prevention of chemotherapy-induced alopecia. *Neth J Med.* 1990; 37: 231-5.
46. Middleton J, Franks D, Buchanan RB, Hall V, Smallwood J, Williams CJ. Failure of scalp hypothermia to prevent hair loss when cyclophosphamide is added to doxorubicin and vincristine. *Cancer Treat Rep.* 1985; 69: 373-5.
47. Massey CS. A multicentre study to determine the efficacy and patient acceptability of the Paxman Scalp Cooler to prevent hair loss in patients receiving chemotherapy. *Eur J Oncol Nurs.* 2004; 8: 121-30.
48. Protiere C, Evans K, Camerlo J, d'Ingrado MP, Macquart-Moulin G, Viens P, et al. Efficacy and tolerance of a scalp-cooling system for prevention of hair loss and the experience of breast cancer patients treated by adjuvant chemotherapy. *Supp Care Cancer.* 2002; 10: 529-37.
49. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol.* 2005; 16: 352-58.
50. Edelstyn GA, MacDonald M, MacRae KD. Doxorubicin-induced hair loss and possible modification by scalp cooling. *Lancet.* 1977; 2: 253-4.
51. Giaccone G, Di Giulio F, Morandini MP, Calciati A. Scalp hypothermia in the prevention of doxorubicin-induced hair loss. *Cancer Nurs.* 1988; 11: 170-3.
52. Ron IG, Kalmus Y, Kalmus Z, Inbar M, Chaitchik S. Scalp cooling in the prevention of alopecia in patients receiving depilating chemotherapy. *Supp Care Cancer.* 1997; 5: 136-8.
53. Macduff C, Mackenzie T, Hutcheon A, Melville L, Archibald H. The effectiveness of scalp cooling in preventing alopecia for patients receiving epirubicin and docetaxel. *Eur J Cancer Care.* 2003; 12: 154-61.
54. Satterwhite B, Zimm S. The use of scalp hypothermia in the prevention of doxorubicin-induced hair loss. *Cancer.* 1984; 54: 34-7.
55. Kennedy M, Packard R, Grant M, Padilla G, Presant C, Chillar R. The effects of using Chemocap on occurrence of chemotherapy-induced alopecia. *Oncol Nurs Forum.* 1983; 10: 19-24.
56. Parker R. The effectiveness of scalp hypothermia in preventing cyclophosphamide-induced alopecia. *Oncol Nurs Forum.* 1987; 14: 49-53.
57. Breed WPM, Hurk van den CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss; scalp cooling potentials and limitations. *Exp Rev Dermatol.* 2012; 6: 109-25.
58. Kolen B, Van de Laar-Müsken J, Van Helvert R, Van der Heul C, Van Riel A. Hoofdhuidkoeling; de moeite waard. [article in Dutch] *Oncologica.* 2002; 4: 9-13.
59. Hurk van den CJG, Gerrits P, Graat J, Kolen B, Laar van de- Müsken J, Breed WPM. Positieve ervaringen met hoofdhuidkoeling in drie ziekenhuizen in Nederland. Tijd voor een standaard aanbod van hoofdhuidkoeling? [article in Dutch] *Oncologica.* 2005; 22: 162-67.





# Part I



Scalp cooling in the context of developing of scalp skin metastases



# Chapter 2



**Unfavourable pattern of metastases in MO breast cancer patients during 1978-2008: a population-based analysis of the Munich Cancer Registry**

C.J.G. van den Hurk, R. Eckel, L.V. van de Poll-Franse, J.W.W. Coebergh,  
J.W.R. Nortier, D. Holzel, W.P.M. Breed, J. Engel

Br Ca Res Treat 2011; 128, 795-805



## Abstract

### Purpose

Little is known about time trends in metastases in patients treated in routine health care facilities without metastases at diagnosis (MO) and about survival after these metastases.

### Methods

Data on 33,771 MO patients with primary breast cancer diagnosed between 1978 and 2003 were obtained from the Munich Cancer Registry. Survival analyses were restricted to patients with metastases within 5 years of the initial diagnosis.

### Results

The incident number of patients approximately doubled each period and 5-year overall survival increased from 77% in the first to 82% percent in the last period. 5490 (16%) MO patients developed metastases within 5 years after the initial diagnosis. The hazard of developing metastases was lowest in the most recent period compared to the first period (HR=0.50,  $p<0.001$ ). The hazard of dying after metastases was equal for patients diagnosed between 1978-1984 and 1995-2003 (HR 1.08,  $p=0.3$ ). The percentage of patients that developed bone metastases decreased each time period, but the percentage primary liver and CNS metastases increased. Exclusion of site of metastases in the multivariate analysis led to a 20% ( $p=0.02$ ) higher hazard of dying following metastases in the last versus the first period.

### Conclusions

In the period 1978-2008, unfavourable changes in the pattern of metastases were exhibited and no improvement was observed in survival of patients after occurrence of metastases. An explanation might be the increased use of adjuvant systemic treatment, which has less effect on the highly lethal liver and CNS metastases than on bone metastases. The increased use also appeared to contribute to the overall prevention of metastases in breast cancer and therefore to improve overall survival.

## Introduction

The prevalence of breast cancer patients without metastases at diagnosis (M0) has increased in industrialised countries. This increase can be explained by the rising incidence and decreasing overall mortality rate of breast cancer<sup>1-4</sup>, which is attributed to earlier detection and therefore advantageous stage distribution, and improvements in treatment.<sup>1</sup> The early detection is largely due to breast cancer screening, developments in imaging and higher awareness of the disease amongst women. One would expect that these developments would influence the occurrence of metastases at diagnosis and in follow-up.

The reported percentage of M0 patients with metastases in follow-up is 20%-30%.<sup>3</sup> The proportion of patients with metastases at initial diagnosis (M1) remains stable at about 5%<sup>1,5</sup> or decreases minimally.<sup>6</sup> In M1 patients, pattern of metastases and survival are frequently described, but the progression patterns and time trends of occurrence of metastases after initial treatment in M0 patients are seldom investigated. The objective of this study was to describe the incidence of metastases and survival after metastases in M0 breast cancer patients since 1978. Therefore, this study will provide knowledge about the level of progress in medical management of metastases in these patients. Data were obtained from the Munich Cancer Registry (MCR), which uniquely documents metastases during follow-up.<sup>7</sup>

## Patients and methods

### Study population and data collection

Data on breast cancer patients diagnosed in the period 1978-1984, 1985-1994 and 1995-2003 were obtained from the population-based MCR. The MCR has in the last period a catchment area of 2.5 million residents (since 2002 3.9 million residents) and records data on all patients newly diagnosed with cancer.<sup>8,9</sup> The unequal subdivision into time periods of initial diagnosis marks steps in the changes from a hospital-based (up to 1984) to a population-based registry of Munich and surrounding areas. The MCR is for breast cancer population based since 1994, when the pathologists of the region started structural cooperation with the MCR. Data on primary diagnosis and progression were provided by the hospitals in the Munich region by means of tumour-specific reporting forms, doctors' letters and pathology reports and nowadays also through online documentation. Diagnosis of metastases was based on radiological imaging, physical evaluation or histological examination in regular oncological follow-up. Life status information was obtained from the population registration offices and death certificates until October 1, 2007 and is complete for more than 90% of the patients.<sup>7</sup> In the Munich catchment area screening for breast cancer has increased over time since the beginning of the 1990s, was initially opportunistic and at the end widespread, before programmed screening was started in 2004.

Between 1978 and 2003, the MCR registered 36,002 female patients diagnosed with primary invasive breast cancer. The data set did not include patients with secondary malignancies or sarcomas or with only a death certificate. Follow-up was complete up to October 30, 2008.

### Statistical analysis

Statistical analyses included time to metastases within 5 years of initial diagnosis and survival following the first metastasis amongst patients who developed a metastasis within 5 years of

initial diagnosis. Metastases were included in the analyses grouped by the most frequent sites of occurrence or combinations of these specific sites. These combinations were independent of sequence of metastatic sites and synchronous or metachronous detection and were only inserted if no additional metastases were present at rarer sites. Loco regional skin or lymph node recurrences were excluded. Event-free patients were censored on October 30, 2008 and patients who were lost to follow-up at their last date of contact. Survival times, time to metastases, and survival after metastases were described with the Life-Table method and tested with the log-rank test. For determining the importance of the independent variables Cox proportional hazards regression models were used, in which missing values were recoded into dummy variables. The enclosed variables were: period of diagnosis, age, tumour size (pT), lymph node status (pN), grade, receptor status and histological type. Analyses regarding time to metastases also included resection margins, initial radiotherapy and systemic therapy. Additional variables for survival following metastases were time to metastases and site(s) of metastases. When evaluating the proportional hazard assumption of the main objective of this study, namely period of diagnosis, the graphs of the survival function versus the survival time yielded parallel curves as did the graphs of the log[-log(survival)] versus log of survival time.

The SAS computer package (version 9.1) was used for all statistical analyses (SAS Institute Inc., Cary, NC, USA, 1999).

## Results

### General characteristics of M0 patients

The MCR comprised 33,771 M0 patients and 2231 (6%) M1 patients who were diagnosed with breast cancer between 1978 and 2003. For M0 patients, median follow-up time for patients alive or lost to follow-up ranged from 177 months in the period 1985-1994 (50% of patients were deceased on October 1, 2008) to 80 months in 1995-2003 (25% of patients were deceased on October 1, 2008) (Table 1). The incident number of patients approximately doubled each period and during follow-up 8183 (24%) patients developed a metastasis after M0 at diagnosis, 5490 (67%) of whom within 5 years of initial diagnosis. An increase in 5-year overall survival was observed for the last period (77% vs. 76% vs. 82%,  $p < 0.0001$ ) (Figure 1).

In time, the observed proportion of patients diagnosed with pT1 and lymph node-negative tumours increased, as did the proportion of older women (70+) (Table 1). About 80% of patients had a tumour of the ductal type and positive estrogen (ER) or progesterone (PR) receptors. Unknown receptor status decreased considerably from the second (46%) to the third study period (16%), whilst the ratio of positive to negative receptors hardly changed. The proportion of patients who underwent mastectomy decreased from 98% in the first to 35% in the last period and systemic treatment was used more often in recent periods (22% vs. 44% vs. 70%). A decrease in the proportion of patients undergoing radiotherapy was seen in period 1985-1994.



**Table 1.** Characteristics of M0 patients with breast cancer according to period of initial diagnosis (n=33,771).

Characteristic	Period of initial diagnosis						p-value
	1978-1984		1985-1994		1995-2003 <sup>b</sup>		
	n	% <sup>a</sup>	n	% <sup>a</sup>	n	% <sup>a</sup>	
<b>Median FU time after initial diagnosis of patients alive or lost to FU (mo)</b>	148		177		80		<0.0001
<b>Deceased (1 Oct. 2008)</b>	2893	(58)	5123	(50)	4571	(25)	<0.0001
<b>M0 at diagnosis, metastasis in FU</b>	1785	(36)	2999	(29)	3399	(18)	<0.0001
<b>M0 at diagnosis, metastasis within 5 years of FU</b>	798	(16)	1159	(11)	1952	(10)	<0.0001
<b>Age (yrs)</b>							
<50	1909	(38)	3522	(35)	4649	(25)	
50 -69	2380	(48)	4731	(46)	9540	(51)	
70+	689	(14)	1948	(19)	4403	(24)	<0.0001
<b>pT</b>							
T1	978	(43)	4155	(47)	9358	(55)	
T2	958	(42)	3524	(40)	6224	(37)	
T3	202	(9)	436	(5)	723	(4)	
T4	149	(6)	693	(8)	747	(4)	<0.0001
Unknown	2691	(54)	1393	(14)	1545	(8) <sup>c</sup>	
<b>pN</b>							
Negative	1071	(48)	4413	(52)	9649	(59)	
Positive	1142	(52)	4114	(48)	6682	(41)	<0.0001
Unknown	2765	(56)	1674	(16)	2261	(12)	
<b>Histological type</b>							
Ductal	3533	(82)	7445	(80)	13,970	(78)	
Lobular/Mixed	419	(10)	1486	(16)	3678	(21)	
Other/n.o.s.	363	(8)	346	(4)	276	(1)	<0.0001
Unknown	663	(13)	924	(9)	668	(4)	
<b>Grade</b>							
1	-	-	485	(6)	1902	(11)	
2	-	-	4440	(58)	9311	(53)	
3+4	-	-	2748	(36)	6206	(36)	<0.0001
Unknown	-	-	2528	(25)	1173	(6)	
<b>Receptor status (ER or PR)</b>							
Positive	-	-	4336	(79)	13,120	(84)	
Negative	-	-	1140	(21)	2577	(16)	<0.0001
Unknown	-	-	4725	(46)	2900	(16)	

Table 1. continues on next page

<b>Initial surgery</b>						
Lumpectomy	49	(2)	2660	(39)	10,835	(65)
Mastectomy	1920	(98)	4248	(61)	5841	(35) <0.0001
Unknown/ Other <sup>d</sup>	3009	(60)	3293	(32)	1916	(10)
<b>Initial radiotherapy</b>	2729	(59)	4534	(44)	10,910	(59) <0.0001
<b>Resection margins</b>						
Negative	-	-	2923	(29)	12,833	(69)
Positive	-	-	152	(1)	590	(3)
Unknown	-	-	7126	(70)	5169	(28) <0.0001
<b>Initial systemic treatment</b>						
Chemotherapy	673	(13)	1959	(19)	4345	(23)
Hormonal therapy	375	(8)	2324	(23)	6271	(34)
Both	59	(1)	217	(2)	2394	(13)
No	3871	(78)	5701	(56)	5582	(30) <0.0001

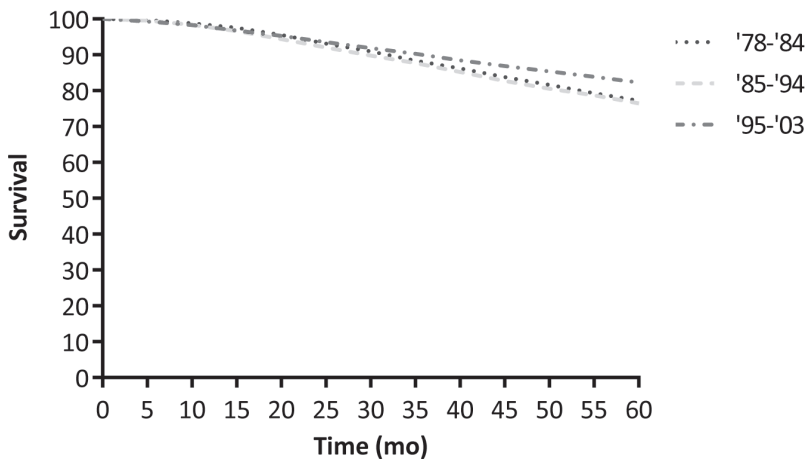
FU=follow-up, n.o.s.= not otherwise specified, ER=estrogen receptor, PR=progesterone receptor

<sup>a</sup> percentage of sub-categories related to the sum of each item with available data; missing values not taken into account

<sup>b</sup> the population based cohort

<sup>c</sup> pT missing in 4% out of 8% because of neo-adjuvant systemic therapy

<sup>d</sup> no differentiation for surgical method in the 1970's and early 1980's. 'Other' is for example surgery following neo-adjuvant systemic therapy



**Figure 1.** 5-year overall survival of M0 breast cancer patients diagnosed between 1978 and 2003 (n=33,771).

## Patterns of metastases

In the cohort of 5490 MO patients with metastases within 5 years of initial diagnosis, 59% developed the first metastasis within 2.5 years (Table 2). Overall 56% of the patients developed metastases at 2 or more sites and the proportion of metachronously diagnosed metastases increased in time from 66 to 82%. The proportion of bone metastases declined (69% vs. 62% vs. 47%) whilst the proportion of liver, central nervous system (CNS) and less common occurring sites of metastases increased. In time, trends were comparable for the first detected metastases. In the first period, 85% of patients died within 5 years of the first metastases versus 95% in the last period. Of patients alive or lost to follow-up, median follow-up was 29 months in the first period, 11 months in 1985-1994 and 50 months in 1995-2003. The patients who developed metastases within 5 years had a positive lymph node status at initial diagnosis more often and had a higher pT status than MO patients in general.

## Time from diagnosis to first metastasis

The proportion MO patients who developed metastases within 5 years of initial diagnosis declined significantly from 27% in 1978-1984 to 15% in 1995-2003 ( $p < 0.0001$ ) (Figure 2a). Overall, the risk of occurrence of metastases was highest in the first 2.5 years of initial diagnosis (65% vs. 60% vs. 56%), as also indicated by the steepness of the curves in Figure 3. For the specified metastatic sites, only small differences emerged in time to detection during 5 years of follow-up, except for skin metastases that appeared later. Detection of metastases occurred within 5 years of initial diagnosis in 76% of patients who developed a combination of bone, liver and lung metastases and in 52% of patients with skin metastases only.

The hazard of developing metastases within 5 years of diagnosis was lowest in the most recent period (HR=0.50,  $p < 0.001$ ) (Table 3). A positive receptor status (HR=0.61,  $p < 0.001$ ) and the combination of chemotherapy and hormonal therapy (HR=0.69,  $p < 0.001$ ) were associated with a lower risk of metastases. Age and radiotherapy were not significantly associated with the occurrence of metastases within 5 years.

## Time from first metastasis to death

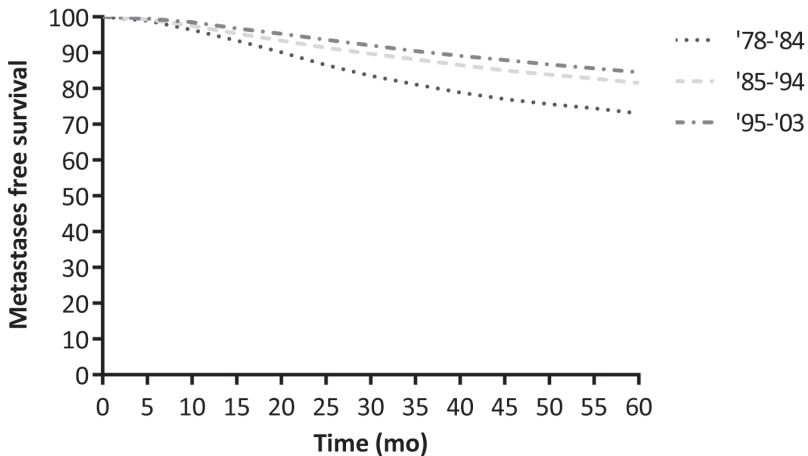
If only the death certificate or a post mortem report indicated metastases, the date of first metastasis was similar to the date of death and these patients were excluded from survival analyses (n=6251).

In MO patients with metastases within 5 years of initial diagnosis, 5-year actuarial survival rates after occurrence of first metastasis decreased and differed significantly between the time periods (17% vs. 12% vs. 8%,  $p = 0.0001$ ) (Figure 2b).

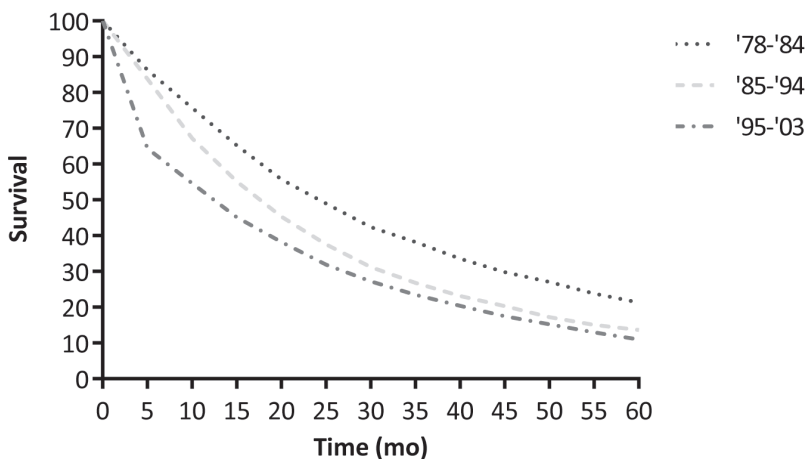
Multivariate regression analysis showed that patients who developed a metastasis within 5 years of diagnosis in the period 1985-1994 had a 20% increased hazard of dying compared to those in 1978-1984 and 1995-2003; this first and last period showed no difference in survival (Table 4). However, when site of metastases was removed from the model, then the hazard ratios became 1.24 ( $p = 0.003$ ) and 1.21 ( $p = 0.02$ ) for the last two periods. Mortality risk increased with the increase in age and a higher pT, positive lymph nodes and differentiation grade. The hazard of dying for patients with metastases was 35% lower for receptor status-

positive patients and decreased 7% in each additional year between initial diagnosis and first metastasis.

Prognosis for patients after metastases varied for the site(s) of metastasis (Table 3). Up to 5 years after detection of metastases, patients with bone metastases or skin metastases alone exhibited best survival (Figure 5). From 5 to 10 years, skin alone and distant lymph node alone had best prognosis up to 10 years after detection of metastases (data not shown).



**Figure 2a.** 5-year actuarial rate of occurrence of first metastases in M0 breast cancer patients according to period of diagnosis of initial tumour.



**Figure 2b.** Survival following first metastasis in M0 breast cancer patients who developed metastasis within 5 years of diagnosis according to period of diagnosis of initial tumour.

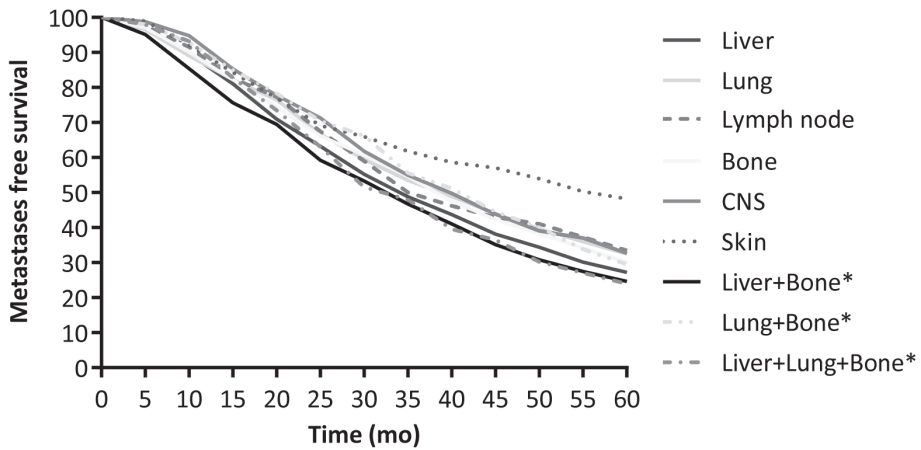
**Table 2.** Characteristics of M0 breast cancer patients with first metastasis within 5 years of initial diagnosis, according to period of initial diagnosis (n=5490)

Characteristic	Period of initial diagnosis				p-value		
	1978-1984 (n=1214)		1985-1994 (n=1677)			1995-2003 (n=2599)	
	n	%	n	%	n	%	
<b>Metastasis within 2.5 years</b>	791	(65)	999	(60)	1449	(56)	<0.0001
<b>Deceased within 5 years of first metastasis</b>	1031	(85)	1484	(88)	2464	(95)	<0.0001
<b>Median FU time after initial diagnosis of patients alive or lost to FU (mo)</b>	29		11		50		<0.0001
<b>Multiple synchronous</b>	603	(50)	862	(51)	1592	(61)	<0.0001
<b>Multiple metachronous</b>	399	(66)	637	(74)	1300	(82)	<0.0001
<b>Metastatic sites at first progression/ all metastases during follow-up<sup>a</sup></b>							
Bone	719 (60) / 838 (69)		881 (53) / 1047 (62)		980 (38) / 1226 (47)		
Lung	286 (24) / 376 (31)		372 (22) / 533 (32)		514 (20) / 783 (29)		
Liver	168 (14) / 286 (24)		266 (16) / 484 (29)		587 (23) / 961 (35)		
CNS	55 (5) / 123 (10)		81 (5) / 232 (14)		265 (10) / 630 (22)		
Skin	92 (8) / 149 (12)		109 (7) / 177 (11)		171 (7) / 290 (11)		
Distant lymph node	74 (6) / 104 (9)		189 (11) / 273 (16)		284 (11) / 413 (15)		
Other	164 (14) / 287 (24)		219 (13) / 427 (25)		630 (24) / 1267 (51)		
Total	1558 / 2163		2117 / 3173		3431 / 5579		
<b>Mean number of metastases per patient</b>	1.28 / 1.78		1.26 / 1.89		1.32 / 2.14		<0.0001
<b>Age (yrs)</b>							
<50	506	(42)	653	(39)	723	(28)	
50 -69	576	(47)	794	(47)	1245	(48)	
70+	132	(11)	230	(14)	631	(24)	

table 2. continues on next page

<b>pT</b>											0.0004
T1	132	(28)	411	(29)	612	(28)					
T2	234	(49)	688	(49)	1118	(51)					
T3	72	(15)	122	(9)	213	(10)					
T4	40	(8)	184	(13)	234	(11)					
Unknown (%)	736	(61)	272	(16)	422	(16)					
<b>pN</b>											0.9
Negative	137	(30)	433	(31)	650	(31)					
Positive	320	(70)	949	(69)	1463	(69)					
Unknown (%)	757	(62)	295	(18)	486	(19)					
<b>Receptor status (ER or PR)</b>											0.7
Negative	-	-	228	(29)	605	(30)					
Positive	-	-	562	(71)	1441	(70)					
Unknown (%)	-	-	887	(53)	553	(21)					

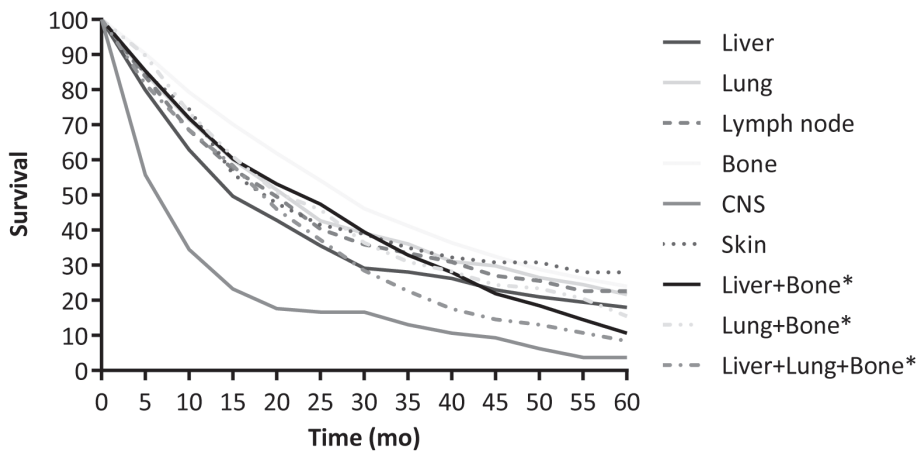
FU= follow-up, M0=no metastases at diagnose, CNS= central nervous system, ER=estrogen receptor, PR=progesterone receptor  
 \* Since one patient can have more than one site of metastasis, percentages are more than 100%



**Figure 3.** Time from diagnosis of primary tumour to first metastasis at the most common single sites and combinations of sites in M0 breast cancer patients with metastases.

CNS= central nervous system

\*Independent of sequence of detection per site, synchronous or metachronous, no additional metastases at other sites



**Figure 4.** 5-Year survival after first metastasis in most common single sites and combinations of sites of metastases in M0 breast cancer patients with metastases within 5 years of diagnosis.

CNS= central nervous system

\*Independent of sequence of detection per site, synchronous or metachronous, no additional metastases at other sites

**Table 3.** Determinants of time to first metastasis in M0 breast cancer patients, within 5 years of initial diagnosis.

Characteristics <sup>b</sup>	HR		95% CI	p-value
	Univariate	Multivariate		
<b>Period of diagnosis</b>				
1978-1984	1.00	1.00	-	
1985-1994	0.67	1.15	(0.98-1.35)	0.09
1995-2003	0.39	0.50	(0.42-0.61)	<0.0001
<b>Age (yrs)</b>				
<50	1.00	1.00	-	
50-69	0.83	0.98	(0.89-1.07)	0.7
70+	0.82	0.98	(0.85-1.12)	0.7
<b>pT</b>				
T1	1.00	1.00	-	
T2	1.60	1.80	(1.63-2.00)	<0.0001
T3	2.21	1.84	(1.58-2.15)	<0.0001
T4	2.98	2.32	(1.99-2.70)	<0.0001
<b>pN</b>				
Negative	1.00	1.00	-	
Positive	3.29	2.11	(1.91-2.34)	<0.0001
<b>Grade</b>				
1	1.00	1.00	-	
2	6.20	3.60	(2.37-5.46)	<0.0001
3/4	12.96	5.21	(3.43-7.91)	<0.0001
<b>Receptor status (ER/PR)</b>				
Negative	1.00	1.00	-	
Positive	0.40	0.61	(0.55-0.69)	<0.0001
<b>Histological type</b>				
Ductal	1.00	1.00	-	
Lobulair	0.62	0.90	(0.79-1.02)	0.1
Other	1.42	1.11	(0.90-1.38)	0.3
<b>Resection margins</b>				
Negative	1.00	1.00	-	
Positive	1.84	1.37	(1.08-1.73)	0.009
Unknown	2.48	1.59	(1.22-2.07)	0.0006
<b>Initial radiotherapy</b>				
	0.75	0.94	(0.86-1.02)	0.1
<b>Initial systemic therapy</b>				
No	1.00	1.00	-	
Chemotherapy	1.01 (NS)	0.95	(0.85-1.06)	0.4
Hormonal therapy	0.50	0.92	(0.81-1.04)	0.2
Both	0.47	0.69	(0.59-0.82)	<0.0001

HR= hazard ratio, 95% CI= 95% confidence interval, ER= estrogen receptor, PR=progesterone receptor, NS= not significant

<sup>a</sup> variables included if univariately significantly associated

<sup>b</sup> pT n=1867 missing, pN n=1959 missing, Differentiation grade n=2193 missing, Receptor status n=3046 missing, Resection margins n=4391 missing, Histological type n=533 missing



## Discussion

In the period 1978-2008, the hazard of developing metastases during follow-up decreased markedly and overall survival improved amongst women diagnosed with MO breast cancer. Concurrently, we observed a change in the anatomic pattern of metastasis, without improvement in survival after occurrence of these metastases. There might be several explanations for our observations.

We attribute the generally improved survival of MO patients in the last period to adjuvant, especially hormonal, treatment which was routinely administered at that time. In addition, patients recorded by the MCR showed advantageous stage distribution over the periods, which also contributed to improved prognosis. Time from initial diagnosis to metastasis is prolonged for pT1 versus pT2<sup>8</sup>, but changes in adjuvant systemic treatment will also have lengthened the time.<sup>10,11</sup> The adjuvant treatment prevents the development of metastases or at least postpones it. However, if dormant tumour cells start growing again, whether due to resistance against the continued systemic therapy or not, then the survival time of the metastasized patients remained as poor as before. Over time, the proportional anatomic distribution of metastasis shifted from bone, with long survival times, towards CNS and liver, which are much more lethal. This shift has also been reported by others, but only for the first site of metastasis.<sup>12</sup> The increased use of hormonal treatment might cause the shift since ER-positive tumours tend to metastasize to bone; ER and PR negativity are commonly associated with visceral metastases, especially liver and CNS.<sup>13-18</sup> The increased proportion of CNS metastases might also reflect improvement in adjuvant systemic treatment; CNS is regarded as a sanctuary site that is less affected by most therapeutics than other sites.<sup>19</sup> In this study liver metastases, alone or in combination, occurred earliest during follow-up and were like CNS metastases, the most lethal. So, the largest benefit in the survival of patients with breast cancer will most likely come from the prevention and better treatment of CNS and liver metastases. In patients with over expression of HER2 major improvements have been reached with trastuzumab<sup>20</sup> and recently lapatinib.<sup>21,22</sup> Bisphosphonates of the third generation seem to have also an anti-tumour effect in the adjuvant setting.<sup>23</sup> In addition poly[adenosine diphosphate (ADP)-ribose] polymerase (PARP) inhibitors are likely to be beneficial for patients with triple-negative tumours.<sup>24</sup> Therefore, the incidence and pattern of metastases will change further in the future. Overall, sites of metastases appeared to contribute largely to the period effect, since exclusion of site of metastases in the multivariate analysis increased the mortality hazard ratio for the last versus the first period to 21%. Unfortunately, no information was available about the type of treatment of the metastasized cancer in the MCR region.

The worse outcome after occurrence of metastases in patients without metastasis at diagnosis might be related to less sensitive tumour cells that developed resistance after adjuvant systemic therapy. This is supported by recent observations of M1 patients who, in particular when the primary tumour had been removed completely, had a more favourable prognosis compared to MO patients with subsequent metastases.<sup>13,25-28</sup> However, contradictory results have been reported of M1 patients, who sometimes had worse survival compared to MO patients who developed metastases in follow-up.<sup>29-32</sup>

Table 4. Determinants of survival after first metastasis in M0 breast cancer patients with metastases within 5 years during follow-up.

Characteristics <sup>a,b</sup>	HR Univariate	HR <sup>c</sup> Multi variate	95% CI	p-value	HR Multi variate	95% CI	p-value
<b>Period of diagnosis</b>							
1978-1984	1.00	1.00	-		1.00	-	
1985-1994	1.31	1.24	(1.08-1.43)	0.003	1.20	(1.04-1.38)	<0.01
1995-2003	1.38	1.21	(1.04-1.40)	0.02	1.08	(0.93-1.26)	0.3
<b>Age (yrs)</b>							
<50	1.00	1.00	-		1.00	-	
50-69	1.13	1.12	(1.04-1.22)	0.004	1.14	(1.05-1.24)	0.001
70+	1.58	1.51	(1.34-1.69)	<0.0001	1.57	(1.40-1.75)	<0.0001
<b>pT</b>							
T1	1.00	1.00	-		1.00	-	
T2	1.20	1.14	(1.05-1.25)	0.003	1.14	(1.04-1.24)	0.004
T3	1.26	1.19	(1.04-1.37)	0.01	1.19	(1.04-1.36)	0.01
T4	1.46	1.23	(1.07-1.41)	0.003	1.22	(1.06-1.40)	0.004
<b>pN</b>							
Negative	1.00	1.00	-		1.00	-	
Positive	1.29	1.21	(1.12-1.32)	<0.0001	1.22	(1.13-1.33)	<0.0001
<b>Grade</b>							
1	1.00	1.00	-		1.00	-	
2	1.70	1.70	(1.21-2.40)	0.002	1.64	(1.17-2.31)	0.005
3/4	2.39	2.17	(1.54-3.06)	<0.0001	2.05	(1.46-2.89)	<0.0001
<b>Receptor status (ER/PR)</b>							
Negative	1.00	1.00	-		1.00	-	
Positive	0.58	0.62	(0.56-0.69)	<0.0001	0.65	(0.59-0.72)	<0.0001

Table 4. continues on next page

Characteristics <sup>a,b</sup>	HR Univariate	HR <sup>c</sup> Multi variate	95% CI	p-value	HR Multi variate	95% CI	p-value
<b>Histological type</b>							
Ductal	1.00	-			-		
Lobular	0.93 (NS)	-			-		
Other	1.03 (NS)	-			-		
<b>Time to first metastasis<sup>d</sup></b>	0.91	0.93	(0.91-0.96)	<0.0001	0.93	(0.90-0.96)	<0.0001
<b>Site(s) of Metastases</b>							
Bone alone	1.00	-			1.00	-	
Liver alone	1.39	-			1.38	(1.15-1.67)	<0.0008
Lung alone	1.09 (NS)	-			1.20	(0.97-1.47)	0.1
CNS alone	3.16	-			2.81	(2.20-3.57)	<0.0001
Skin alone	1.01 (NS)	-			0.97	(0.71-1.33)	0.9
Distant lymph nodes alone	1.13 (NS)	-			0.94	(0.72-1.23)	0.6
Liver, Bone	1.38	-			1.50	(1.25-1.79)	<0.0001
Lung, Bone	1.28	-			1.18	(0.92-1.50)	0.2
Bone, Liver, Lung	1.66	-			1.67	(1.33-2.10)	<0.0001

HR= hazard ratio, 95% CI= 95% confidence interval, ER= estrogen receptor, PR=progesterone receptor, NS= not significant, CNS= central nervous system

<sup>a</sup> variables included if they were univariate significantly associated

<sup>b</sup> pT n=1334 missing, pN n=1413 missing, Grade n=1720 missing, Receptor status n=2379 missing, site of metastases 'Other' n=2646

<sup>c</sup> HR when site of metastases is excluded

<sup>d</sup> in years

Higher incidence of more aggressively growing tumours might be an additional explanation of the unimproved survival after metastases, since the increasing use of breast cancer screening mainly eliminates the slowly growing tumours. This is also reflected by the highly significant relationship between time to first metastasis and survival after occurrence of metastases, which remained after correction for period of diagnosis and site(s) of metastases. More aggressive growth might also be partly attributed to the lack of effective therapies for aggressive subtypes of breast cancer, such as triple negative, non-basal and basal-like subtypes.<sup>33</sup> These subtypes are known to influence the growth rate, site of metastases, time to occurrence and survival after metastases.<sup>12,34</sup> In this study, the majority of metastases became manifest within 2.5 years of initial diagnosis, as observed by others.<sup>11,13,35,36</sup>

The MCR hosts unique data on clinically evident metastases in follow-up, but the prevalence of metastases in the MCR is slightly underdocumented. Surgically treated and histopathologically confirmed metastases are obtained from pathology reports and are therefore nearly complete. However, not histopathologically confirmed metastases will be documented in about 70% of cases, based on estimations of tumour-specific survival and relative survival that should equalize the proportion of metastases.<sup>7,37</sup> Some of the metastases are likely to remain unreported by physicians to the MCR and some might never be detected because there were no clinical manifestations before death. The MCR's completeness is difficult to check with literature, whilst proportions of metastatic sites in breast cancer vary considerably, both within clinical and within autopsy studies.<sup>18,26,38-43</sup> Only a few studies were population based, and the subdivision of metastatic sites and follow-up times differed. The most adequate comparisons should be based on patients with breast cancer as the cause of death. It is likely that for the period 1995-2003, data on metastases in the MCR were more complete and most representative, whilst at that time the database became approximately population based. In time, methods of detection have improved and indications for diagnostics have changed, as exhibited by the decreased proportion of missing data on pT, pN and receptor status. In addition, the last period showed an increased number of metastases per patient, as well as increased detection of metastases at rarer sites. Nevertheless, the observed change in pattern of metastases can be considered to be a mirror for general specialised care in a variety of hospitals, whilst there were no systematic or specific diagnostics for metastases in the MCR region.

In conclusion, the enhanced use and extensive developments in systemic treatment of patients with breast cancer might have prevented development of metastases in breast cancer. It changed the anatomic distribution of sites of metastases, but did not improve survival after occurrence of metastases. The most important reason seems to be the shift from bone metastases towards CNS and liver metastases. Furthermore, there might have been a natural selection of more aggressively growing tumours in the recent period. So, at the time metastases became manifest, treatment possibilities remained insufficient, at least up to 2008. It seems that therapies for liver and CNS metastases might yield the largest gains in survival of MO breast cancer patients. And finally, changes in patterns of metastases as a result of new treatments, illustrate the importance of including registration of metastases and secondary treatment in cancer registries. They can be used to study long term effects in the population and the usefulness of new treatment strategies.


## References

1. Louwman WJ, Voogd AC, van Dijck JA, Nieuwenhuijzen GA, Ribot J, Pruijt JF, et al. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: a long-term population-based study in southeastern Netherlands. *Cancer Caus Contr.* 2008; 19: 97-106.
2. Jatoi I, Chen BE, Anderson WF, Rosenberg PS. Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. *J Clin Oncol.* 2007; 25: 1683-90.
3. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005; 365 (9472) : 1687-717.
4. Gondos A, Bray F, Brewster DH, Coebergh JW, Hakulinen T, Janssen-Heijnen ML, et al. Recent trends in cancer survival across Europe between 2000 and 2004: A model-based period analysis from 12 cancer registries. *Eur J Cancer.* 2008; 44: 1463-75.
5. Edwards MJ, Gamel JW, Feuer EJ. Improvement in the prognosis of breast cancer from 1965 to 1984. *J Clin Oncol.* 1998; 16: 1030-5.
6. Jensen AR, Madsen AH, Overgaard J. Trends in breast cancer during three decades in Denmark: stage at diagnosis, surgical management and survival. *Acta Oncol.* 2008; 47: 537-44.
7. Schlesinger-Raab A, Treiber U, Zaak D, Holzel D, Engel J. Metastatic renal cell carcinoma: results of a population-based study with 25 years follow-up. *Eur J Cancer.* 2008; 44: 2485-95.
8. Engel J, Eckel R, Kerr J, Schmidt M, Furstenberger G, Richter R, et al. The process of metastasisation for breast cancer. *Eur J Cancer.* 2003; 39: 1794-806.
9. Curado MP, Edwards BS, H.R., Ferlay J, Heanue M, Boyle P, Storm H. *Cancer Incidence in Five Continents.* Lyon: IARC 2009.
10. Johansson P, Fohlin H, Arnesson LG, Dufmats M, Nordenskjold K, Nordenskjold B, et al. Improved survival for women with stage I breast cancer in south-east Sweden: a comparison between two time periods before and after increased use of adjuvant systemic therapy. *Acta Oncol.* 2009; 48: 504-13.
11. Toi M, Yamashiro H, Tsuji W. Risk reduction of distant metastasis in hormone-sensitive postmenopausal breast cancer. *Breast cancer (Tokyo, Japan).* 2009; 16: 207-18.
12. Yerushalmi R, Woods R, Kennecke H, Speers C, Knowling M, Gelmon K. Patterns of relapse in breast cancer: changes over time. *Br Cancer Res Treat.* 2010; 120: 753-9.
13. Coleman RE, Smith P, Rubens RD. Clinical course and prognostic factors following bone recurrence from breast cancer. *Br J Cancer.* 1998; 77: 336-40.
14. Blanco G, Holli K, Heikkinen M, Kallioniemi OP, Taskinen P. Prognostic factors in recurrent breast cancer: relationships to site of recurrence, disease-free interval, female sex steroid receptors, ploidy and histological malignancy grading. *Br J Cancer.* 1990; 62: 142-6.
15. Solomayer EF, Diel IJ, Meyberg GC, Gollan C, Bastert G. Metastatic br cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Br Cancer Res Treat.* 2000; 59: 271-8.
16. Pestalozzi BC, Zahrieh D, Price KN, Holmberg SB, Lindtner J, Collins J, et al. Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). *Ann Oncol.* 2006; 17: 935-44.
17. Smid M, Wang Y, Klijn JG, Sieuwerts AM, Zhang Y, Atkins D, et al. Genes associated with breast cancer metastatic to bone. *J Clin Oncol.* 2006; 24: 2261-7.
18. Kamby C. The pattern of metastases in human breast cancer: methodological aspects and influence of prognostic factors. *Cancer Treat Rev.* 1990; 17: 37-61.
19. Duchnowska R, Szczylik C. Central nervous system metastases in breast cancer patients administered trastuzumab. *Cancer Treat Rev.* 2005; 31: 312-8.
20. Mannocci A, De Fo E, de Waure C, Specchia ML, Gualano MR, Barone C, et al. Use of trastuzumab in HER2-positive metastatic breast cancer beyond disease progression: a systematic review of published studies. *Tumori.* 2010; 96: 385-91.

21. Curran MP. Lapatinib: in postmenopausal women with hormone receptor-positive, HER2-positive metastatic breast cancer. *Drugs*. 2010; 70: 1411-22.
22. Arslan C, Dizdar O, Altundag K. Systemic treatment in breast-cancer patients with brain metastasis. *Exp Opin Pharmaco*. 2010; 11: 1089-100.
23. Reeder JG, Brufsky AM. The role of bisphosphonates in the adjuvant setting for breast cancer. *Oncology*. 2010; 24: 462-7, 75.
24. Underhill C, Toulmonde M, Bonnefoi H. A review of PARP inhibitors: from bench to bedside. *Ann Oncol*. 2010; 22: 268-279.
25. Engel J, Eckel R, Aydemir U, Aydemir S, Kerr J, Schlesinger-Raab A, et al. Determinants and prognoses of locoregional and distant progression in breast cancer. *Int J Radiat Oncol Biol Phys*. 2003; 55: 1186-95.
26. Jimeno A, Amador ML, Gonzalez-Cortijo L, Tornamira MV, Ropero S, Valentin V, et al. Initially metastatic breast carcinoma has a distinct disease pattern but an equivalent outcome compared with recurrent metastatic breast carcinoma. *Cancer*. 2004; 100: 1833-42.
27. Rapiti E, Verkooijen HM, Vlastos G, Fioretta G, Neyroud-Caspar I, Sappino AP, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol*. 2006; 24: 2743-9.
28. Schlesinger-Raab A, Eckel R, Engel J, Sauer H, Lohrs U, Molls M, et al. Metastasiertes Mammakarzinom: Keine Lebensverlängerung seit 20 Jahren. *Deutsches Arzteblatt*. 2005; 102: A2706-A14.
29. Andre F, Slimane K, Bachelot T, Dunant A, Namer M, Barrelier A, et al. Breast cancer with synchronous metastases: trends in survival during a 14-year period. *J Clin Oncol*. 2004; 22: 3302-8.
30. Smigal C, Jemal A, Ward E, Cokkinides V, Smith R, Howe HL, et al. Trends in breast cancer by race and ethnicity: update 2006. *CA Cancer J Clin*. 2006; 56: 168-83.
31. Wilcken N, Dear R. Chemotherapy in metastatic breast cancer: A summary of all randomised trials reported 2000-2007. *Eur J Cancer*. 2008; 44: 2218-25.
32. Ernst MF, van de Poll-Franse LV, Roukema JA, Coebergh JW, van Gestel CM, Vreugdenhil G, et al. Trends in the prognosis of patients with primary metastatic breast cancer diagnosed between 1975 and 2002. *Breast*. 2007; 16: 344-51.
33. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. *Cancer*. 2008; 113: 2638-45.
34. Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, et al. Metastatic behavior of breast cancer subtypes. *J Clin Oncol*. 2010; 28: 3271-7.
35. Elder EE, Kennedy CW, Gluch L, Carmalt HL, Janu NC, Joseph MG, et al. Patterns of breast cancer relapse. *Eur J Surg Oncol*. 2006; 32: 922-7.
36. Mansell J, Monypenny IJ, Skene AJ, Abram P, Carpenter R, Gattuso JM, et al. Patterns and predictors of early recurrence in postmenopausal women with estrogen receptor-positive early breast cancer. *Br Cancer Res Treat*. 2009; 117: 91-8.
37. [http://www.tumorregister-muenchen.de/facts/surv/surv\\_C50f\\_G.pdf](http://www.tumorregister-muenchen.de/facts/surv/surv_C50f_G.pdf). [cited 2009]
38. Manders K, van de Poll-Franse LV, Creemers GJ, Vreugdenhil G, van der Sangen MJ, Nieuwenhuijzen GA, et al. Clinical management of women with metastatic breast cancer: a descriptive study according to age group. *BMC Cancer*. 2006; 6: 179.
39. Hess KR, Varadhachary GR, Taylor SH, Wei W, Raber MN, Lenzi R, et al. Metastatic patterns in adenocarcinoma. *Cancer*. 2006; 106: 1624-33.
40. Perez JE, Machiavelli M, Leone BA, Romero A, Rabinovich MG, Vallejo CT, et al. Bone-only versus visceral-only metastatic pattern in breast cancer: analysis of 150 patients. A GOCS study. Grupo Oncologico Cooperativo del Sur. *Am J Clin Oncol*. 1990; 13: 294-8.
41. Giordano SH, Buzdar AU, Smith TL, Kau S-W, Yang Y, Hortobagyi GN. Is breast cancer survival improving? Trends in survival for patients with recurrent breast cancer diagnosed from 1974 through 2000. *Am Cancer Soc*. 2003; 44-52.
42. Lee YT. Breast carcinoma: pattern of metastasis at autopsy. *J Surg Oncol*. 1983; 23: 175-80.

43. Sanuki-Fujimoto N, Takeda A, Amemiya A, Ofuchi T, Ono M, Yamagami R, et al. Pattern of tumor recurrence in initially nonmetastatic breast cancer patients: distribution and frequency of metastases at unusual sites. *Cancer*. 2008; 113: 677-82.

# Chapter 3



**Adjuvant chemotherapy with and without scalp cooling  
in breast cancer patients: very low incidence of scalp skin  
metastases in retrospective studies**

C.J.G. van den Hurk, M.A.E. van de Sande, W.P.M. Breed, J.W.R. Nortier

2013; submitted





## Summary

### Introduction

We assessed the incidence of (scalp) skin metastases in 2 cohorts of non scalp-cooled and scalp-cooled breast cancer patients which contributes to the discussion as to whether reservations concerning scalp cooling in the adjuvant chemotherapy setting are justified.

### Methods

Two retrospective observational studies are described. Non scalp-cooled patients comprised 885 very thoroughly evaluated high-risk ( $\geq 4$  positive lymph nodes) MO breast cancer patients. Scalp-cooled MO patients (n=303) were collected in a registry of patients undergoing scalp cooling. Information on (scalp) skin metastases was obtained from patient files.

### Results

After a median follow-up of 110 months, 25 of the non scalp-cooled patients (3%) developed skin metastases of whom four (0.5%) were located on the scalp. Scalp skin metastases always occurred synchronous with metastases elsewhere or in a later stage. After a median follow-up of 26 months, six scalp-cooled MO patients (2%) developed skin metastases, none of which were on the scalp skin.

### Discussion

Metastases in the scalp skin occurred with a very low frequency, even in high risk patients, and were never the first manifestation of advanced disease. Therefore the potential risk of scalp cooling during adjuvant chemotherapy is likely to be very low.

## Introduction

Patients who are treated with chemotherapy report that they experience hair loss to be one of the most distressing side effects.<sup>1,2</sup> Since 1970 scalp cooling has been used to reduce chemotherapy-induced hair loss. Scalp cooling causes vasoconstriction and decreased biochemical activity, which may protect hair root cells from extensive damage. Given the theoretical risk that hypothermia may increase the occurrence of scalp skin metastases, there are some reservations about the use, in particular in patients who are receiving curative, adjuvant chemotherapy. In order to assess whether these reservations about scalp cooling are justified, we studied the incidence of scalp skin metastases in cohorts of breast cancer patients without and with scalp cooling.

## Methods

Patients without scalp cooling were studied in the database of the so-called 'N4+study'.<sup>3</sup> This trial (1993–1999) included 885 breast cancer patients who had at least four positive axillary lymph nodes and who were referred for curative adjuvant systemic treatment (M0) in 10 Dutch hospitals (Table 1). They were randomized between conventional chemotherapy at that time consisting of 5 cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), or for high-dose chemotherapy consisting of four cycles of FEC followed by one treatment with high dose cyclophosphamide, thiotepa and carboplatin (CTC) followed by autologous stem cell transplantation.<sup>3</sup> During long-term follow-up the occurrence of recurrence or distant metastases were systematically recorded.

For the current study we analyzed the data of all 25 patients in whom skin metastases had occurred after 9.4 years of follow-up of the N4+study. We retrospectively collected data from the N4+database and from medical records.<sup>4</sup>

Retrospective systematic research in patient files was performed in 390 scalp-cooled breast cancer patients from four Dutch hospitals (1997-2005), among whom 303 M0 patients (78%). These patients received different types of chemotherapy (Table 1). The patients had been included in a scalp cooling registry and permission was obtained to study the files. Sites of metastases were recorded for all patients, including scalp skin, as well as dates of detection of metastases, and first and last chemotherapy and scalp cooling sessions. Axillary lymph node status at primary diagnosis was known for patients from three hospitals.

The database comprised 303 M0 patients, who received different types of chemotherapy (Table 1). Eighty-seven patients (22%) had metastases before initiating chemotherapy with scalp cooling (M1).

**Table 1.** M0 Breast cancer patients' characteristics and main outcomes.

	No scalp cooling (n=885)	Scalp cooling (n=303)
<b>Characteristics</b>		
N4+	100%	8%
Surgery	100%	Unknown
Age (years)	<56	Mean 54
<b>Chemotherapy</b>		
FEC	+/- 50 % <sup>a</sup>	
FEC+CTCar	+/- 50 % <sup>a</sup>	0
AC	0	56%
CMF	0	8%
FAC	0	6%
Paclitaxel	0	1%
Docetaxel	0	1%
Unknown	0	17%
<b>Outcomes</b>		
Median follow-up (months)	110	26
Patients with skin metastases	3%	2%
Patients with scalp skin metastases	0.5%	0%

F=5-fluorouracil, E=epirubicin, C=cyclophosphamide, T=thiotepa, Car=carboplatin, A=doxorubicin, M=methotrexate

<sup>a</sup> Exact percentages unknown, while only access to data of patients with skin metastases from the N4+study

## Results

### No scalp cooling

After a median follow-up of 110 months, 403 out of the 885 patients (46%) had recurrent or metastasized breast cancer. Overall, 356 patients had deceased (40%).

The 25 patients with skin metastases (3%, n=885) all had died in follow-up. The mean time to develop a skin metastasis was 2.1 years after surgery. Four of these 25 patients (16%) developed skin metastases as the first sign of progression. Twelve patients (48%) also had concurrent metastases at other sites and in nine patients (36%) skin metastases were detected later in follow-up. One patient had only skin metastases, located on the chest wall. All other 24 patients also had metastases at other sites. These sites were mainly the lungs (n=15), bones (n=13), lymph nodes (n=13) and liver (n=12). One patient developed metastases in the central nervous system.

The skin metastases were found on the chest wall adjacent to the surgery scar in 18 (72%) of the patients and in two patients (8%) it was detected elsewhere on the trunk. Three patients (12%) had skin metastases in several locations, of whom two also had scalp skin metastases (Table 2a). Two (8%) of the patients with skin metastases had solely scalp skin metastases. So, scalp skin metastases were diagnosed in four patients (0.5%, n=885). These metastases

occurred at the same time (n=1) or later (n=3) than non-skin metastases elsewhere. The mean time to scalp skin metastases was 2.6 years (missing in 1 patient).

### Scalp cooling

After a median follow-up of 26 months from the start of chemotherapy, 57 (19%) of the 303 M0 patients developed metastases. Axillary lymph node status at initial diagnosis was NO for 50 (17%) patients, N1-3 for 75 (25%) patients, N4+ for 25 (8%) patients and unknown in 153 (50%). Fifteen (12%) of the N4- patients developed metastases as opposed to 10 (43%) of the N4+ patients.

Skin metastases occurred in six (2%) M0 patients, four located on the chest wall, one on the abdomen and one in the axilla (Table 2b). In one patient a skin metastases on the chest wall was the first and only recurrence, others were detected concurrent or later than non-skin metastases elsewhere. Five of the six patients with skin metastases had deceased in follow-up.

Seven (2%) of the patients developed brain metastases, 15 (5%) skull metastases and three (1%) a combination of both, all concurrent with metastases elsewhere.

Additional analyses showed that two of the M1 patients developed a scalp skin metastasis, both after occurrence of metastases at other sites. Any relation with scalp cooling was unlikely; The first patient had bone metastases shortly after primary diagnosis. Two years later she received one cycle of chemotherapy with scalp cooling, after one month scalp skin metastases were detected, shortly followed by leptomeningeal metastases. The second patient was treated with chemotherapy for local recurrence and lung metastases two years following initial diagnosis, subsequently a scalp skin metastasis was detected three months later, followed by liver metastases.

**Table 2a.** Information on non scalp-cooled patients with scalp skin metastases.

Patient	Chemotherapy	Metastatic sites	Year last FU
1	1993 Conventional	1995 Bone, 1996 Skin (scalp+ head+ thorax)	1996 <sup>a</sup>
2	1996 High-dose	1999 Skin (thorax), 2002 Bone+Lung (c), 2004 Skin (scalp)	2004 <sup>a</sup>
3	1997 Conventional	1999 Skin (scalp)+Bone+Liver (c)	2002 <sup>a</sup>
4	1997 Conventional	2001 Lymph, 2002 Skin (scalp), 2002 Liver, 2002 Lung	2002 <sup>a</sup>

Conventional=5-fluorouracil, epirubicin, cyclophosphamide (FEC), High-dose=4xFEC+ 1xcyclophosphamide, thiotepa, carboplatin (CTC)+ autologous stem cell transplantation, c=concurrent with skin metastasis, FU=follow-up  
<sup>a</sup>deceased

**Table 2b.** Information on scalp-cooled patients with skin metastases.

Patient	Chemotherapy/ Scalp cooling	Site skin	Metastatic sites	Year last fu
1	2001 9x CMF/ 9x	2003 Chest wall	2003 Liver (c), 2003 Skull+ Pleura (fu)	2004 <sup>a</sup>
2	2004 6x FEC/ 2x	2005 Chest wall	2005 Pleuritis carcinomatosa (c)	2005 <sup>a</sup>
3	1997 7x? / 5x	2003 Abdomen	2001 Ovarium, 2001 Liver, 2001 Bone	2003 <sup>a</sup>
4	2004 4x AC/ 1x	2006 Axilla	2005 Bone, 2005 Locoregional recurrence	2006
5	2004 5x FAC/ 5x	2003 Nipple	2001 Bone, 2001 Pleuritis carcinomatosa, 2004 Liver, 2004 Skull	2004 <sup>a</sup>
6	2002 7x paclitaxel/ 7x	2003 Chest wall	2004 Endometrium, 2004 Cervix	2004 <sup>a</sup>

c=concurrent with skin metastasis, fu=in follow-up, ?=type of chemotherapy unknown, C= cyclophosphamide, M=methotrexate, F=5-fluorouracil, E=epirubicin, A=doxorubicin  
<sup>a</sup>deceased

## Discussion

We describe the incidence of scalp skin metastases in two cohorts of MO breast cancer patients without and with scalp cooling. The first cohort is a very thoroughly evaluated homogenous group of high risk patients with a long follow-up. The second cohort is a heterogeneous group of scalp-cooled patients, mirroring daily practice in general hospitals several years ago, with a short follow-up. Therefore outcomes cannot directly be compared, but nevertheless some important conclusions can be drawn.

Firstly, skin metastases were scarce (2-3%) in both cohorts, which is in accordance with a 3% incidence in a report of breast cancer patients from the Munich Cancer Registry (MCR) (n= 33.771, 56% adjuvant chemotherapy).<sup>5</sup> Besides, despite the high risk of progression for the non scalp-cooled patients, the incidence of scalp skin metastases was very low (0,5%). This corresponds with the results of another study reporting a 1.2% incidence among 87 non scalp-cooled MO patients, but also with a 1.1% incidence (all stage II or III disease) among 553 scalp-cooled MO patients.<sup>6</sup> These incidence rates indicate that the scalp skin is not a particularly good seeding ground for metastases. If the low incidences are a consequence of the circulation of blood with a high concentration cytotoxics through the skin, one would expect that without adjuvant chemotherapy skin metastases would be observed more frequently. This however was not shown in the data of the MCR.<sup>5</sup> Also no differences have been reported when comparing the incidence of scalp skin metastases in other non scalp-cooled and scalp-cooled cohorts.<sup>6-8</sup>

Secondly, skin metastases were very rarely the first sign of progression of the disease, and never on the scalp. Scalp skin metastases could indicate a risk of scalp cooling if it is the

first and only metastasis, long before detection of other metastases. In the literature, two scalp-cooled patients have been described with scalp skin metastases as the presenting sign after adjuvant treatment; however it was concluded that this was not related to scalp-cooling treatment.<sup>9</sup>

3

Also brain and skull metastases were all detected concurrent with metastases elsewhere. Only Spaeth et al. compared the incidence of skull and brain metastases and found no difference between scalp-cooled and non scalp-cooled patients.<sup>8</sup> This is in line with a mathematical model that predicted no substantial decrease of brain temperature during scalp cooling.<sup>10</sup>

Maybe the risk of scalp skin metastases after scalp cooling is somewhat underestimated, because scalp cooling was prematurely ceased in half of the 303 MO patients (n=154, 51%). On average patients had three (3-weekly) chemotherapy cycles without scalp cooling (mean 69 days). In general patients stop scalp cooling because of severe hair loss<sup>11</sup>, and in 5-10% because of intolerance<sup>12</sup>, but in the large majority before the third cycle of chemotherapy.<sup>11,13,14</sup> So, if scalp cooling becomes more effective, it might slightly increase the incidence rates, but it is expected to remain low.

For most scalp cooling studies, follow-up time is short.<sup>7</sup> In this study, without scalp cooling the mean time to skin metastasis was 2.1 years and to scalp skin metastases 2.6 years, which approaches the overall 2.2 years follow-up in the scalp-cooled cohort. Many first metastases have become prevalent at that time, as was also shown by highest risk for metastases in the 2.5 years after diagnosis in the MCR.<sup>5</sup> In addition Lemieux et al. reported for adjuvant treated patients a median interval of 2.4 years between diagnosis and first metastasis and 3.4 months from first metastasis to scalp skin metastasis.<sup>6</sup> Nevertheless, the fact remains that in breast cancer the first metastasis can also appear more than 10 years following diagnosis.<sup>5</sup> Besides, it is unknown whether hypothermia changes the process of (time to) metastases.

There are several limitations in the comparison of these retrospective studies. Patient characteristics are incomparable, including chemotherapy regimens, there is uncertain staging in the scalp-cooled cohort and the mean follow-up times differ. Given the very small numbers of breast cancer patients who ever develop scalp skin metastases in follow up, outcomes of the current study have to be interpreted with care.

Possibly in breast cancer no or very few tumor cells nest in the scalp skin directly. In any case there seems to be no increase of clinical manifest scalp skin metastases after scalp cooling in the short term. Moreover, in our scalp-cooled cohort, as well as in the remaining literature after 40 years of scalp cooling, it has never been reported to negatively influence the course of the disease for MO or M1 patients with solid tumors.<sup>7,12</sup> All in all, this indicates that the potential risk of scalp cooling during adjuvant chemotherapy is likely to be very low. Nevertheless, in nearly all studies the total number of scalp-cooled patients is too low and the follow-up is too short to draw definite conclusions and patients should always be informed about the potential risk. In the Netherlands, most medical oncologists estimate the risk for developing scalp skin metastases to be negligible and offer scalp cooling in the adjuvant setting. The ultimate proof that this is safe would be to perform a randomized

trial in patients who are treated with adjuvant chemotherapy with or without scalp cooling. However, due to the very low incidence of scalp skin metastases, we believe this is not feasible as a very high number of patients needs to be included to have enough power to detect a possible difference between groups.

### **Acknowledgments**

We thank Anke Willemse for data collection of the scalp-cooled patients.



## Literature

1. Mulders M, Vingerhoets A, Breed W. The impact of cancer and chemotherapy: Perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nurs*. 2008; 12: 97-102.
2. Hurk van den CJ, Mols F, Vingerhoets AJ, Breed WP. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psych Oncol*. 2010; 19: 701-9.
3. Rodenhuis S, Bontenbal M, Beex LV, Wagstaff J, Richel DJ, Nooij MA, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for high-risk breast cancer. *NEJM*. 2003; 349: 7-16.
4. Sande van de MA, Hurk van den CJ, Breed WP, Nortier JW. Allow scalp cooling during adjuvant chemotherapy in patients with breast cancer; scalp metastases rarely occur. *Ned Tijdschr Geneeskd* [in Dutch]. 2010; 154: A2134.
5. Hurk van den CJ, Eckel R, Poll van de-Franse LV, Coebergh JW, Nortier JW, Holzel D, et al. Unfavourable pattern of metastases in M0 breast cancer patients during 1978-2008: a population-based analysis of the Munich Cancer Registry. *Br Cancer Res Treat*. 2011; 128: 795-805.
6. Lemieux J, Amireault C, Provencher L, Maunsell E. Incidence of scalp metastases in breast cancer: a retrospective cohort study in women who were offered scalp cooling. *Br Cancer Res Treat*. 2009; 118: 547-52.
7. Hurk van den CJG, Poll van de-Franse LV, Breed W, Coebergh JWW, Nortier JWR. Scalp cooling to prevent alopecia after chemotherapy can be considered safe in patients with breast cancer. 2013; submitted.
8. Spaeth D, Luporsi E, Weber B, Guiu S, Braun D, Rios M, et al. Efficacy and safety of cooling helmets (CH) for the prevention of chemotherapy-induced alopecia (CIA): A prospective study of 911 patients (pts). *J Clin Oncol*. 2008; 26.
9. Lemieux J, Desbiens C, Hogue JC. Breast cancer scalp metastasis as first metastatic site after scalp cooling: two cases of occurrence after 7- and 9-year follow-up. *Br Cancer Res Treat*. 2011; 128: 563-6.
10. Janssen FE, Van Leeuwen GM, Van Steenhoven AA. Modelling of temperature and perfusion during scalp cooling. *Phys Med Biol*. 2005; 50: 4065-73.
11. Hurk van den CJ, Peerbooms M, van de Poll-Franse LV, Nortier JW, Coebergh JW, Breed WP. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - results of the Dutch Scalp Cooling Registry. *Acta Oncol*. 2012; 51: 497-504.
12. Breed WPM, Hurk van den CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss; scalp cooling potentials and limitations. *Exp Rev Dermatol*. 2012; 6: 109-25.
13. Hurk van den CJ, Breed WP, Nortier JW. Short post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia. *Supp Care Cancer*. 2012; 20: 3255-60.
14. Betticher DC, Delmore G, Breitenstein U, Anchisi S, Zimmerli-Schwab B, Muller A, et al. Efficacy and tolerability of two scalp cooling systems for the prevention of alopecia associated with docetaxel treatment. *Supp Care Cancer*. 2013.

# Chapter 4



**Scalp cooling to prevent alopecia after chemotherapy can be considered safe in patients with breast cancer**

C.J.G. van den Hurk, L.V. van de Poll-Franse, W.P.M. Breed,  
J.W.W. Coebergh, J.W.R. Nortier

Breast. 2013; in press



## Abstract

With modern scalp cooling equipment cytotoxic damage of hair root cells can be prevented in half of the patients with cancer at high risk of alopecia. However, traditionally doubt has existed whether scalp cooling might facilitate hiding and disseminating scalp skin metastases and thus decrease survival. We discuss this risk using frequency data on metastases in breast cancer from observational and autopsy studies and the Munich Cancer Registry. They showed the incidence of scalp skin metastases to be very low and not differ between scalp-cooled (0.04-1%) and non scalp-cooled (0.03-3%) patients with breast cancer and in need of chemotherapy. We found it rather unlikely that the incidence of scalp skin metastases might increase at all after scalp cooling, whereas a very small proportion of patients receiving chemotherapy are at risk to develop metastases at this site. Scalp cooling can thus safely be offered to patients treated with alopecia-inducing chemotherapy.

## Viewpoints and debates

Scalp cooling probably diminishes the cytotoxic damage of hair root cells through vasoconstriction and a reduced biochemical activity of the cytotoxic agents and their metabolites.<sup>1</sup> It is mainly used in Western Europe by breast cancer patients and prevents severe chemotherapy-induced alopecia (CIA) in half of them.<sup>2</sup> Scalp cooling is usually applied continuously about 30 minutes before, until 90 minutes after chemotherapy infusion<sup>1</sup>, lowering scalp skin temperature to a mean of 18°C (range 12-25°C) (unpublished results). But can hypothermia by scalp cooling also promote outgrowth of scalp skin metastases?

This risk is particularly important for patients without metastases at primary diagnosis (M0), as in metastatic disease (M1) a scalp skin metastasis will rarely be unique, nor lethal. If after adjuvant chemotherapy scalp skin metastases would occur more frequently with than without scalp cooling, this supportive care modality might affect that risk. We now discuss the incidence of (scalp) skin metastases in different groups of breast cancer patients according to treatment with chemotherapy and/ or scalp cooling.

### Incidence of scalp skin metastases in non scalp-cooled breast cancer patients

Without scalp cooling the incidence of *skin metastases* in patients with breast cancer varied between 2-30% in retrospective patient file studies<sup>3-5</sup> and 3% in a German cancer registry (Table 1).<sup>6</sup> In addition, it varied between 9-32% in autopsy studies before chemotherapy was used.<sup>7-10</sup> These broad ranges may be caused by the distinction between true distant metastasis and local chest wall involvement, selection of microscopically confirmed metastases or maybe differences in incidence determined by race.<sup>4</sup> Skin metastases are rarely the first presenting sign of distant metastatic breast cancer<sup>11-15</sup>, also when patients did not undergo systemic treatment after primary local treatment.<sup>16</sup> The majority (53-84%) of skin metastases is detected on the trunk or near the scar of the primary neoplasm.<sup>3, 12, 15, 17, 18</sup>

The incidence of skin metastases alone has been studied among 33,771 M0 breast cancer patients in the Munich Cancer Registry (MCR) in the periods 1978-84, 1985-94 and 1994-2003.<sup>6</sup> Combining all periods, skin metastases were prevalent in 929 (3%) patients and skin metastases alone in 191 (0.6%) patients. In this last group, 27% of the patients had received adjuvant chemotherapy as initial treatment. Skin metastases alone became prevalent later in follow-up than other single sites or combinations of metastases.<sup>6</sup> In 20% of these patients they were diagnosed >10 years after initial diagnosis. The sub-site of skin metastases alone as well type of systemic treatment after metastases were unknown.

Active follow-up of the frequency of *scalp skin metastases* in breast cancer patients without scalp cooling showed the incidence to vary between 0.03-3%<sup>3, 11, 12, 19-22</sup>, remaining low in a study population of high risk patients only<sup>20</sup>, even in M1 patients<sup>3, 11, 12</sup> or when the study was prospective.<sup>19</sup> Incidence rates were not associated with time since diagnosis (110 months)<sup>20</sup> or receiving no adjuvant chemotherapy.<sup>12</sup> One study showed that also scalp skin metastases occurred at the same time or later than non-skin metastases elsewhere.<sup>20</sup>

## Incidence of scalp skin metastases in scalp-cooled breast cancer patients that were systematically followed

Active follow-up of the frequency of *scalp skin metastases* in scalp-cooled breast cancer patients showed an incidence below 1.1% (Table 2).<sup>19, 22, 28</sup> Lemieux et al. described at a follow-up of 5.8 years six patients (1.1%) with stage II and III breast cancer (n=553) who had developed scalp skin metastases, but never as an isolated site of relapse.<sup>22</sup> Besides, two breast cancer patients were reported in whom seven and nine years after diagnosis scalp skin metastases were detected as first metastatic site,<sup>28</sup> but scalp cooling most likely had not affected the prognosis unfavourably; The first patient only had used scalp cooling for two out of four cycles and lost her hair. A few months after detection of the scalp skin metastases many other metastases were found. The second patient used scalp cooling during one out of six cycles of chemotherapy. Six years later she received another six cycles without scalp cooling and two years later the scalp skin metastases were diagnosed.

## Incidence of scalp skin metastases in scalp-cooled breast cancer patients that were not systematically followed

Literature research of the frequency of *scalp skin metastases* in scalp-cooled patients (n=2315), at least 49% with breast cancer, led to 38 original articles carried out during 1970 to 2012<sup>1, 29</sup>, and four additional studies (Table 2).<sup>30-33</sup> At least 37% of these patients had received adjuvant chemotherapy. These studies never assessed scalp skin metastases systematically and follow-up was mostly short (2-46 months) or unknown (n=30). Overall 17 studies addressed scalp skin metastases, which were detected in nine patients (0.4%). Seven of these patients had advanced disease and scalp skin metastases were never the first and only site of relapse. For two patients the course of disease was unknown.<sup>26</sup>

Data of >2000 Dutch scalp-cooled patients have been analysed in our studies from 2004 to 2012.<sup>2, 34-37</sup> Of >1800 (87%) female breast cancer patients 77% were treated in the adjuvant setting, mainly with anthracyclines or taxanes. In one patient, a scalp skin metastasis had been spontaneously reported, after the first treatment cycle with docetaxel monotherapy for liver metastases and previous chemo- and hormonal therapy. However, scalp skin metastases were not systematically assessed.

## Discussion

This overview shows that the incidence of scalp skin metastases in breast cancer patients seems to be comparable for scalp-cooled (0.04-1%) and for non scalp-cooled patients (0.03-3%). Despite the high vascularisation and immobile environment of the scalp skin<sup>38</sup>, the low incidence indicates that it is not a site where metastases seed easily. The limited occurrence probably cannot be attributed to the effectiveness of chemotherapy. Firstly, because the incidence of (*scalp*) *skin metastases* was also low when chemotherapy was not yet available.<sup>7-10, 12</sup> Secondly, the MCR exhibited the proportion of *skin metastases* not to differ in the periods 1978-84, 1985-94 and 1994-2003, despite changes in systemic treatment and stage distribution.<sup>6</sup> This would indicate that scalp cooling does not pose a risk for development of scalp skin metastases.

Of all patients receiving chemotherapy, only patients who have proliferating micro-metastases in the scalp skin, which survive despite chemotherapy, are at risk for scalp skin metastases due to scalp cooling. If metastases develop as a result of primary resistance for chemotherapy<sup>40</sup>, or in case of late relapses from micro-metastases in a dormant state for many years after cytotoxic treatment<sup>41, 42</sup>, scalp cooling cannot cause any additional harm. However, as long as the risk of scalp skin metastases before and after adjuvant systemic therapy cannot be predicted accurately, the potential -but likely low- harmful effect of scalp cooling for an individual patient remains unknown and needs to be acknowledged.

Scalp skin metastases are usually detected later than or concurrent with metastases at other sites, possibly due to intrinsic mechanisms that initiate late relapses of dormant cells.<sup>39</sup> <sup>41</sup> Cutaneous metastases might thus often be an indication for other distant metastases elsewhere in the body.<sup>43</sup>

During scalp cooling cytotoxics do reach the *scalp skin*, but with a decrease of scalp skin perfusion of approximately 20% at a local temperature of around 20°C.<sup>23</sup> After chemotherapy infusion the concentration of the cytotoxic agents and its metabolites decreases gradually, remaining there when scalp cooling is ceased. Thus, hair follicle cells of scalp-cooled patients are probably damaged, but able to recover. Therefore, hair production is temporarily diminished, resulting in a small constricted section of the hair.<sup>24</sup> And indeed, mostly there is some additional hair loss in the period between chemotherapy cycles.<sup>25</sup> Furthermore, two studies reported independently that pre-existing scalp skin metastases regressed during chemotherapy despite scalp cooling.<sup>26, 27</sup> One patient preserved the hair, while the other lost it.

Should the low risk for scalp skin metastases be taken for granted from the existing medical literature? Firstly, the follow-up of most studies is short. However, the first peak of relapses in breast cancer occurs one to two years after clinical diagnosis.<sup>41, 44</sup> Nevertheless, scalp cooling might change the time to the emergence of scalp skin metastasis. Secondly, it is likely that the incidence of scalp skin metastases has been underreported, as the patient is often asymptomatic and physical examination of the scalp is on demand only, on the patients indication.<sup>13, 18</sup> Thirdly, it seems rather complicated to measure micro-metastases in the highly vascularised scalp skin.

Although medical professionals may be more alert of scalp skin metastases in a scalp-cooled patient, they might still be overlooked because of their low incidence, (concurrent) skin metastases at other sites or other life threatening metastases elsewhere that kill the patient probably before the detection of a scalp skin metastasis. The true proportion of these patients is unknown, also because in autopsy studies the skin is often excluded.<sup>45</sup> But this also indicates that these metastases are mostly not clinically important.<sup>22</sup>

In conclusion, in patients with solid tumours, an unfavourable development of the disease due to scalp cooling has never been documented. It is therefore unlikely that the local efficacy of chemotherapy is decreased to such an extent, that the extremely low baseline risk increases. It is never a reason to omit scalp cooling with palliative treatment, which also

seems safe for the adjuvant chemotherapy setting. Most Dutch medical oncologists currently consider the risk so low that they provide scalp cooling in the adjuvant setting in 80% of the >70 Dutch scalp cooling hospitals. Remaining doubts might be addressed by studying a large cohort of scalp-cooled patients<sup>36</sup> using a cancer registry and prospectively compare survival between scalp-cooled and non scalp-cooled patients.



**Table 1.** Overview of studies of skin and scalp skin metastases in patients with breast cancer without scalp cooling.

Study	n=	Skin mets		Scalp skin		Syst	Duration of		Chemo (%) /		Type <sup>a</sup>	Remarks
		(%)	(?) <sup>c</sup>	mets (%)	mets (<3)		Follow up	Adj (%)	0			
Brownstein 1972 <sup>20</sup>	NR <sup>b</sup>	168	(?) <sup>c</sup>	5	(<3)	Yes	NR	(included in 1948-1963)	0			<sup>b</sup> % M1 <sup>a</sup> unknown
Fisher 1982 <sup>21</sup>	7800	NR		2 <sup>d</sup>	(0.03)	Yes	NR		?/100	?		<sup>c</sup> 100% biopsy proven
Lookingbill 1990 <sup>22</sup> /1993 <sup>23</sup>	992 <sup>e,f</sup>	71 <sup>g</sup>	(7)	18	(2)	Yes	NR	(included in 1976-1986)	?/?	?		<sup>d</sup> first occurrence <sup>e</sup> distant (n=20) or distant combined with local (n=51) metastasis
Spaeth 2008 (abstract) <sup>2</sup>	141 <sup>h,j</sup>	NR		(<3) <sup>i</sup>		Yes	Median 3 yrs		100/?		Anthraand/ or taxanes	<sup>f</sup> % M1 unknown <sup>g</sup> 79% biopsy proven <sup>h</sup> 93% breast ca <sup>i</sup> % M1 unknown <sup>j</sup> includes also skull and brain metastases
Lemieux 2009 <sup>24</sup>	87	M0	NR	1 <sup>k</sup>	(1)	Yes	Median 5.4 yrs		100/100		Anthra/ CMF/ taxanes	<sup>k</sup> no scalp cooling during adjuvant treatment, developing scalp skin metastasis after 6 out of 9 systemic treatments for metastatic disease with scalp cooling

table 1. continues on next page

Van de Sande 2010 <sup>25</sup>	885 M0 <sup>l</sup>	25 (3)	4 <sup>m</sup> (0.5)	Yes	Mean 9.2 yrs	100/100	FEC/ FEC+CTC	<sup>l</sup> high risk: 4+ lymph nodes <sup>m</sup> Scalp skin concurrent with other sites <sup>n</sup> scalp skin <u>alone</u>
MCR 2011	33.771 M0	929 (3)/ 191 (0.6) skin alone	( $<0.6$ ) <sup>n</sup>	No	Mean 8.2 yrs	29/100	NR	

Syst= (scalp) skin metastases systematically studied, Pt=patient, Chem= chemotherapy, Adj=adjuvant chemotherapy, Type= type of chemotherapy, NR= not reported, yrs=years, M0= without metastases at diagnosis, M1=metastasised disease at diagnosis

<sup>a</sup> Anthra= anthracyclines, CMF= Cyclophosphamide, Methotrexate, 5-Fluorouracil, FEC=5-Fluorouracil, Epirubicin, Cyclophosphamide, CTC= Cyclophosphamide, Thiotepa, Carboplatin



**Table 2.** Overview of studies of scalp skin metastases in scalp-cooled patients with (mainly) breast cancer.

Study	n=	Scalp skin			Follow up	Adj (%)	Type <sup>a</sup>	Remarks
		nets (%)	Syst	mets (%)				
Van den Hurk (1997-2005)	390	3 (0.8) <sup>b</sup>	Yes	Median 2.2 y	NR	Anthra/ taxane/ CMF	<sup>b</sup> 1x before start chemotherapy, 2x following metastases at other sites	
Spaeth 2008 (abstract) <sup>2</sup>	770 <sup>c</sup>	3 (0.04) <sup>d</sup>	Yes	Median 3 y	NR	Anthra and/or taxane	<sup>c</sup> 93% breast ca <sup>d</sup> personal communication	
Lemieux 2009 <sup>24</sup>	553	6 (1.1) <sup>e</sup>	Yes	Median 5.8 y	100	Anthra/ CMF/ taxane	<sup>e</sup> not first metastatic site	
Lemieux 2011 <sup>26</sup>	2	2 <sup>f</sup>	Yes	7+9 y	100		<sup>f</sup> first and only site, stop scalp cooling after 1 or 2 cycles	
Van den Hurk (2004-12) <sup>4,27-30</sup>	>2000 <sup>g</sup>	1 (0.04) <sup>h</sup>	No	n.a.	77	Diverse	<sup>g</sup> 87% breast ca <sup>h</sup> detected after first chemotherapy	
Literature (1970-2013)	2315 <sup>i</sup>	9 (0.4)	No	n.a.	>439 (37)	Diverse	<sup>i</sup> at least 1287 (49%) breast ca	
No mets info <sup>n</sup>	1204 <sup>j</sup>	NR	No	n.a.	>237 (46)	Diverse	<sup>j</sup> at least 511 (42%) breast ca	
No mets -FU <sup>o</sup>	268 <sup>k</sup>	0	No	NR	NR	Diverse	<sup>k</sup> at least 190 (71%) breast ca	
No mets +FU <sup>p</sup>	309 <sup>l</sup>	0	No	9-46 m	133 (58)	Diverse	<sup>l</sup> 74% breast ca	
Mets <sup>q</sup>	307 <sup>m</sup>	9	No	2-20 m	NR	Diverse	<sup>m</sup> at least 131 (43%) breast ca	

Syst= scalp skin metastases systematically studied, Adj=adjuvant chemotherapy, Type= type of chemotherapy, NR= not reported, y=years, m= months, n.a. not applicable, mets=metastases, FU=follow-up

<sup>a</sup> Anthra= anthracyclines, CMF= Cyclophosphamide, Methotrexate, 5-Fluorouracil

<sup>n</sup> No information about scalp skin metastases, references: Adams 1992, Anderson 1981, Auvinen 2010, Belpomme 1982, Benglia 1986, Ciambellotti 1993, David 1987, Dean 1983, Dougherty 1996, Goldhirsch 1982, Gregory 1982, Hunt 1982, Kargar 2011, Keizer-Heldens 2009, Kennedy 1983, Kolen 2002, Nakazawa 1985, Robinson 1987, Samonigg 1984, Symonds 1986, Tierney 1992

<sup>o</sup> No scalp skin metastases, follow up unknown, references: Giaccone 1988, Hillen 1990, Katsimbri 2000, Macduff 2003, Massey 2004, Satterwhite 1984

<sup>p</sup> No scalp skin metastases, follow up known, references: Lemenager 1997, Parker 1987, Protiere 2002, Ridderheim 2003, Ron 1997, Tollenaar 1994

<sup>q</sup> Scalp skin metastases, references: Christoudoulou 2006, Kiser 1982, Middleton 1985, Peck 2000, Vendelbo-Johansen 1985

## Literature

1. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol* 2005;16:352-58.
2. Hurk van den CJG, Peerbooms M, Komen M, Nortier JWR, Smorenburg CH, Breed WPM. Multicenter results of scalp cooling to prevent chemotherapy-induced alopecia in 1500 breast cancer patients. *Suppl to Cancer Res* 2011;71:1s-653s Page 594s.
3. Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. *J Am Acad Dermatol* 1993;29:228-36.
4. Hu SC, Chen GS, Wu CS, Chai CY, Chen WT, Lan CC. Rates of cutaneous metastases from different internal malignancies: experience from a Taiwanese medical center. *J Am Acad Dermatol* 2009;60:379-87.
5. Manders K, van de Poll-Franse LV, Creemers GJ, et al. Clinical management of women with metastatic breast cancer: a descriptive study according to age group. *BMC Cancer* 2006;6:179.
6. Hurk van den CJ, Eckel R, Poll van de-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. *Breast Cancer Res Treat* 2011;128:795-805.
7. Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma; analysis of 1000 autopsied cases. *Cancer* 1950;3:74-85.
8. Spencer PS, Helm TN. Skin metastases in cancer patients. *Cutis* 1987;39:119-21.
9. Enticknap JB. An analysis of 1,000 cases of cancer with special reference to metastasis. *Guys Hosp Rep* 1952;101:273-9.
10. Lee YT. Breast carcinoma: pattern of metastasis at autopsy. *J Surg Oncol* 1983;23:175-80.
11. Lookingbill DP, Spangler N, Sexton FM. Skin involvement as the presenting sign of internal carcinoma. A retrospective study of 7316 cancer patients. *J Am Acad Dermatol* 1990;22:19-26.
12. Brownstein MH, Helwig EB. Metastatic tumors of the skin. *Cancer* 1972;29:1298-307.
13. Schwartz RA. Cutaneous metastatic disease. *J Am Acad Dermatol* 1995;33:161-82; quiz 183-6.
14. Carson HJ, Pelletiere EV, Lack E. Alopecia neoplastica simulating alopecia areata and antedating the detection of primary breast carcinoma. *J Cutan Pathol* 1994;21:67-70.
15. Pivot X, Asmar L, Hortobagyi GN, Theriault R, Pastorini F, Buzdar A. A retrospective study of first indicators of breast cancer recurrence. *Oncology* 2000;58:185-90.
16. Dean JC. Prevention of doxorubicin-induced hair loss. *N Engl J Med* 1980;302:921.
17. Gates O. Cutaneous metastases of malignant disease. *Am J Cancer* 1937;30:718-30.
18. Krathen RA, Orengo IF, Rosen T. Cutaneous metastasis: a meta-analysis of data. *South Med J* 2003;96:164-7.
19. Spaeth D, Luporsi E, Weber B, et al. Efficacy and safety of cooling helmets (CH) for the prevention of chemotherapy-induced alopecia (CIA): A prospective study of 911 patients (pts). *J Clin Oncol* 2008;26.
20. Sande van de MAE, Hurk van den CJG, Breed WPM, Nortier JWR. Hoofdhuidmetastasen bij hoogrisico borstkankerpatienten. *Ned Tijdschr Geneesk* 2010;154:A2134.
21. Dean JC, Griffith S, Cetas TC, Mackel CL, Jones SE, Salmon SE. Scalp hypothermia: a comparison of ice packs and the kold kap in the prevention of doxorubicin-induced alopecia. *JCO* 1983;1:33-7.
22. Lemieux J, Amireault C, Provencher L, Maunsell E. Incidence of scalp metastases in breast cancer: a retrospective cohort study in women who were offered scalp cooling. *Breast Cancer Res Treat* 2009;118:547-52.
23. Janssen FE. Modelling physiological and biochemical aspects of scalp cooling. Eindhoven: Technical University Eindhoven; MSc Thesis 2007.
24. Hurk van den CJG, Breed WPM, Mols F. Chemotherapy-induced hair loss. In: Preedy Ve, editor. *Handbook of Hair in Health and Disease*. Wageningen, The Netherlands: Wageningen Academic Publishers; 2012. p. 403-16.

25. Komen M, Smorenburg, CH, Breed, WPM, Van den Hurk, CJG, Nortier, JW. Evaluation of a trichometer to quantify the prevention of hair loss by scalp cooling during chemotherapy. Poster 546 ECCO Stockholm 2011.
26. Christodoulou C, Tsakalos G, Galani E, Skarlos DV. Scalp metastases and scalp cooling for chemotherapy-induced alopecia prevention. *Ann Oncol* 2006;17:350.
27. Satterwhite B, Zimm S. The use of scalp hypothermia in the prevention of doxorubicin-induced hair loss. *Cancer* 1984;54:34-7.
28. Lemieux J, Desbiens C, Hogue JC. Breast cancer scalp metastasis as first metastatic site after scalp cooling: two cases of occurrence after 7- and 9-year follow-up. *Breast Cancer Res Treat* 2011;128:563-6.
29. Breed WPM, Hurk van den CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss; scalp cooling potentials and limitations. *Exp Rev Dermatol* 2011;6:109-125.
30. Hurk van den CJG, Gerrits P, Graat J, Kolen B, Laar van de- Müskens J, Breed WPM. Positieve ervaringen met hoofdhuidkoeling in drie ziekenhuizen in Nederland. *Tijd voor een standaard aanbod van hoofdhuidkoeling?* *Oncologica* 2005;22:162-67 [article in Dutch].
31. Nakazawa M, Sakamoto T, Honda M, et al. Scalp hypothermia: a prevention of hair-loss in clinical oncology. *Dokkyo J Med Sci* 1985;12:17-24.
32. Keizer-Heldens P. Hoofdhuidkoeling bij haarverlies door chemotherapie. *Oncologica* 2009:29-34 [article in Dutch].
33. Kargar M, Sarvestani RS, Khojasteh HN, Heidari MT. Efficacy of penguin cap as scalp cooling system for prevention of alopecia in patients undergoing chemotherapy. *J Adv Nurs* 2011 epub ahead.
34. Hurk van den CJ, Mols F, Vingerhoets AJ, Breed WP. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psych Oncol* 2010;19:701-9.
35. Hurk van den CJ, Breed WP, Nortier JW. Short post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia. *Supp Care Cancer* 2012;20:3255-60.
36. Hurk van den CJ, Peerbooms M, van de Poll-Franse LV, Nortier JW, Coebergh JW, Breed WP. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - results of the Dutch Scalp Cooling Registry. *Acta Oncol* 2012;51:497-504.
37. Hurk van den CJG, Akker van den -van Marle ME, Breed WPM, Poll van de-Franse LV, Nortier JWR, Coebergh JWW. Impact of scalp cooling on chemotherapy-induced alopecia, wig use and hair growth of patients with cancer *J Oncol Nurse* (in press) 2013.
38. Mallon E, Dawber RP. Alopecia neoplastica without alopecia: a unique presentation of breast carcinoma scalp metastasis. *J Am Acad Dermatol* 1994;31:319-21.
39. Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. *Cell* 2011;147:275-92.
40. Retsky MW, Demicheli R, Hrushesky WJ, Baum M, Gukas ID. Dormancy and surgery-driven escape from dormancy help explain some clinical features of breast cancer. *Apmis* 2008;116:730-41.
41. Demicheli R, Biganzoli E, Boracchi P, Greco M, Retsky MW. Recurrence dynamics does not depend on the recurrence site. *Breast Cancer Res* 2008;10:R83.
42. Goss PE, Chambers AF. Does tumour dormancy offer a therapeutic target? *Nat Rev Cancer* 2010;10:871-7.
43. Moore S. Cutaneous metastatic breast cancer. *Clin J Oncol Nurs* 2002;6:255-60.
44. Toi M, Yamashiro H, Tsuji W. Risk reduction of distant metastasis in hormone-sensitive postmenopausal breast cancer. *Breast Cancer* 2009;16:207-18.
45. Kamby C. The pattern of metastases in human breast cancer: methodological aspects and influence of prognostic factors. *Cancer Treat Rev* 1990;17:37-61.


# Part II



Effectiveness and the impact of scalp cooling time



# Chapter 5



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

C.J.G. van den Hurk, M. Peerbooms, L.V. van de Poll-Franse,  
J.W.R. Nortier, J.W.W. Coebergh, W.P.M. Breed

*Acta Oncol.* 2012; 51, 497-504





## Abstract

### Background

Chemotherapy-induced alopecia is a frequently occurring side effect of cancer treatment with high a psychological impact which can be prevented by scalp cooling. With this multi-centre patient series we estimated the results of scalp cooling for currently used chemotherapies to provide patient information and we identified characteristics associated with the results.

### Material and methods

The Dutch Scalp Cooling Registry collected data on scalp-cooled patients in 28 Dutch hospitals. Nurses and patients completed questionnaires on patients, chemotherapy and scalp cooling characteristics. Logistic regression analysis was used to examine associated characteristics of the scalp cooling result.

### Results

Overall, 50% of the 1411 scalp-cooled patients did not wear a head cover during their last chemotherapy session. Patients were satisfied with the results in 8% of cases after TAC chemotherapy and up to 95% after paclitaxel treatment. Besides type of chemotherapy, higher dose and shorter infusion time, older age, female gender and non-West-European type of hair significantly increased the proportion head cover use. Hair length, quantity, chemical manipulation (dyeing, waving, colouring), wetting hair before scalp cooling, and treatment with chemotherapy ever before did not influence the degree of head covering among patients.

### Conclusions

Scalp cooling results as recorded in this open patient registry were positive for most regimens, justifying it's use by all eligible patients, except for those needing TAC. Lengthening infusion time may improve the results.

## Background

Chemotherapy-induced alopecia (CIA) is a common side effect of cancer treatment and one of the most distressing side effects for many patients.<sup>1,2</sup> CIA may be prevented by scalp cooling prior to, during and some time after chemotherapy infusion. Scalp cooling has been practised since the 1970's but the physiological and biochemical aspects have scarcely been modelled.<sup>3</sup> Until 2011 only 48 publications focussed on scalp cooling results<sup>4-11</sup>, largely from mono-centric studies with small patient numbers. Generally, efficacy is exhibited, although it is not defined uniformly and is inconclusive for most of the currently used chemotherapies. In fact, determinants of scalp cooling results vary tremendously, i.e. especially type, dose and frequency of chemotherapy infusion, the type of scalp cooling equipment and duration.<sup>6</sup>

Clinical impressions of oncologists and nurses are often insufficient for predicting the scalp cooling result for a patient needing a particular chemotherapy regimen.<sup>12</sup> Systematic registration of all patients receiving chemotherapy and scalp cooling aims to standardise and clarify the various issues of hair preservation in currently used chemotherapies.

## Material and methods

The Dutch Scalp Cooling Registry started in January 2006 with eight community hospitals and 1 academic hospital. In December 2009, the registry comprised 28 hospitals, two of which were academic hospitals. Nurses asked all patients who started scalp cooling in that time period to participate, i.e. chemo-naïve as well as patients with chemotherapy ever before. Nurses reported the year of birth, gender, cancer type, chemotherapy type, dose and infusion time, the adjuvant or palliative nature and reasons for stopping scalp cooling. Infusion times depended on the protocol of a particular hospital. Some of the examined chemotherapies were sequential schemes.

During the first scalp cooling session patients reported hair characteristics: the length and quantity, the type of hair determined by ethnical background, and whether they had dyed, waved or coloured it within two months of the start of chemotherapy. Patients also stated whether they had received alopecia-inducing chemotherapy ever before. During each session nurses recorded the scalp cooling times and whether they had dampened the patient's hair or used hair conditioner before the start of scalp cooling, thus trying to achieve a lower scalp skin temperature. Tolerance was evaluated by recording reasons for stopping scalp cooling.

Scalp cooling was performed using the Paxman PSC1 or PSC2 system. The result was evaluated by asking patients whether or not they wore a head cover (including wig) during their last scalp cooling session. Head cover use is the most important outcome measure, because it represents perceived satisfaction with hair preservation by scalp cooling; For some patients with minimal CIA, this is a severe burden so they choose to wear a head cover, but the opposite is also true. The result of scalp cooling was also evaluated by patients indicating the severity of hair loss on the WHO scale, with score 0 for none, 1 for minimal, 2 for severe and 3 for total alopecia.<sup>13</sup> Final analyses included only patients who had completed at least two scalp cooling sessions or if they discontinued scalp cooling because of severe CIA after the first session.

## Statistics

Differences between patients with and without head covering were compared by the Chi square test or Mann Whitney U test. Whether the patient, chemotherapy and scalp cooling characteristics were associated with not wearing head covering after scalp cooling was evaluated by logistic regression analyses and expressed as Odds Ratio's (OR). In these overall analyses chemotherapy dosages were not taken into account, because of too much variance within the regimens. For the largest subgroup, i.e. women treated with 5-Fluorouracil, Epirubicine and Cyclophosphamide (FEC) chemotherapy (with epirubicine dosages from 50-100 mg/m<sup>2</sup>) separate regression analyses were performed, now including dosage. The various patient, chemotherapy and scalp cooling characteristics, included for adjustment in the multivariate analyses, were determined a priori.<sup>14</sup> Statistical differences were indicated if  $p < 0.05$  and reported  $p$ -values were two-sided. Statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC).

## Results

Between 2006 and 2009 1411 patients were registered in the Dutch Scalp Cooling Registry (Table 1). The majority of patients were women (96%) with breast cancer (86%), who were treated in the adjuvant setting (69%). The mean age was 53 years (range 18-81 yrs). The median pre-infusion cooling time was 38 minutes (standard deviation (sd) 12, range 3-115) and the median post-infusion cooling time was 90 minutes (sd 17, range 15-210) (data not shown). The median number of cooling sessions was 4 (sd 3, range 1-27).

Half of the patients (n=709, 50%) wore no head cover during the last scalp cooling session (Table 2). Use of head covering varied according to type and dose of chemotherapy from 8% to 94% of patients. Results were best for monotherapy with low dose taxanes: 94% of patients on docetaxel (D75) wore no head cover, as well as 81% of patients with paclitaxel (T70-90) chemotherapy. Results were worst for TAC chemotherapy (8%), despite the relatively low dose of taxane (D75) and anthracycline (A50). In the multivariate analysis, these chemotherapy regimens (D, T and TAC), together with irinotecan, independently influenced the scalp cooling result (Table 3). WHO scores for alopecia (WHO 0, 1, 2, 3) for patients wearing head covering, were 2%, 2%, 9% and 87% respectively and for patients not wearing head covering 26%, 49%, 25% and 0%.

Multivariate analysis, including all patients, showed that elderly patients (OR 0.6,  $p=0.04$ ) and those with Asian type of hair (OR 0.4,  $p=0.008$ ) exhibited the worst scalp cooling results (Table 3). Similar results were found for the more homogeneous group of women receiving FEC chemotherapy (Table 4). Male gender was positively associated (OR 6.3,  $p=0.0004$ ) (Table 3). When using WHO scores 0 and 1 ('no/ minimal') versus WHO 2 and 3 ('severe/ total' alopecia) multivariate analyses showed similar results.

The subgroup analysis of patients receiving FEC showed that increase in dosage led to inferior scalp cooling results (Table 4). The indication of a dose-effect relationship was also observed when comparing D75 to D100 (94 vs 61% no head cover) and T70-100Carbo to T175Carbo (75 vs 38% no head cover) (Table 2). Longer FEC infusion times reduced the use of head covering (Table 4). This effect was also observed marginally for the total patient group (Table 3).

Patients with chemically manipulated hair because of dying, waving or colouring did not exhibit higher head cover use after scalp cooling, neither did those with longer length and larger quantities of hair or longer post-infusion cooling times (Table 3 and 4). Wetting hair also did not contribute to the result. Corrected for the type of chemotherapy in the multivariate analysis, the results were better for patients who had had no chemotherapy before.

Scalp cooling was stopped because of intolerance in only 3% of patients. No scalp skin metastases were reported following the last chemotherapy session up to August 2011.

**Table 1.** Result of scalp cooling according to patient and scalp cooling characteristics (n=1411).

<b>Characteristics</b>	<b>All patients (%)</b>	<b>No head cover/all (%)</b>	<b>p-value</b>
<b>Overall</b>	1411 (100)	709/1411 (50)	
<b>Patient characteristics</b>			
<b>Age group (years)</b>			0.02
-44 (n=287)	287 (21)	124/287 (43)	
45-54 (n=492)	492 (35)	269/492 (55)	
55-64 (n=413)	413 (30)	207/413 (50)	
65+ (n=201)	201 (14)	95/201(47)	
Missing	18		
<b>Gender</b>			<0.0001
Male	50 (4)	40/50 (80)	
Female	1357 (96)	665/1357 (49)	
Missing	4		
<b>Cancer</b>			<0.0001
Breast	1216 (86)	598/1216 (49)	
Female genital cancer	65 (5)	30/65 (46)	
Gastro-intestinal/ Colorectal	63 (4)	25/63 (40)	
Lung	19 (1)	15/19 (79)	
Prostate	27 (2)	27/27 (100)	
Other	16 (1)	12/16 (75)	
Missing	5		
<b>Chemotherapy setting</b>			0.0008
Adjuvant	979 (71)	460/979 (47)	
Palliative	404 (29)	230/404 (57)	
Missing	28		

Table 1. continues on next page

<b>Chemotherapy ever before</b>			0.007
Yes	176 (12)	105/176 (60)	
No	1235 (88)	603/1235 (49)	
Hair characteristics			
<b>Dyed</b>			0.8
Yes	131 (9)	64/131 (49)	
No <sup>a</sup>	1280 (91)	644/1280 (50)	
<b>Waved</b>			1.0
Yes	42 (3)	21/42 (50)	
No <sup>a</sup>	1369 (97)	687/1369 (50)	
<b>Coloured</b>			0.2
Yes	461 (33)	219/461 (48)	
No <sup>a</sup>	950 (67)	489/950 (51)	
<b>Length</b>			0.02
<5 cm	379 (30)	210/379 (55)	
>5 cm	864 (70)	416/864 (48)	
Missing	168		
<b>Quantity</b>			0.1
Small	60 (5)	38/60 (63)	
Medium	597 (48)	294/597 (49)	
Large	587 (47)	289/587 (49)	
Missing	167		
<b>Type of hair</b>			0.07
African	11 (1)	4/11 (36)	
Asian	40 (3)	13/40 (33)	
West-European	1160 (93)	596/1160 (51)	
South-European	39 (3)	17/39 (44)	
Missing	161		
Wetting hair before scalp cooling by			
<b>Dampen hair</b>			0.8
Yes	182 (13)	93/182 (51)	
No <sup>a</sup>	1229 (87)	615/1229 (50)	
<b>Use hair conditioner</b>			0.9
Yes	77 (5)	39/77 (51)	
No <sup>a</sup>	1334 (95)	669/1334 (50)	

<sup>a</sup>'No' includes missings

**Table 2.** Head cover use during the last scalp cooling session according to type of chemotherapy.

Chemotherapy and planned dosage (mgr/m <sup>2</sup> ) <sup>a</sup>	No head cover/total (%)	Median infusion time (min.) (sd/min/max)	Number of sessions planned <sup>d</sup>
A60C600 (AC)	29/74 (39)	30 (13/10/90)	4
A60C600/D100 <sup>b</sup> (ACD)	10/16 (63)	20 (11/10/40) / 60 (0/60/60)	4/4
ACT Overall	20/50 (40)		
A60C600/T80 <sup>b</sup> (ACT80)	14/29 (48)	30 (15/10/75) / 60 (31/60/180)	4/12
A60C600/T175 <sup>b</sup> (ACT175)	6/21 (29)	30 (22/20/120) / 180 (0/180/180)	4/4
D75A50C500 (TAC)	5/66 (8)	90 (14/45/135)	6
D Overall <sup>f</sup>	87/120 (73)		
D75	31/33 (94)	60 (0/60/60)	n.a.
D100	27/44 (61)	60 (8/60/90)	n.a.
D75combi <sup>c</sup>	21/33 (64)	105 (26/60/150)	n.a.
F500A50C500 (FAC)	21/39 (54)	45 (13/25/90)	5
FEC Overall <sup>f</sup>	371/752 (56)		
F500E50-70C500 (FE50-70C)	22/38 (58)	45 (9/25/75)	5
F500/600E75-85C500/600 (FE75-85C)	16/32 (50)	45 (10/25/60)	5
F500E90C500 (FE90C)	292/558 (52)	45 (16/15/120)	5
F500/600E100C500/600 (FE100C)	40/123 (33)	45 (14/15/90)	6
F500E100C500/D100 <sup>b</sup> (FE100CD)	22/46 (48)	60 (21/15/90) / 60 (12/60/140)	3/3
TCarbo Overall <sup>f</sup>	31/68 (46)		
T70-100Carbo	9/12 (75)	120 (31/90/210)	n.a.
T175Carbo	20/52 (38)	210 (31/90/240)	6
T70-90	34/42 (81)	60 (28/60/180)	n.a.
Irino350	12/42 (29)	60 (24/30/90)	n.a.
Other <sup>e</sup>	49/64 (77)		
Total	709/1411 (50)		

table 2. continues on next page

A= doxorubicine C=cyclophosphamide D=docetaxel T=paclitaxel F=5-fluorouracil E=epirubicine Carbo=carboplatin Irino=irinotecan, All 3-weekly schemes, with exception of T780 and T70-90

<sup>a</sup>Dosage other/missing, but included in multivariate analyses= TAC n=1, FAC n=4, FECD n=6, T n=2, Irino n=5

<sup>b</sup>Sequential scheme

<sup>d</sup>D combi= D combined with Cyclophosphamide, Capecitabine, Carboplatin, Gemcitabine, Methotrexat, Myocet or Xeloda

<sup>e</sup>According to Dutch guidelines

<sup>e</sup>Other= <10 patients had a particular regimen with a specific dosage

<sup>f</sup>Including also other dosages than specified in this table



**Table 3.** Univariate and multivariate logistic regression analysis of all patients (n=1411); odds of wearing no head cover during the last scalp cooling session (hc) and odds of WHO score 0-1 (who).

Characteristics	Uni	Multi variate			
	variate OR (hc)	OR (hc)	95% CI	P-value	OR (who)
<b>Age group (years)</b>					
-44	1.0	1.0	-	-	1.0
45-54	1.5	1.3	(0.9-1.8)	0.1	1.2
55-64	1.2 (NS)	1.1	(0.7-1.5)	0.8	1.1
65+	1.1 (NS)	0.6	(0.4-1.0)	0.04	0.8
<b>Gender</b>					
Female	1.0	1.0	-	-	1.0
Male	4.2	6.3	(2.3-17.2)	0.0004	9.4 <sup>c</sup>
<b>Chemotherapy</b>					
FEC	1.0	1.0	-	-	1.0
AC	0.7 (NS)	1.0	(0.6-1.7)	0.9	0.6
AC/D	1.7 (NS)	1.7	(0.5-5.2)	0.4	1.4
AC/T	0.7 (NS)	1.2	(0.6-2.5)	0.6	0.9
TAC	0.08	0.08	(0.03-0.2)	<0.0001	0.04 <sup>c</sup>
D <sup>b</sup>	2.7	2.0	(1.2-3.5)	0.01	1.6
FAC	1.2 (NS)	1.2	(0.6-2.5)	0.6	1.7
FEC/D	1.0 (NS)	0.9	(0.4-1.9)	0.8	1.1
TCarbo	0.9 (NS)	1.1	(0.5-2.4)	0.8	1.1
T	3.4	4.6	(2.1-10.2)	0.0002	4.3 <sup>c</sup>
Irino	0.4	0.3	(0.1-0.7)	0.004	0.2 <sup>c</sup>
Other	3.2	4.9	(2.3-10.3)	<0.0001	4.3 <sup>c</sup>
<b>Infusion time<sup>a</sup> (minutes)</b>					
0-15	1.0	1.0	-	-	1.0
16-30	0.8 (NS)	1.2	(0.6-2.4)	0.6	0.9
31-45	1.0 (NS)	1.5	(0.8-2.8)	0.2	1.3
46-60	1.5 (NS)	1.8	(1.0-3.3)	0.07	1.5
61-90	0.7 (NS)	1.8	(0.9-3.7)	0.09	1.8
90+	0.9 (NS)	1.6	(0.7-3.4)	0.2	1.2
<b>Chemotherapy ever before</b>	1.6	0.8	(0.6-1.3)	0.4	1.0
<b>Dyed</b>					
No	1.0	1.0	-	-	1.0
Yes	1.0 (NS)	0.9	(0.6-1.3)	0.6	0.9
<b>Waved</b>					
No	1.0	1.0	-	-	1.0
Yes	1.0 (NS)	1.2	(0.6-2.3)	0.7	1.1

Table 3. continues on next page

<b>Coloured</b>					
No	1.0	1.0	-	-	1.0
Yes	0.9 (NS)	0.9	(0.7-1.1)	0.3	1.0
<b>Length</b>					
<5 cm	1.0	1.0	-	-	1.0
≥5 cm	0.7	0.9	(0.7-1.1)	0.3	0.9
<b>Quantity</b>					
Small	1.0	1.0	-	-	1.0
Medium	0.6	0.6	(0.4-1.2)	0.09	0.8
Large	0.6	0.7	(0.3-1.1)	0.2	0.9
<b>Type of hair<sup>a</sup></b>					
West-European	1.0	1.0	-	-	1.0
South-European	0.7 (NS)	0.6	(0.3-1.3)	0.2	0.7
African	0.5 (NS)	0.4	(0.1-1.6)	0.2	0.3
Asian	0.5	0.4	(0.2-0.8)	0.008	0.5
<b>Mean post infusion cooling time (minutes)</b>					
0-80	1.0	1.0	-	-	1.0
81-100	0.9 (NS)	0.6	(0.6-1.2)	0.3	0.9
101+	1.0 (NS)	0.7	(0.7-1.6)	0.9	0.8
Wetting hair before scalp cooling by					
<b>Dampen hair</b>					
No	1.0	1.0	-	-	1.0
Yes	1.0 (NS)	1.2	(0.8-1.7)	0.4	1.4
<b>Use hair conditioner</b>					
No	1.0	1.0	-	-	1.0
Yes	1.0 (NS)	1.1	(0.7-1.9)	0.6	1.0

OR= Odds Ratio, NS= non significant, CI=Confidence Interval

F=5-fluorouracil E=epirubicine C=cyclophosphamide A= doxorubicine D=docetaxel T=paclitaxel

Carbo=carboplatin I=irinotecan,

<sup>a</sup>missings included in analysis

<sup>b</sup>D= mono and combination chemotherapy

<sup>c</sup>Significantly associated



**Table 4.** Univariate and multivariate logistic regression analysis of females with breast cancer, receiving FE50C-FE100C chemotherapy (n=751); odds of wearing no head cover during the last scalp cooling session.

FEC50-100	n=	Uni	Multi variate		
		variate OR	OR	95% CI	p-value
<b>FEC dosage epirubicine (mgr/m<sup>2</sup>)</b>					
50-70	38	1.0	1.0	-	-
75-85	32	0.7 (NS)	0.7	(0.3-1.9)	0.5
90	558	0.8 (NS)	0.6	(0.3-1.3)	0.2
100	122	0.3	0.3	(0.1-0.6)	0.002
<b>Age group (years)</b>					
-44	163	-	1.0	-	-
45-54	305	1.4 (NS)	1.4	(0.9-2.1)	0.2
55-64	216	1.1 (NS)	1.1	(0.7-1.8)	0.7
65+	61	0.6 (NS)	0.4	(0.2-0.8)	0.01
<b>Infusion time<sup>a</sup> (minutes)</b>					
0-15	34	1.0	1.0	-	-
16-30	82	1.9 (NS)	2.3	(0.9-5.8)	0.08
31-45	309	2.9	2.9	(1.2-6.7)	0.01
46-60	188	3.0	3.1	(1.3-7.3)	0.01
61-90	39	4.4	5.4	(1.8-16.0)	0.002
<b>Chemotherapy ever before</b>	39	0.8 (NS)	0.6	(0.3-1.3)	0.2
<b>Chemically damaged hair</b>					
Dyed	71	0.7 (NS)	0.6	(0.4-1.1)	0.09
Waved	21	0.8 (NS)	1.2	(0.4-3.3)	0.7
Coloured	279	0.9 (NS)	0.9	(0.6-1.2)	0.5
<b>Length</b>					
<5 cm	191	1.0	1.0	-	-
≥5 cm	475	0.9 (NS)	1.0	(0.7-1.4)	0.9
<b>Quantity</b>					
Small	27	1.0	1.0	-	-
Medium	306	0.8 (NS)	0.7	(0.3-1.6)	0.3
Large	331	0.9 (NS)	0.8	(0.3-1.8)	0.5
<b>Type of hair</b>					
West-European	627	1.0	1.0	-	-
African/ Asian/ South-European	37	0.5	0.5	(0.2-1.0)	0.05

Table 4. continues on next page

**Mean post infusion cooling time**

(minutes)

0-80	59	-	1.0	-	-
81-100	502	1.2 (NS)	1.0	(0.6-1.8)	0.9
101+	167	1.4 (NS)	1.4	(0.8-2.7)	0.3

Wetting hair before scalp cooling by

**Dampen hair**

No	654	1.0	1.0	-	-
Yes	96	1.0 (NS)	1.0	(0.6-1.7)	0.9

**Use hair conditioner**

No	700	1.0	1.0	-	-
Yes	50	1.0 (NS)	1.0	(0.5-1.9)	1.0

OR= Odds Ratio, NS= non significant, CI=Confidence Interval

F=5-fluorouracil E=epirubicine C=cyclophosphamide

<sup>a</sup>missings included in analysis

## Discussion

To our knowledge this is the largest prospective multi-centre patient series on scalp cooling among patients receiving chemotherapy reported in the literature and the first one to study multi-variate characteristics associated with head cover use after scalp cooling. The Dutch Scalp Cooling Registry data showed that no head cover was used by 50% of patients who received chemotherapy regimens that normally cause severe CIA. This outcome is not very optimal; however when a patient has a chance of 1 out of 2 to keep their hair during chemotherapy, it will be an incentive for many patients to choose scalp cooling. Our results are in accordance with the literature, when comparing corresponding dosages.<sup>6</sup> However, in our registry dosages were generally higher than in several recent studies<sup>15-19</sup> and several new chemotherapy regimens were evaluated. Since all scalp-cooled patients in the hospitals could participate, significant patient groups with a specific chemotherapy regimen emerged, which properly reflected daily practice at day care units.

The outcome parameters -proportion head cover use and WHO score- are only an indication of scalp cooling efficacy. For example, patients receiving docetaxel were twice as likely to wear no head cover as patients on FEC (OR 2.0 vs 1.0). However, scalp cooling improved the chance of no head covering in FEC from about 5%<sup>12</sup> to 49% (factor 10) and in docetaxel from about 30%<sup>20</sup> to 75% (factor 2.5). The net scalp cooling efficacy remains unknown for most chemotherapy regimens, while severity of CIA without scalp cooling was not evaluated and varies tremendously in phase II and III trials.

Less head cover use after longer infusion times has not been reported previously. It seems that a lower peak plasma concentration causes more damage to hair root cells than a longer chemotherapeutic exposure time. Lengthened infusion times are regularly used to prevent

hypersensitivity reactions and to lower the risk of cardiotoxicity.<sup>21,22</sup> However, variation in infusion time may alter treatment outcomes and toxicity differently in each regimen.<sup>23,24</sup>

The finding that after scalp cooling patients older than 65 years were more likely to wear a head cover is new. Only Macduff et al. reported in a small study that patients aged 50 or over lost more hair than those younger than 50 years.<sup>25</sup> It is possibly due to higher chemotherapeutic concentrations in hair root cells during scalp cooling. Aged skin has a diminished cold-induced vasoconstriction<sup>26</sup> and an age-related decline in organ function may increase toxicity.<sup>27</sup> Chemotherapeutics mainly affect anagen hairs, i.e. hair in the growth phase, and cause a sharp constriction of the hair shaft, where hairs may break.<sup>28</sup> Therefore the reduced hair diameter at older age may also increase the risk of breakage.

Reduced scalp cooling results for Asian patients may be caused by a lower maximum tolerable chemotherapeutic dose and higher toxicity rates compared to their Western counterparts.<sup>29</sup> The satisfactory scalp cooling results reported in a recent Japanese study may be attributed to lower chemotherapy dosages (T60, C400, E40) than currently used in the Netherlands.<sup>17</sup> Biochemical characteristics of hair from people of different ethnical backgrounds have proved to be very similar, whereas geometry, mechanical properties and phase and rate of hair growth are particularly different.<sup>30-33</sup> These factors might contribute to hair breakage rates.

Unsatisfied scalp-cooled patients exhibited overall worse quality of life and body image compared to patients who did not undergo scalp cooling.<sup>1</sup> Therefore, scalp cooling should not be advised if poor results are expected, i.e. up to now with TAC.

The unspecified patient group with very diverse chemotherapy regimens had good scalp cooling results. The regimens and dosages for this group might have caused somewhat less often severe CIA, also without scalp cooling.

The good scalp cooling results for males may be caused by a difference in chemotherapy. Males most frequently received docetaxel 75mg/m<sup>2</sup> (52%), for which scalp cooling results are particularly good.<sup>20</sup> Moreover, the result in males is likely to be somewhat overestimated, since they are in general less inclined to wear a wig or head cover. The low number of male patients is not because they do not value their hair<sup>34</sup>, but probably because scalp cooling is rarely offered to them. In one of our studies all eligible patients were actively recruited and one third of the 168 scalp-cooled patients were males.<sup>20</sup>

Continuous multi-centric registration ensures rapid availability of the scalp cooling results patients may expect in new or uncommon chemotherapy regimens. Furthermore, registration may be used to detect easily differences in results between hospitals; actions may be undertaken in case of extra good outcomes or if outcomes are below average. As found in the past in the Netherlands, several hospitals quickly stopped scalp cooling after disappointing results in a minimal number of patients.



In conclusion, for daily practice this study implies that scalp cooling results are better with certain chemotherapy types (taxanes), decrease at higher doses and might be improved by longer infusion times. Medical doctors and nurses have to be aware that males are also eligible for scalp cooling and that patients of older age or non-West-European hair type may have somewhat less chance of satisfactory results. Scalp cooling results need to be improved, mainly by a more patient-tailored approach. Progress can be achieved by a better patient selection and when optimal scalp skin temperature and cooling times for each type of chemotherapy are known. Scalp cooling intensity should be adapted to the optimal scalp skin temperature for each patient. Post-infusion cooling times (PICT) are currently only used arbitrarily, with the exception of docetaxel.<sup>20</sup> Optimal PICTs may vary in particular chemotherapy regimens, while half life times of chemotherapeutics vary tremendously. We continued multi-centre registration, because it improved patient information while analysis of characteristics provided a better understanding of the determinants that improve scalp cooling results. This registry should be expanded internationally to obtain a consistent picture.

### **Acknowledgements**

Special thanks go to all patients who participated in the registration, to the nurses and MDs who performed the registration ([www.scalpcooling.nl](http://www.scalpcooling.nl)), to A. Willemse who assisted in data collection and Eindhoven Cancer Registry/ Comprehensive Cancer Centre South for hosting the scalp cooling research centre.

## References


1. Hurk van den CJ, Mols F, Vingerhoets AJ, Breed WP. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psych-Oncol*. 2010; 19: 701-9.
2. Mulders M, Vingerhoets A, Breed W. The impact of cancer and chemotherapy: Perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nurs*. 2008; 12: 97-102.
3. Janssen FE. Modelling physiological and biochemical aspects of scalp cooling. Eindhoven: Technical University Eindhoven; Thesis 2007.
4. Hurk van den CJG, Gerrits P, Graat J, Kolen B, Laar van de- Müskens J, Breed WPM. Positieve ervaringen met hoofdhuidkoeling in drie ziekenhuizen in Nederland. Tijd voor een standaard aanbod van hoofdhuidkoeling? *Oncologica*. 2005; 22: 162-67 [in Dutch].
5. Christodoulou C, Tsakalos G, Galani E, Skarlos DV. Scalp metastases and scalp cooling for chemotherapy-induced alopecia prevention. *Ann Oncol*. 2006; 17: 350.
6. Breed WPM, Hurk van den CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss; scalp cooling potentials and limitations. *Exp Rev Dermatol*. 2011; 6: 109-25.
7. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol*. 2005; 16: 352-58.
8. Konishi Y, Kuroki T. Prevention of adrimycin-induced alopecia by scalp hypothermia with a deep-frozen Duncool-cap. *Gan To Kagaku Ryoho*. 1988; 15: 3081-85.
9. Nakazawa M, Sakamoto T, Honda M, Sawa Y, Sato K, Oguro K, et al. Scalp hypothermia: a prevention of hair-loss in clinical oncology. *Dokkyo J Med Sci*. 1985; 12: 17-24.
10. Keizer-Heldens P. Hoofdhuidkoeling bij haarverlies door chemotherapie. *Oncologica*. 2009; 29-34 [in Dutch].
11. Kargar M, Sarvestani RS, Khojasteh HN, Heidari MT. Efficacy of penguin cap as scalp cooling system for prevention of alopecia in patients undergoing chemotherapy. *J Adv Nurs*. 2011 epub ahead.
12. Geerts P, Hendriks M, van den Hurk C, Dercksen M, Breed W. Hair preservation in FEC-chemotherapy; not an exception. Submitted. 2011.
13. World Health Organisation. Handbook for Reporting Results of Cancer Treatment. Geneva: WHO Offset Publ. 1979.
14. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med*. 2004; 66: 411-21.
15. Auvinen PK, Mahonen UA, Soininen KM, Paananen PK, Ranta-Koponen PH, Saavalainen IE, et al. The effectiveness of a scalp cooling cap in preventing chemotherapy-induced alopecia. *Tumori*. 2010; 96: 271-5.
16. Massey CS. A multicentre study to determine the efficacy and patient acceptability of the Paxman Scalp Cooler to prevent hair loss in patients receiving chemotherapy. *Eur J Oncol Nurs*. 2004; 8: 121-30.
17. Kato M, Sakuyama A, Imai R, Kobayashi T. Evaluation of dignicap system for the prevention of chemotherapy-induced hair loss in breast cancer patient. *The Breast*. 2011; 20, Suppl 1: S80, abstr 811.
18. Lenaerts E, Meyen M, Maes T, Maes H, El Mousati A, Lemmens J, et al. Scalp cooling in the prevention of anthracycline-induced alopecia. *Eur J Cancer*. 2001; 37: Suppl. 6, 360.
19. Peck HJ, Mitchell H, Stewart AL. Evaluating the efficacy of scalp cooling using the Penguin cold cap system to reduce alopecia in patients undergoing chemotherapy for breast cancer. *Eur J Oncol Nurs*. 2000; 4: 246-8.
20. Hurk van den CJG, Breed WPM, Nortier JWR. Short post-infusion scalp cooling times in the prevention of docetaxel-induced alopecia. submitted. 2011.
21. Kingsley CD. Hypersensitivity reactions. In: Perry MC, ed. *The chemotherapy source book*: Wolters Kluwer 2008.
22. Rasheed ZA, Rubin EH. Topoisomerase-Interacting Agents. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer Principles&Practice of Oncology*. 8 ed. Philadelphia: Wolters Kluwer 2008:437-44.

23. Williams C, Bryant A. Short versus long duration infusions of paclitaxel for any advanced adenocarcinoma. Cochrane database of systematic reviews (Online). 2011; 5: CD003911.
24. Mikkelsen TS, Sparreboom A, Cheng C, Zhou Y, Boyett JM, Raimondi SC, et al. Shortening infusion time for high-dose methotrexate alters antileukemic effects: a randomized prospective clinical trial. *J Clin Oncol*. 2011; 29: 1771-8.
25. Macduff C, Mackenzie T, Hutcheon A, Melville L, Archibald H. The effectiveness of scalp cooling in preventing alopecia for patients receiving epirubicin and docetaxel. *Eur J Cancer Care*. 2003; 12: 154-61.
26. Holowatz LA, Kenney WL. Peripheral mechanisms of thermoregulatory control of skin blood flow in aged humans. *J Appl Physiol*. 2010; 109: 1538-44.
27. Hurria A, Lichtman SM. Pharmacokinetics of chemotherapy in the older patient. *Cancer Contr*. 2007; 14: 32-43.
28. Hurk van den CJG, Breed WPM, Mols F. Chemotherapy-induced hair loss. In: Preedy VR, ed. *The Handbook of Hair in Health and Disease*: Wageningen Academic Publishers 2011.
29. O'Donnell PH, Dolan ME. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. *Clin Cancer Res*. 2009; 15: 4806-14.
30. Blume-Peytavi U, Tosti A, Whiting DA, Trueb RM. *Hair growth and disorders*. Berlin Springer 2008.
31. Franbourg A, Hallegot P, Baltenneck F, Toutain C, Leroy F. Current research on ethnic hair. *J Am Ac Dermatol*. 2003; 48: S115-9.
32. Takahashi T, Hayashi R, Okamoto M, Inoue S. Morphology and properties of Asian and Caucasian hair. *J Cosm Science*. 2006; 57: 327-38.
33. Loussouarn G, El Rawadi C, Genain G. Diversity of hair growth profiles. *Int J Dermatol*. 2005; 44 Suppl 1: 6-9.
34. Hilton S, Hunt K, Emslie C, Salinas M, Ziebland S. Have men been overlooked? A comparison of young men and women's experiences of chemotherapy-induced alopecia. *Psych-Oncol*. 2008; 17: 577-83.





# Chapter 6



**Post-infusion scalp cooling time in the prevention of  
docetaxel-induced alopecia**

C.J.G. van den Hurk, W.P.M. Breed, J.W.R. Nortier

Supp Care Cancer. 2012; 20, 3255-3260



## Abstract

### Purpose

The patient impact of chemotherapy-induced alopecia (CIA) is high. Scalp cooling is applied to reduce CIA. The potential optimum post-infusion cooling times (PICTs) are currently unknown.

### Methods

Scalp cooling was applied in 53 patients receiving docetaxel chemotherapy with 90 minutes PICT (observational part). Also 15 non scalp-cooled patients were included. If hair preservation was observed in >80% of the patients, randomisation between 45 and 90 minutes PICT was planned. Patients reported tolerance of scalp cooling and use of head covering.

### Results

Observational study: 81% of scalp-cooled patients did not require head covering, versus 27% of non scalp-cooled patients. Randomised study: 79% of 38 patients with 90 minutes PICT did not need head covering versus 95% of 38 patients with 45 minutes PICT ( $p=0.04$ ). Scalp cooling was very well tolerated (Visual Analogue Scale= 79).

### Conclusion

A 45 minutes PICT can be recommended in 3-weekly docetaxel regimens with a dose of 75 or 100 mg/m<sup>2</sup>, administered in 60 minutes. The shorter PICT is a major advantage in time investment for patients. Patients (women and men) who receive docetaxel, except combined with doxorubicin and cyclophosphamide (taxotere, adriamycin and cyclophosphamide (TAC)), should be informed about the protective effect and high tolerance of scalp cooling in avoiding CIA.

## Introduction

Chemotherapy-induced alopecia (CIA) is one of the most distressing side effects of chemotherapy. Scalp cooling is applied preceding, during and following chemotherapy to prevent CIA. It is a worthwhile supportive care for cancer patients, as demonstrated by the rapid increase of its use in Europe. The reported success rates of scalp cooling vary widely<sup>1,2</sup> depending on many factors like the type and dose of cytotoxics and the number of chemotherapy cycles. Theoretically, the influence of post-infusion cooling time (PICT), the time from finishing chemotherapy infusion to finishing scalp cooling, may also be important for the success rates, but has never been studied.

Success rates in studies with 3-weekly docetaxel as monotherapy or in combination with other agents, are very favourable: 83% - 100% of the patients does not require head covering<sup>3-9</sup> In these studies PICTs vary from 15 minutes to three hours and in three of the studies the infusion time was reported to be 60 minutes. The PICTs are based on clinical impressions and on calculations of half-life times of cytotoxic drugs and their metabolites in the plasma.<sup>10</sup> These calculations seem reasonable because CIA is often dose dependent and the concentration of cytotoxic drugs in the hair follicle cells is very likely related to the concentration in the plasma. However, the calculations are questionable, because there is a very large patient variability in plasma half-life times and bioavailability of cytotoxics.<sup>11</sup> Moreover, combination chemotherapy might change the pharmacokinetic profile of docetaxel.<sup>10,12</sup> In addition, the influence of scalp cooling on pharmacokinetics, pharmacodynamics and toxicity in hair follicle cells is unknown. Optimal PICTs probably also depend on the duration of the cytotoxic infusion rates, but this has never been studied.

Up to now, the only method to develop a PICT advice for a particular chemotherapy schedule is to study the hair preservation results in patients randomised for various PICTs. In this study we report the tolerance and efficacy of a standard PICT of 90 minutes in patients receiving docetaxel containing chemotherapy schedules in daily practice in the Netherlands. In the second part of the study patients were randomised between a PICT of 45 or 90 minutes.

## Materials and methods

The design was an observational study followed by a randomised study. In the observational part it was investigated whether hair preservation with a 90 minutes PICT resulted in less or more than 80% of the patients not requiring a wig or head cover. If hair preservation was present in more than 80% of the patients, randomisation between 90 and 45 minutes PICT was planned. If hair preservation turned out to be present in less than 80% of the patients, randomisation between 90 and 150 minutes PICT was planned. Patients included in the observational part did not participate in the randomised study. Randomisation was scheduled in a 1:1 ratio, stratified by hospital. Non scalp-cooled patients, who rejected scalp cooling, were included as controls during the observational part of the study.

Patients were systematically enrolled between August 2005 and December 2008 in 11 Dutch hospital locations. Inclusion criteria were included intravenously administered 3-weekly docetaxel schedules as a single agent or in combination with other cytotoxics, and age 18 years or more. Exclusion criteria were included treatment with docetaxel in sequential

schemes (subsequent to doxorubicin and cyclophosphamide (AC) or 5-fluorouracil, epirubicin and cyclophosphamide (FEC)), docetaxel combined with doxorubicin and cyclophosphamide (taxotere, adriamycin and cyclophosphamide (TAC)), alopecia before the start of the study, haematological malignancies, clinical signs of scalp metastases, cold sensitivity, cold agglutinin disease, cryoglobulinemia, cryofibrinogenemia and cold post traumatic dystrophy.

Medical doctors and oncology nurses informed patients about the study. Patients who decided to participate completed a written questionnaire at the day care unit during each chemotherapy session.

The efficacy of scalp cooling was patient reported and defined by satisfaction with hair preservation, reflected by the use of a wig or head cover during the final scalp cooling session. Patients were considered admissible for evaluation of hair preservation if they had received at least two cycles of chemotherapy or if they discontinued scalp cooling after one cycle due to severe CIA. Hair loss is usually most severe after the first two cycles, thereafter it stabilises gradually.

Scalp cooling was applied 30 minutes prior to the chemotherapy infusion until 45 or 90 minutes after the end of the infusion. In all 11 hospitals the Paxman scalp cooling system (PSC1 or PSC2) was used.

Patients' acceptability of scalp cooling was assessed by a Visual Analogue Scale (VAS) from 0 for not acceptable to 100 for very well acceptable. In addition, patients were asked on a 4-point Likert scale to what extent they experienced any headache.

The comprehensive cancer centre south (IKZ, Eindhoven) was responsible for randomisation and data collection. Approval for this study was obtained from the Medical Ethics Committees of the participating hospitals and all enrolled patients provided informed consent. This study was registered as an International Standard Randomised Controlled Trial, number ISRCTN00283877.

### Statistical analyses

The proportions of patients with and without head covering were compared between the groups with different PICTs and between scalp-cooled and non scalp-cooled patients. Differences were tested by the chi-square test or Mann-Whitney U test. Randomised patients were analysed according to assigned PICT. Power analysis was based on a 30% difference in requiring a wig or head cover between the standard treatment of 90 minutes and the experimental treatment of 45 or 150 minutes. This difference could be detected by 38 patients in each randomisation arm with 80% power and  $\alpha=0.05$ . Statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC).

## Results

The characteristics of the patients with and without scalp cooling in the observational part and in the randomized part of the study are depicted in Table 1. The majority of patients had breast cancer (49%), were treated with docetaxel monotherapy with a dose of 75 mg/m<sup>2</sup>

**Table 1.** Patient and scalp cooling characteristics of patients assessable for evaluation of CIA status, with and without scalp cooling (n=144).

	No scalp cooling (n=15) (%)	Scalp-cooled, 90 min PICT <sup>i</sup>		Scalp-cooled Randomisation		p-value
		(n=53) (%)	(n=38) (%)	90 min PICT (n=38) (%)	45 min PICT (n=38) (%)	
<b>Total number of patients included (n=188)</b>						
Unsuitable/ CIA status unknown (n=44)	20	65	50	53		
Suitable/ CIA status known (n=144)	5	12	12	15		
	15	53	38	38		
<b>Age (mean)</b>	61	56	61	61		0.9
<b>Gender</b>						
Male	6 (40)	12 (23)	17 (45)	19 (50)		0.6
Female	9 (60)	41 (67)	21 (55)	19 (50)		
<b>Cancer</b>						
Breast	9 (60)	29 (55)	18 (47)	14 (37)		0.3
Prostate	5 (33)	9 (17)	14 (37)	11 (29)		
Lung	1 (7)	10 (19)	5 (13)	12 (31)		
Ovary	0	4 (8)	1 (3)	1 (3)		
Gastro-intestinal/ Colorectal	0	1 (2)	0	0		
<b>Chemotherapy: Docetaxel</b>						
Monotherapy	10 (67)	38 (72)	29 (76)	26 (68)		0.5
Carboplatin	0	9 (17)	5 (13)	9 (24)		
Herceptin	3 (20)	4 (8)	4 (11)	3 (8)		

table 1. continues on next page

Doxorubicin (Myocet)	1 (7)	1 (2)	0	0	
Capecitabine (Xeloda)	1 (7)	1 (2)	0	0	
<b>Dosage Docetaxel</b>					0.8
75 mg/m <sup>2</sup>	11 (73)	29 (55)	23 (61)	22 (58)	
100 mg/m <sup>2</sup>	4 (27)	24 (45)	15 (39)	16 (42)	
Cumulative dosage (mean)	Unknown	447	428	470	0.5
<b>Chemotherapy setting</b>					0.08
Adjuvant	0	4 (8)	2 (5)	7 (18)	
Palliative	15 (100)	49 (92)	36 (95)	31 (82)	
<b>Median pre cooling time<sup>2</sup> (min)<sup>3</sup></b> (min-max) <sup>4</sup>	-	35 (10-140)	30 (0-125)	30 (15-100)	1.0
<b>Median PICT<sup>2</sup> (min)<sup>3</sup></b> (min-max) <sup>4</sup>	-	90 (5-155)	90 (15-150)	45 (25-165)	<0.0001
<b>Median number of cooling sessions,</b> in patients not wearing a wig or head cover (min-max) <sup>4</sup>	-	6 (2-18)	6 (2-10)	6 (2-15)	0.8
<b>Median number of cooling sessions,</b> in patients wearing a wig or head cover (min-max) <sup>4</sup>	-	3.5 (1-8)	2.5 (1-6)	3.5 (1-6)	1.0

<sup>1</sup>PICT= Post Infusion Cooling Time <sup>2</sup>Median of all cooling sessions; multiple sessions per patient possible <sup>3</sup>min= minutes <sup>4</sup>min=minimal, max=maximal



(59%) and most frequently in the palliative setting (91%). The infusion time of docetaxel was 60 minutes in all but one patient, who had 90 minutes infusion time and was randomised for 90 minutes PICT. In patients who wore no head cover, scalp cooling results were evaluated after a median of 6 chemotherapy cycles. The median PICTs were conform the protocol. However, some deviations of the planned cooling times occurred after randomisation: in the 45 minutes PICT group 3 patients had a median PICT longer than 55 minutes (range 58-68), versus 3 patients with a median below 80 minutes (range 45-53) in the 90 minutes PICT group. All these 6 patients were analysed in the assigned group and ultimately wore no wig or head cover. Patient characteristics did not significantly differ between both randomised groups (except median PICT).

In the observational part of the study, 90 minutes PICT resulted in 81% of the 53 patients not requiring a wig or head cover (Table 2), compared to 27% of the 15 non scalp-cooled patients ( $p < 0.0001$ ). In the randomised part of the study, 90 minutes PICT resulted in 79% of the 38 patients not requiring a wig versus 95% of the 38 patients with 45 minutes PICT ( $p = 0.04$ ).

In 11 patients in whom the pre-infusion cooling time was at least once  $\leq 20$  minutes (range 0-20 minutes) and in 14 patients with at least once a shorter post-infusion cooling time than planned (range 5-30 minutes), all but 1 patient wore no wig or head cover.

6

Results did not differ between docetaxel monotherapy and combinations of docetaxel with carboplatin, trastuzumab, doxorubicin or capecitabin ( $p = 0.4$ ). Only two of the 54 males reported to wear a wig or head cover, both had no scalp cooling. All but 2 males in the 45 minutes PICT group had a docetaxel dosage of 75 mg/m<sup>2</sup>. Overall 65% of the scalp-cooled female patients had a dosage of 100 mg/m<sup>2</sup>.

A VAS for tolerance was performed 632 times, resulting in a mean score of 79 (sd 20, range 0-100), regardless if the patient was assessable for evaluation of hair preservation. Information about headaches was reported 645 times: in 512 (80%) sessions patients reported no headache, in 86 (13%) minimal, in 29 (4%) moderate and in 18 (3%) sessions patients reported severe headaches. Furthermore, no side effects were reported with the exception of one patient who had cold sensations.

Follow up of scalp-cooled patients was completed in May 2010. At that time 65% of the patients ( $n = 129$ ) were deceased. With an overall median follow-up of 17 months after completion of chemotherapy no scalp metastases were reported.

Among patients of whom CIA status was known ( $n = 129$ ) 115 stopped scalp cooling as their chemotherapy treatment was completed, 10 patients stopped because of severe CIA, 1 patient due to intolerance and 3 patients died in the period they received chemotherapy.

Out of 39 scalp cooled patients in whom CIA status was unknown, 6 stopped scalp cooling due to intolerance during the first chemotherapy cycle. Other reasons for missing CIA status were: stopping chemotherapy before completing the second cycle ( $n = 10$ ), deceased before hair loss could be assessed ( $n = 3$ ), questionnaires lost at the day care unit ( $n = 7$ ), scalp

cooling was stopped due to detection of a scalp skin metastasis after the first chemotherapy treatment (n=1) or various other reasons (n=12).

**Table 2.** Use of wig or head cover in scalp cooled patients with different PICTs.

	PICT (minutes)	n=	% no wig or head cover
<b>Observational</b>	90	53	81
<b>Randomised</b>	90	38	79*
	45	38	95*

\*90 vs 45 minutes, p=0.04

## Discussion

This study showed a significant advantageous result of scalp cooling in patients randomised for a PICT of 45 minutes compared to a PICT of 90 minutes. These patients were treated with 3-weekly docetaxel containing chemotherapy, administered in 60 minutes, with or without other cytotoxic drugs. The very good hair preservation, 79% - 95% of scalp-cooled patients receiving docetaxel (75 to 100 mg/m<sup>2</sup>) wore no head cover, is in accordance with the results reported in other studies with docetaxel as single agent or in certain combinations (83% - 100%).<sup>3-9</sup> As long as no clinically feasible method is available to measure hair preservation objectively, the best approach of measuring the satisfaction with scalp cooling is in our opinion whether patients use a wig or head cover.

Reducing the PICT to 45 minutes was not an expected course, because a review showed a general trend in favour of a longer PICT: 'the longer, the better'.<sup>1</sup> However, in Breed's review PICTs were compared for many chemotherapy types and dosages. Better results of a short versus a long PICT, may be explained by a decreased exposure time of hair follicles to toxic drugs. Longer PICTs may delay the efflux of cytotoxic agents from the hair follicle cells to the blood stream, at the time blood concentrations of cytotoxics decrease. Moreover, repair mechanisms of hair root cells may be inhibited for a longer time by the low temperature if there is an unnecessary long PICT. This hypothesis is to some extent supported by the preservation of hair in each of the 14 patients in this study who had at least once a very short PICT ( $\leq 30$  minutes) due to protocol deviation.

The tolerance of scalp cooling was very high (VAS=79) and no headaches were reported in the majority of the scalp cooling sessions. Only 5% of the patients stopped scalp cooling due to intolerance, which is comparable with the literature.<sup>1</sup>

In this study 37% of scalp-cooled patients were males, indicating that they also value their hair important, as confirmed by the literature.<sup>13-15</sup> Scalp cooling should regularly be offered to them too. None of the scalp-cooled males used a wig or head cover, partly because scalp cooling results are better in lower docetaxel dosages (75 mg/m<sup>2</sup>).<sup>16</sup> Besides, some of them might not have felt the need of head covering when CIA ultimately occurred. Therefore

the efficacy of scalp cooling in this study may be somewhat overestimated. The significant advantage of 45 minutes PICT remains because of equal division of gender and dosages in both randomised groups.

Scalp cooling was effective, but the exact quantitative advantage of scalp cooling regarding hair preservation in docetaxel treated patients is still unknown, while too few non scalp-cooled patients were included and no reliable data from other non scalp cooling studies are available. In phase II and III clinical trials of 3-weekly docetaxel monotherapy regimens of 100 mg/m<sup>2</sup>, the incidence of CIA differed from 42% (grade 1-4) of the patients in one study to 100% (only grade 2+3) of the patients in another study.<sup>17-24</sup> For docetaxel 75 mg/m<sup>2</sup> monotherapy or combined with cisplatin or carboplatin or capecitabine, CIA was reported in 40% - 89% of the patients.<sup>20,25-27</sup> Efficacy of scalp cooling has been proven in six out of seven randomised studies that compared scalp-cooled with non scalp-cooled patients.<sup>2</sup>

To routinely use a 45 minutes PICT at present may only carefully be justified in patients who are treated with docetaxel monotherapy or the combinations used in our study. Confirmation of our findings in a larger cohort of patients is certainly warranted. Further implementation of scalp cooling devices and improving the results can only be successful if national, preferably international, standardization is achieved.

## 6

### Conclusion

This study showed very good results and tolerance of scalp cooling in 3-weekly docetaxel containing chemotherapy regimens. A 45 minutes PICT is advantageous for the patients, as a longer than necessary stay in the hospital while receiving chemotherapy is often a reason for rejecting scalp cooling. Time investment is frequently considered a reason for not introducing scalp cooling in a hospital or to offer it only to a restricted patient group. Patients (women and men) who are treated with docetaxel containing regimens, except combined with doxorubicin and cyclophosphamide (TAC), should be informed on the protective effect and high tolerance of scalp cooling in avoiding CIA.

### Acknowledgements

Special thanks go to all patients who participated in the study, to A. Willemse who assisted in data collection, M. Peerbooms who assisted in data entry and to W. Peters, MD., Catharina Hospital Eindhoven, who was willing to function as an independent advisor and to answer patients' questions. Furthermore, we would like to thank the nurses and doctors who performed the study in the following hospitals: Medisch Centrum Alkmaar, Alkmaar; Tergooiziekenhuizen, Blaricum; Máxima Medisch Centrum, Eindhoven; Elkerliek, Helmond; Jeroen Bosch, 's-Hertogenbosch; Leids Universitair Medisch Centrum, Leiden; St. Antonius, Nieuwegein; St. Elisabeth, Tilburg; Twee Steden, Tilburg; Diaconessen, Utrecht.


This work was supported by Sanofi Aventis.

## References

1. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol.* 2005; 16: 352-58.
2. Breed WPM, Hurk van den CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss; scalp cooling potentials and limitations. *Exp Rev Dermatol.* 2011; 6: 109-25.
3. Christodoulou C, Klouvas G, Efstathiou E, Zervakis D, Papazachariou E, Plyta M, et al. Effectiveness of the MSC cold cap system in the prevention of chemotherapy-induced alopecia. *Oncology.* 2002; 62: 97-102.
4. Katsimbri P, Bamias A, Pavlidis N. Prevention of chemotherapy-induced alopecia using an effective scalp cooling system. *Eur J Cancer.* 2000; 36: 766-71.
5. Lemenager M, Lecomte S, Bonnetterre ME, Bessa E, Dauba J, Bonnetterre J. Effectiveness of cold cap in the prevention of docetaxel-induced alopecia. *Eur J Cancer.* 1997; 33: 297-300.
6. Lundgren-Eriksson L, Edbom G, Olofsson Y, Ridderheim M, Hendriksson R. Total prevention of taxoid-induced alopecia by a new model of cold cap (dignitana). *Eur J Cancer.* 1999; 35 (suppl. 4): 376.
7. Auvinen PK, Mahonen UA, Soininen KM, Paananen PK, Ranta-Koponen PH, Saavalainen IE, et al. The effectiveness of a scalp cooling cap in preventing chemotherapy-induced alopecia. *Tumori.* 2010; 96: 271-5.
8. Ridderheim M, Bjurberg M, Gustavsson A. Scalp hypothermia to prevent chemotherapy-induced alopecia is effective and safe: a pilot study of a new digitized scalp-cooling system used in 74 patients. *Support Care Cancer.* 2003; 11: 371-7.
9. ElGenidi M. Prevention of Chemotherapy-induced alopecia by the new digital scalp cooler device. *Eur J Cancer.* 2001; 37: Suppl 6, 357.
10. Massey CS. A multicentre study to determine the efficacy and patient acceptability of the Paxman Scalp Cooler to prevent hair loss in patients receiving chemotherapy. *Eur J Oncol Nurs.* 2004; 8: 121-30.
11. Cortes JE, Pazdur R. Docetaxel. *J Clin Oncol.* 1995; 13: 2643-55.
12. Middleton J, Franks D, Buchanan RB, Hall V, Smallwood J, Williams CJ. Failure of scalp hypothermia to prevent hair loss when cyclophosphamide is added to doxorubicin and vincristine. *Cancer Treat Rep.* 1985; 69: 373-5.
13. Hilton S, Hunt K, Emslie C, Salinas M, Ziebland S. Have men been overlooked? A comparison of young men and women's experiences of chemotherapy-induced alopecia. *Psych-Oncol.* 2008; 17: 577-83.
14. Baxley KO, Erdman LK, Henry EB, Roof BJ. Alopecia: effect on cancer patients' body image. *Cancer Nurse.* 1984; 7: 499-503.
15. de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, v Beurden V, Stoter G, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. *Br J Cancer.* 1997; 76: 1055-61.
16. Hurk van den CJ, Peerbooms M, van de Poll-Franse LV, Nortier JW, Coebergh JW, Breed WP. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - results of the Dutch Scalp Cooling Registry. *Acta Oncol.* 2012; 51: 497-504.
17. Taberero J, Climent MA, Lluch A, Albanell J, Vermorken JB, Barnadas A, et al. A multicentre, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer. *Ann Oncol.* 2004; 15: 1358-65.
18. Ravdin PM, Burris HA, 3rd, Cook G, Eisenberg P, Kane M, Bierman WA, et al. Phase II trial of docetaxel in advanced anthracycline-resistant or anthracenedione-resistant breast cancer. *J Clin Oncol.* 1995; 13: 2879-85.
19. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol.* 2005; 23: 4265-74.
20. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol.* 2002; 20: 2812-23.

21. Sjostrom J, Blomqvist C, Mouridsen H, Pluzanska A, Ottosson-Lonn S, Bengtsson NO, et al. Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure: a randomised phase III study with crossover on progression by the Scandinavian Breast Group. *Eur J Cancer*. 1999; 35: 1194-201.
22. Chan S, Friedrichs K, Noel D, Pinter T, Van Belle S, Vorobiof D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol*. 1999; 17: 2341-54.
23. Chevallier B, Fumoleau P, Kerbrat P, Dieras V, Roche H, Krakowski I, et al. Docetaxel is a major cytotoxic drug for the treatment of advanced breast cancer: a phase II trial of the Clinical Screening Cooperative Group of the European Organization for Research and Treatment of Cancer. *J Clin Oncol*. 1995; 13: 314-22.
24. Bonnetterre J, Roche H, Monnier A, Guastalla JP, Namer M, Fargeot P, et al. Docetaxel vs 5-fluorouracil plus vinorelbine in metastatic breast cancer after anthracycline therapy failure. *Br J Cancer*. 2002; 87: 1210-5.
25. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *NEJM*. 2004; 351: 1502-12.
26. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol*. 2003; 21: 3016-24.
27. Chang HR, Glaspy J, Allison MA, Kass FC, Elashoff R, Chung DU, et al. Differential response of triple-negative breast cancer to a docetaxel and carboplatin-based neoadjuvant treatment. *Cancer*. 2010; 116: 4227-37.

# Chapter 7



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

C.J.G. van den Hurk, M.E. van den Akker-van Marle, W.P.M. Breed,  
L.V. van de Poll-Franse, J.W.R. Nortier, J.W.W. Coebergh

J Oncol Nurse. 2013; in press



## Abstract

### Introduction

Cytotoxic therapy for patients with cancer frequently induces reversible, but long-lasting alopecia which might be prevented by scalp cooling. This study evaluates the effectiveness of scalp cooling with respect to the severity of chemotherapy-induced alopecia (CIA) and the purchase and use of wigs and head covers.

### Materials and Methods

In this observational study, scalp-cooled patients (n=160) were compared with non scalp-cooled patients (n=86) with several types of cancer. Patients were enrolled in 15, mostly general hospitals prior to taxane and/or anthracycline-based chemotherapy. Patients completed four questionnaires between the start and one year after the last chemotherapy.

### Results

Severity of CIA, and purchasing and actually wearing wigs and head covers were significantly lower among scalp-cooled than non scalp-cooled patients. Overall, scalp cooling reduced the use of wigs and head covers by 40%. Among 84 scalp-cooled patients who purchased a wig (53%), only 52 patients actually wore it (62%), and they just wore it intensively (86% daily) for less than six months (80%). Especially young patients camouflaged CIA with a head cover instead of a wig.

### Discussion

The relatively long duration of CIA, the wish of many patients to camouflage or rather prevent it and the 40% reduction for head covering by scalp cooling, makes it a worthwhile supportive intervention. However, (cost-) effectiveness can be improved. Many scalp-cooled patients purchased a wig unnecessarily.



## Introduction

Alopecia is a common side-effect of systemic cancer treatment. Even before patients commence chemotherapy, they foresee a high psychological impact at the moment hair loss actually occurs<sup>1</sup>, and it appears in fact to be distressing for many patients.<sup>2-7</sup> In a breast cancer focus group, organised by the authors, patients reported that their personal identity disappeared simultaneously with the sudden hair loss: *“You don’t recognise the person in the mirror anymore, although you have known that person your whole life”*. At that moment patients feel labelled as a cancer patient and state that *“If you look ill, you feel more ill”*. CIA is an outward sign of cancer – it makes cancer visible. It reminds patients and their relatives continuously about cancer and its treatment: *“On good days between chemotherapies, you don’t think about the disease... until you look in the mirror”*.

Severe chemotherapy-induced alopecia (CIA) occurs mostly within three weeks of the first chemotherapy cycle.<sup>8,9</sup> While cytostatics mainly influence anagen hair follicles<sup>10</sup>, i.e. in the growth phase, the growth of hairs is diminished until some weeks to months after the last chemotherapy cycle.<sup>8,9</sup> Alopecia-inducing chemotherapy schedules continue for at least nine weeks, but more often up to 21 weeks<sup>11</sup>, so patients often have to deal with a bald head or short hair for up to about nine months. It may take some additional time before patients have their usual appearance again, because when hair grows back, the structure is often temporarily different from the hair they used to have.<sup>8</sup>

Many patients camouflage CIA by wearing a wig or head cover. Wearing a wig is a compensation for the changed appearance and makes the patient look normal again. However, some patients prefer not to hide hair loss and share their baldness.<sup>3</sup>

CIA is however not inevitable. Scalp cooling is a supportive care treatment that overall prevents severe CIA in about half of the patients, who otherwise would have lost their hair.<sup>12</sup> Its effectiveness has been shown in 6 out of 7 randomised studies with several types of chemotherapy, published between 1977 and 2003.<sup>13</sup> An overview of the results after 40 years of scalp cooling has been provided in recent reviews.<sup>13,14</sup> These reviews however show a broad diversity in CIA evaluation methods.

This study evaluates the effectiveness of scalp cooling by comparing severity of CIA and the purchase and use of wigs and head covers between scalp-cooled and non scalp-cooled patients. Furthermore, the duration of CIA is taken into consideration.

## Methods

### Patients and setting

In this observational prospective study scalp-cooled patients were compared with non scalp-cooled patients. Patients were treated in 13 hospitals which used scalp cooling and two which did not. Patients in the participant scalp cooling hospitals who did not want scalp cooling, could participate in the non scalp-cooled group. Patients were eligible if they received a chemotherapy schedule with the potential of inducing severe CIA and for which scalp cooling was commonly applied. They had to be at least 18 years old and had to understand the Dutch language. Exclusion criteria for scalp cooling were baldness before the

start of chemotherapy, haematological malignancies with generalised metastases, clinical signs of scalp skin metastases, cold sensitivity, cold agglutinin disease, cryoglobulinaemia, cryofibrinogenaemia and cold post-traumatic dystrophy.

Scalp cooling was performed using the Paxman system (type PSC1 or PSC2) with a standardised cooling time from 30 min before starting the chemotherapy infusion to 90 min after stopping the infusion.

Approval for this study was obtained from the Medical Ethics Committees and all participating patients signed forms of informed consent.

## Measures

Patients received four sets of questionnaires with return envelopes and completed them at home before the start of chemotherapy (M1) and three weeks (M2), six (M3) and twelve months (M4) after completing chemotherapy. If the questionnaires were not returned in time, patients received a reminder. Patients were eligible for analysis if they completed at least the first and second questionnaire. Clinical patient characteristics were collected from patient files.

Patients evaluated in M2 the severity of CIA as defined by the World Health Organisation (WHO) scale for alopecia: grade 0 for none, grade 1 for mild, grade 2 for pronounced and grade 3 for total alopecia.<sup>15</sup> Furthermore, patients filled in a Visual Analogue Scale (VAS) ranging from 0 (for no alopecia) to 100 (for total baldness).

Patients reported whether they had purchased (M1, M2, M3) and used (M2, M3, M4) a wig or head cover and during what time period (M3 and M4). They also stated whether they had used it inside or outside of the home. In addition, they reported when their hair started to grow again (M3) and whether they were satisfied with their hairstyle 3 weeks and 6 months after the last chemotherapy cycle (M2, M3).

## Statistics

The Chi-square test was used to compare the proportion of scalp-cooled and non scalp-cooled patients with respect to demographics and clinical characteristics, purchase and use of wigs or head covers, WHO scores, and growth of hair. VAS for CIA was compared between scalp-cooled and non scalp-cooled groups with the standard t test for unequal variances. Associations between the outcome measures were tested by the Spearman's rank correlation test, using the SAS computer package (version 9.1, SAS Institute Inc., Cary, North Carolina, USA, 1999).

## Results

### Patients and setting

In this observational study 160 scalp-cooled and 86 non scalp-cooled patients were available for analysis (Figure 1). Only six men were included, all underwent scalp cooling (Table 1). The majority of patients had a Dutch ethnicity (96%), had breast cancer (93%), were treated in the adjuvant setting (87%) and had oncological surgery (93%). Scalp-cooled patients received

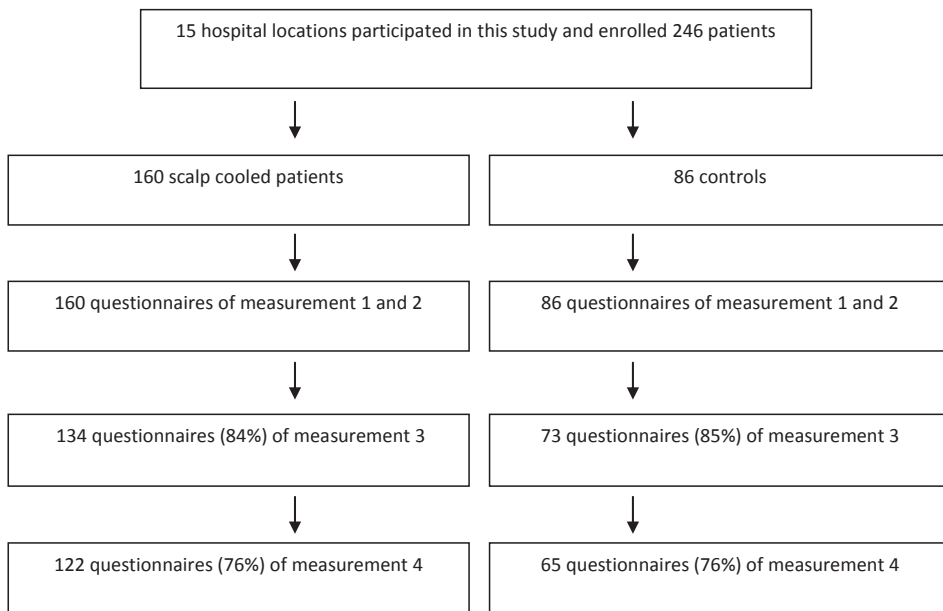


FEC chemotherapy (5-Fluorouracil, Epirubicin, Cyclophosphamide) more often than those who did not undergo scalp cooling. Scalp-cooled patients received a mean of six (range 1-27) chemotherapy cycles and five (range 1-27) scalp cooling cycles. Non scalp-cooled patients received a mean of six (range 3-16) chemotherapy cycles, and 56% of them were treated in the two hospitals that did not offer scalp cooling.

All four measurements were complete in 76% of the patients (Figure 1). Reasons for incompleteness (n=59) were: 75% unknown, 17% died, 3% missing patient identification (impossible to send a reminder) and 5% actively discontinued participation. Compliance with scalp cooling was high, only four patients (3%) stopped it because of intolerance, others stopped only because of CIA. No scalp skin metastases were reported from the inclusion of patients in 2007 and 2008 until January 2012.

### Severity of CIA

Hair loss was significantly less pronounced in scalp-cooled than in non scalp-cooled patients ( $p < 0.0001$ ) (Table 2). Mean VAS scores and proportion head cover use increased when categories of WHO scores increased. Correlation coefficients were 0.86 for VAS versus WHO, 0.63 for WHO versus head cover use and 0.65 for VAS versus head cover use. Scalp-cooled patients with pronounced CIA on the WHO scale reported that they had lost half of their hair (VAS 52) and overall 45% of them did use a head cover.



**Figure 1.** Flow-chart of the data collection process.

**Table 1.** Socio-demographic and clinical characteristics of patients treated with or without scalp cooling (n=246).

	Scalp-cooled n=160 (%)	Non scalp-cooled n=86 (%)	p-value scalp-cooled vs non scalp-cooled
<b>Age (years)</b>			0.6
≤49	70 (44)	43 (50)	
50-59	63 (39)	29 (34)	
≥ 60	27 (17)	14 (16)	
<b>Gender</b>			0.07
Male	6 (4)	0	
Female	152 (96)	86 (100)	
Missing	2		
<b>Ethnicity</b>			0.4
West-European	154 (97)	82 (95)	
Else	4 (3)	4 (5)	
Missing	2		
<b>Site of Cancer</b>			0.001
Breast	152 (95)	77 (90)	
Ovary	0	8 (9)	
Gastro-intestinal	3 (2)	0	
Lung	3 (2)	1 (1)	
Prostate	2 (1)	0	
<b>Chemotherapy<sup>a</sup></b>			0.0006
FEC	101 (66)	39 (45)	
Paclitaxel combination	4 (3)	7 (8)	
Docetaxel mono/ combination	8 (5)	1 (1)	
ACTH	11 (7)	11 (13)	
FAC	12 (8)	4 (5)	
FECD	6 (4)	7 (8)	
DAC	5 (3)	14 (16)	
Other	6 (4)	3 (4)	
Missing	7		
<b>Chemotherapy setting</b>			0.3
Adjuvant	131 (86)	78 (91)	
Palliative	22 (14)	8 (9)	
Missing	7		
<b>Surgery</b>			0.9
Yes	147 (96)	83 (96)	
<b>Comorbidity</b>			0.3
Yes	31 (19)	22 (26)	
No	129 (81)	64 (74)	

<sup>a</sup> F=5-fluorouracil E=epirubicin C=cyclophosphamide A=adriamycin T=paclitaxel H=herceptin D=docetaxel

## Purchase and use of wigs and head covers

Purchase and use of wigs and head covers differed significantly between scalp-cooled and non scalp-cooled patients (Table 3). Overall, scalp cooling reduced the use of a wig or head cover by 40% ( $p<0.0001$ ). Among 84 scalp-cooled patients who purchased a wig, only 52 (62%) patients used it, whereas of 66 non scalp-cooled patients who purchased a wig 59 (89%) used it.

Additional analysis for patients aged  $\leq 49$  years ( $n=113$ ) and  $>60$  years ( $n=133$ ) showed that 29% of the young age group bought only a head cover and no wig, versus 13% of those over 50 years ( $p=0.0016$ ). There was no difference in the use of wigs or head covers between age groups, once they purchased one.

Wigs were used inside and outside of the home by 75% of the patients who reported wearing one; 86% of them wore it daily or almost daily. Head covers were used only inside the house by 26% of the patients who reported wearing one, others used it also outside of the home. About 80% of the 159 patients wore their wig or head cover less than six months after the last chemotherapy cycle, of whom 15 (12%) had hardly used it anymore in that time period.

## Growth of hair

In 24% of the scalp-cooled and 7% of the non scalp-cooled patients hair kept growing during chemotherapy (Table 3). The remaining patients most often reported that their hair started to grow again between three and six weeks after the last chemotherapy. Most patients were satisfied with their hairstyle three weeks and six months after chemotherapy.

**Table 2.** WHO, VAS score of alopecia and head covers used in scalp-cooled and non scalp-cooled patients ( $n=246$ ).

CIA	Scalp-cooled ( $n=160$ )			Non scalp-cooled ( $n=86$ )		
	WHO <sup>a</sup> n (%)	VAS Mean (sd)	Head cover use n (%) <sup>b</sup>	WHO n (%)	VAS Mean (sd)	Head cover use n (%) <sup>b</sup>
No	7 (4)	4 (9)	0	0	-	0
Mild	25 (16)	25 (26)	3 (12)	2 (2)	8 (6)	1 (50)
Pronounced	80 (50)	52 (20)	36 (45)	6 (7)	74 (21)	4 (67)
Total	48 (30)	95 (8)	42 (88)	78 (91)	97 (5)	73 (94)
Overall		58 (33) <sup>a</sup>	81 (51)		94 (16) <sup>a</sup>	78 (91)

WHO: World Health Organisation scale for alopecia

VAS: Visual Analogue Scale, ranging from 0 (no alopecia) to 100 (total baldness)

Spearman's rho: 0.86 (WHO vs VAS), 0.63 (WHO vs head cover use), 0.65 (VAS vs head cover use)

<sup>a</sup> Both, WHO and VAS: group comparison scalp cooling versus no scalp cooling:  $p<0.0001$

<sup>b</sup> Including wigs

**Table 3.** Purchase and use of wig and head cover (from before starting chemotherapy to 6 months after chemotherapy) and growth of hair during and after chemotherapy (n=246).

	Scalp-cooled	Non scalp-cooled	p-value
	(n=160)	(n=86)	
	n (%)	n (%)	
<b>Purchase/use</b>			
Purchased wig	84 (53)	66 (77)	0.0002
Used wig	52 (33)	59 (69)	<0.0001
Purchased head cover <sup>a</sup>	117 (73)	83 (97)	<0.0001
Used head cover <sup>a</sup>	81 (51)	78 (91)	<0.0001
<b>Growth</b>			
			0.03
During chemotherapy	31 (24)	5 (7)	
Within 3 weeks after chemotherapy	19 (19)	10 (16)	
3-6 weeks after chemotherapy	45 (46)	27 (43)	
6-8 weeks after chemotherapy	18 (18)	18 (28)	
8 weeks after chemotherapy	17 (17)	8 (13)	
Missing	30	18	
<b>Satisfied with current hair style?<sup>b</sup></b>			
3 weeks after chemotherapy	111 (85)	57 (78)	0.23
6 months after chemotherapy	111 (94)	50 (86)	0.08

<sup>a</sup> wig included<sup>b</sup> n<246 because measured in M3 and M4

## Discussion

Scalp cooling significantly reduced the severity of CIA and the purchase and use of wigs and head covers after anthracycline- or taxane-based chemotherapy. However, a head cover was still used by 51% of the scalp-cooled patients, so improvement in effectiveness is desirable. Meanwhile, cost-effectiveness can be improved because 38% of the scalp-cooled patients were thought to have purchased a wig needlessly (unpublished results). In another study this unnecessary purchase totalled 80% of the patients.<sup>16</sup> Nowadays, many Dutch scalp-cooled patients consult their hairdressers and agree that the wig will not be purchased when scalp cooling is effective. Ideally, a wig is chosen and reserved before starting chemotherapy, but only styled and delivered once hair loss occurs. Such an arrangement should not be restricted to scalp-cooled patients, as the incidence of CIA without scalp cooling is sometimes overestimated and also 7 (11%) non scalp-cooled patients did not use their wig.

Patients, who used their wig or head cover, used it intensively for several months. It has been shown previously that breast cancer patients (n=175) were generally satisfied with their wig, but about two-thirds of them felt it was expensive<sup>17</sup>, which is again a reason for postponing the purchase. Especially younger patients regularly (29%) preferred a head cover above a

wig. Therefore, in our opinion, head covering in general should be reimbursed by health insurance companies instead of only wigs.

The high frequency of wigs and head covers purchased to camouflage potential hair loss illustrates the importance of CIA for patients undergoing systemic therapy. The psychological impact of CIA, for males and females, has been described in several studies.<sup>1,5,7,8,18,19</sup> While a high proportion of patients were satisfied with their hairstyle shortly following the last chemotherapy, hair quality for successfully scalp-cooled patients seems to be good. The satisfaction among non scalp-cooled or unsuccessfully scalp-cooled patients might be explained by adaptation to the situation<sup>3</sup> or hair growth may visualise the healing process.<sup>20</sup> Nevertheless, the majority of patients with CIA reported wearing head coverings until several months after the last chemotherapy. In other studies it was reported that six months following chemotherapy, whether or not combined with scalp cooling, the majority of patients were satisfied with the rate of growth and length, thickness and texture of the hair, but less with the colour.<sup>17,21</sup> Patients valued scalp cooling to be worthwhile, as shown by the small proportion of patients who stopped scalp cooling for reasons other than CIA.

Up to now, there is no optimal outcome measure for severity of CIA. This study showed correlation but also inconsistencies between three subjective measures (WHO, VAS, head cover use, table 2). Other scales like the Common Toxicity Criteria<sup>22</sup> or Dean's scale<sup>23</sup> are comparable to WHO scores and therefore not inferior in distinguishing CIA. The Dutch Scalp Cooling Group now uses the Hair Check device in studies<sup>24,25</sup>, which is an objective measure, but time consuming and therefore not clinically feasible for daily use at oncology wards. Moreover, Hair Check outcomes also show inconsistency with the patients' opinion of whether head covering is desirable. While some patients loose almost all of their hair but do not wear head covering and vice versa, in our opinion head cover use still best reflects the patients' satisfaction with scalp cooling.

This study has some limitations. The most important one is the difference in the proportion of patients with FEC and DAC chemotherapy between the scalp-cooled and non scalp-cooled groups. For the other types of chemotherapies the number of patients was small, but hardly differed. While the expert opinion is that all regimens almost always cause total baldness without scalp cooling, it is unlikely to fully explain the differences in amount of hair loss and head cover use between both groups. Nevertheless, while it is a non randomised design, outcomes have to be interpreted with care. Another limitation is the lack of information about chemotherapy dosages, which is associated with the scalp cooling result. However, it is improbable that it differs between both groups; firstly, proportions of adjuvant and palliative treated patients were equal and besides, our registration of results shows adherence to the Dutch treatment guidelines.<sup>12</sup>

In conclusion, the reasonably long duration of CIA, the wish of many patients to camouflage or rather prevent it and the reduced need for head covering in 40% of the patients, makes scalp cooling a worthwhile supportive intervention. However, scalp cooling (cost-) effectiveness can be improved. Improvement can be obtained by studying scalp-cooling times<sup>26</sup> and temperatures, by adapting indications (e.g. type of chemotherapy and patient motivation),

but also by adapting patient information about CIA and scalp cooling. For example, patients should be advised not to buy a wig as a precaution, but to wait until it becomes necessary. The use of scalp cooling will probably increase, because of increasing cancer incidence, more frequent use of chemotherapy in solid tumours and improved acquaintance with scalp cooling in hospitals but also among patients.

In order to compare scalp cooling outcomes in the future, a questionnaire should be developed and validated to evaluate the extent of CIA and its impact on patient's lives.



## References

1. Hurk van den CJ, Mols F, Vingerhoets AJ, Breed WP. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psych Oncol.* 2010; 19: 701-9.
2. McGarvey EL, Baum LD, Pinkerton RC, Rogers LM. Psychological sequelae and alopecia among women with cancer. *Cancer Pract.* 2001; 9: 283-93.
3. Williams J, Wood C, Cunningham-Warburton P. A narrative study of chemotherapy-induced alopecia. *Oncol Nurs forum.* 1999; 26: 1463-8.
4. Frith H, Harcourt D, Fussell A. Anticipating an altered appearance: women undergoing chemotherapy treatment for breast cancer. *Eur J Oncol Nurs.* 2007; 11: 385-91.
5. Hilton S, Hunt K, Emslie C, Salinas M, Ziebland S. Have men been overlooked? A comparison of young men and women's experiences of chemotherapy-induced alopecia. *Psych Oncol.* 2008; 17: 577-83.
6. Rosman S. Cancer and stigma: experience of patients with chemotherapy-induced alopecia. *Pat Edu Couns.* 2004; 52: 333-9.
7. Tighe M, Molassiotis A, Morris J, Richardson J. Coping, meaning and symptom experience: A narrative approach to the overwhelming impacts of breast cancer in the first year following diagnosis. *Eur J Oncol Nurs.* 2011; 15: 226-32.
8. Batchelor D. Hair and cancer chemotherapy: consequences and nursing care-a literature study. *Eur J Cancer Care.* 2001; 10: 147-63.
9. Trueb RM. Chemotherapy-induced alopecia. *Semin Cutan Med Surg.* 2009; 28: 11-4.
10. Cotsarelis G, Millar SE. Towards a molecular understanding of hair loss and its treatment. *Trends Mol Med.* 2001; 7: 293-301.
11. Guideline mamma carcinoma 2012 [Richtlijn mammacarcinoom 2012 ]. Integraal Kankercentrum Nederland 2012 [Available from: <http://www.oncoline.nl/mammacarcinoom>, in Dutch]
12. Hurk van den CJ, Peerbooms M, van de Poll-Franse LV, Nortier JW, Coebergh JW, Breed WP. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - results of the Dutch Scalp Cooling Registry. *Acta Oncol.* 2012; 51: 497-504.
13. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol.* 2005; 16: 352-58.
14. Breed WPM, Hurk van den CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss; scalp cooling potentials and limitations. *Exp Rev Dermatol.* 2011; 6: 109-25.
15. World Health Organisation. Handbook for Reporting Results of Cancer Treatment. Geneva: WHO Offset Publ. 1979.
16. Auvinen PK, Mahonen UA, Soininen KM, Paananen PK, Ranta-Koponen PH, Saavalainen IE, et al. The effectiveness of a scalp cooling cap in preventing chemotherapy-induced alopecia. *Tumori.* 2010; 96: 271-5.
17. Mols F, van den Hurk CJ, Vingerhoets AJ, Breed WP. Scalp cooling to prevent chemotherapy-induced hair loss: practical and clinical considerations. *Supp Care Cancer.* 2009; 17: 181-9.
18. Mulders M, Vingerhoets A, Breed W. The impact of cancer and chemotherapy: Perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nurs.* 2008; 12: 97-102.
19. Can G, Demir M, Erol O, Aydiner A. A comparison of men and women's experiences of chemotherapy-induced alopecia. *Eur J Oncol Nurs.* 2012 in press.
20. Zannini L, Verderame F, Cucchiara G, Zinna B, Alba A, Ferrara M. 'My wig has been my journey's companion': perceived effects of an aesthetic care programme for Italian women suffering from chemotherapy-induced alopecia. *Eur J Cancer Care.* 2012; 21: 650-60.
21. Protiere C, Evans K, Camerlo J, d'Ingrado MP, Macquart-Moulin G, Viens P, et al. Efficacy and tolerance of a scalp-cooling system for prevention of hair loss and the experience of breast cancer patients treated by adjuvant chemotherapy. *Supp Care Cancer.* 2002; 10: 529-37.
22. [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). [cited 11 November 2012]

23. Dean JC, Salmon SE, Griffith KS. Prevention of doxorubicin-induced hair loss with scalp hypothermia. *NEJM*. 1979; 301: 1427-9.
24. Cohen B. The cross-section trichometer: a new device for measuring hair quantity, hair loss, and hair growth. *Dermatol Surg*. 2008; 34: 900-10; discussion 10-1.
25. Hendriks MAE, Geerts PAF, Dercksen PAF, van den Hurk CJG, Breed WPM. The usefulness of Cohen's cross-section trichometer for measuring hair quantity. *Dermatol Surg* (in press). 2012.
26. Hurk van den CJ, Breed WP, Nortier JW. Short post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia. *Supp Care Cancer*. 2012; 20: 3255-60.




# Part III



Impact of chemotherapy-induced alopecia and scalp cooling  
on quality of life



# Chapter 8



**Impact of alopecia and scalp cooling on the well-being of  
breast cancer patients**

C.J.G. van den Hurk\*, F. Mols\*, A.J.J.M. Vingerhoets, W.P.M. Breed

\*Both authors contributed equally to this work.

Psych Oncol. 2010; 19: 701-709



## Abstract

### Objective

Chemotherapy-induced hair loss may be prevented by scalp cooling. This study focuses on the impact of chemotherapy-induced hair loss and the effect of scalp cooling on well-being.

### Methods

A prospective multi-centre study was performed in 13 hospitals. Breast cancer patients treated with (n=98) and without (n=168) scalp cooling completed questionnaires (EORTC QLQ-C30 and QLQ-BR23, WHOQOL-BREF, BIS, MBA, HADS) before chemotherapy, and three weeks and six months after chemotherapy.

### Results

Scalp cooling was effective in 52% of the cases. Hair loss was considered among the most distressing problems at all three moments of measurement. A trend towards higher well-being was found in successfully scalp-cooled patients, as indicated by a general better health related quality of life (HRQOL), better body image and a lower importance of hair for body image. Explanations for reduced well-being in unsuccessfully scalp-cooled patients might be disappointment due to hair loss despite scalp cooling or a higher biological availability of cytotoxics.

### Conclusions

Scalp cooling contributes to the well-being of successfully scalp-cooled patients, but also seems to cause additional distress when patients lose their hair despite scalp cooling. Therefore effort has to be undertaken to provide additional support to patients when scalp cooling is ineffective and to further improve the results of scalp cooling.



## Introduction

Hair plays a major role in our appearance and in our unique individuality: who we are is tied in varying degrees to how we look.<sup>1</sup> Hair is a symbol of identity and personality and there is an important link between hair and feelings of attractiveness, sexuality and femininity or masculinity.<sup>1-3</sup> Sudden severe hair loss is generally associated with illness. Alopecia, ranging from partly to total hair loss, is a common side effect of chemotherapy. Severe alopecia stigmatizes by changing the individual's identity from a healthy person into a cancer patient, for the person him- or herself, but also for others.<sup>2,3</sup> Therefore, it is not surprising that cancer patients frequently rate alopecia among the most severe, troublesome and distressing side effects of chemotherapy.<sup>4-14</sup>

Alopecia may seriously affect one's body image, which in turn has an impact on self-esteem and self-confidence.<sup>15-17</sup> Consequently, it may cause emotional suffering, may lead to personal, social and work related problems and may have a negative effect on quality of life.<sup>1-3,18,19</sup> However, the magnitude of the impact of alopecia might have been reduced since, first, nurses pay more and serious attention to the patients' coping with alopecia and, second, the possibilities for head covering have improved significantly in the past decades.

In an increasing number of countries, scalp cooling has been introduced to prevent or reduce chemotherapy-induced alopecia. Scalp cooling reduces toxicity of cytotoxics in the hair matrix cells and is applied in chemotherapy schedules that normally cause severe alopecia. However, the reported success rates of scalp cooling vary widely.<sup>20</sup>

Preservation of hair during chemotherapy is expected to contribute positively to the well-being of cancer patients. However, it is plausible that only those patients choose for scalp cooling who attach much value to their hair. If these specific patients lose their hair, despite scalp cooling, it is possible that they experience this as an additional burden. The current study focuses on the impact of chemotherapy-induced alopecia and the effect of scalp cooling on health related quality of life (HRQOL), body image, anxiety and depression in breast cancer patients.

## 8

## Materials and methods

### Setting and Participants

Breast cancer patients were enrolled in this prospective multi-centre study between October 2004 and February 2007. Thirteen hospital locations participated, with six offering scalp cooling using the Paxman system. If patients in the scalp cooling hospitals did not choose for scalp cooling, they were not included in this study.

Specialised oncology nurses informed patients about the study. Patients who decided to participate, received a set of questionnaires (see measures section below) and return envelopes in the clinic and completed them at home. If questionnaires were not returned in time, the patient received a reminder.

Approval for this study was obtained from the Medical Ethics Committees of all participating hospitals.

## Inclusion and exclusion criteria

Inclusion criteria were having invasive breast cancer without distant metastases and signed informed consent. Moreover patients had to be treated with one of the following intravenous administered chemotherapies: 4 or 6 Adriamycine (60 mg/m<sup>2</sup>) and Cyclophosphamide (600 mg/m<sup>2</sup>) treatments (AC); 5 or 6 5-Fluorouracil (500 mg/m<sup>2</sup>), Epirubicine (90 mg/m<sup>2</sup>) and Cyclophosphamide (500 mg/m<sup>2</sup>) treatments (FEC); 5 or 6 5-Fluorouracil (500 mg/m<sup>2</sup>), Adriamycine (50 mg/m<sup>2</sup>) and Cyclophosphamide (500 mg/m<sup>2</sup>) treatments (FAC); and 5 or 6 Docetaxel (75 mg/m<sup>2</sup>), Adriamycine (50 mg/m<sup>2</sup>) and Cyclophosphamide (500 mg/m<sup>2</sup>) treatments (TAC). These schedules had to be administered in the adjuvant setting within a cycle of 21 days. Without scalp cooling these chemotherapies usually cause severe alopecia. Patients treated with intravenous trastuzumab for a year following chemotherapy were excluded of the third measurement because of the possible influence of long-lasting intensive contact with oncology nurses and other cancer patients on their answers on the questionnaires. Patients were also excluded if they lacked basic proficiency in Dutch, if they were unable to understand the patient information folder, or if they already suffered from alopecia before the onset of chemotherapy.

## Measures

### Patient and tumour characteristics

The measured patient and tumour characteristics were date of birth, marital status, educational level, type of surgery and lymph node dissection. Lymph node dissection includes sentinel node dissection as well as axillary lymphadectomy.

### Severity of alopecia

The success of scalp cooling was defined on the basis of whether the patient reported the use of a wig or head covering inside or outside the house. Patients additionally evaluated the severity of alopecia on the 4-point scale for alopecia of the World Health Organisation (WHO) with grade 0 for no alopecia, grade 1 for mild alopecia, grade 2 for pronounced alopecia and grade 3 for total alopecia.<sup>21</sup> Furthermore, patients filled in a Visual Analogue Scale (VAS) ranging from 0 (for no alopecia) to 100 (for total baldness).

### Impact of side effects of chemotherapy and consequences of cancer

Impact of side effects and consequences of cancer were measured by a so called 'psychophysical scaling method' that ranks physical and psychosocial disease and treatment effects that could possibly be experienced by breast cancer patients.<sup>4</sup> Patients rated the impact of each item, with alopecia serving as a reference value.<sup>22</sup> The following items were added to the original measure: arm problems, total mastectomy, breast changes, loss of appetite, change in taste, early hot flashes, and scalp cooling. Before the start of chemotherapy, this questionnaire assessed the patient's expectations regarding side effects and after chemotherapy it assessed the actually experienced side effects.

### Health related quality of life

HRQOL was measured by the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (EORTC-QLQ-C30, version 3) and the EORTC breast cancer module (EORTC-QLQ-BR23).<sup>23</sup> These internationally validated questionnaires were

scored according to algorithms recommended by the EORTC, resulting in a 0 to 100 scale.<sup>23,24</sup> Higher scores represent better functioning or higher levels of symptoms.

### Body image

Body image was assessed with the revised version of the Body Image Scale (BIS, version 2).<sup>25</sup> Higher scores represent more symptoms or increased distress regarding body image.

Concern over body image was assessed by the Measure of Body Apperception (MBA).<sup>26</sup> The two subscales of this measure, labelled 'concern about appearance' and 'concern about body integrity', assess personal investment in body image, rather than assessing the body image the person currently holds, with higher scores mean more concerns.

Two self-defined items were added to measure the importance of hair for the respondent's body image. These items were 'my hair is important to me' and 'my hair is important for my appearance'. Response options were rated on a 5-point Likert scale ranging from 'strongly agree' to 'strongly disagree'. Higher scores mean higher importance of hair.

### Hospital Anxiety and Depression Scale (HADS)

The Dutch version of the HADS, which assesses anxiety (HADS-A) and depression (HADS-D),<sup>27,28</sup> was scored in the range from 0 to 21, with higher scores representing more distress.

### Time points

Patients reported the severity of alopecia three weeks after completing chemotherapy. All remaining questionnaires were completed before the onset of chemotherapy and three weeks after the last cycle of chemotherapy. Only the questionnaire on the impact of side effects and consequences of cancer was also measured six months after completing chemotherapy. These time points were chosen because after three weeks the final result of scalp cooling is known and after six months the hair has regrown to some extent.

### Statistical analyses

Statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC). Patient and tumour characteristics were compared between scalp-cooled patients and non scalp-cooled patients by a t-test for age and chi-square tests for categorical variables.

Data collected before the onset of chemotherapy were compared between patients who were about to have scalp cooling and those who were not. Three weeks and six months after having completed chemotherapy, scores of scalp-cooled patients who did or did not preserve their hair and patients who did not receive scalp cooling were compared. All group comparisons were made with analyses of variance followed by Tukey's test for multiple group comparison.

## Results

### Patient and tumour characteristics

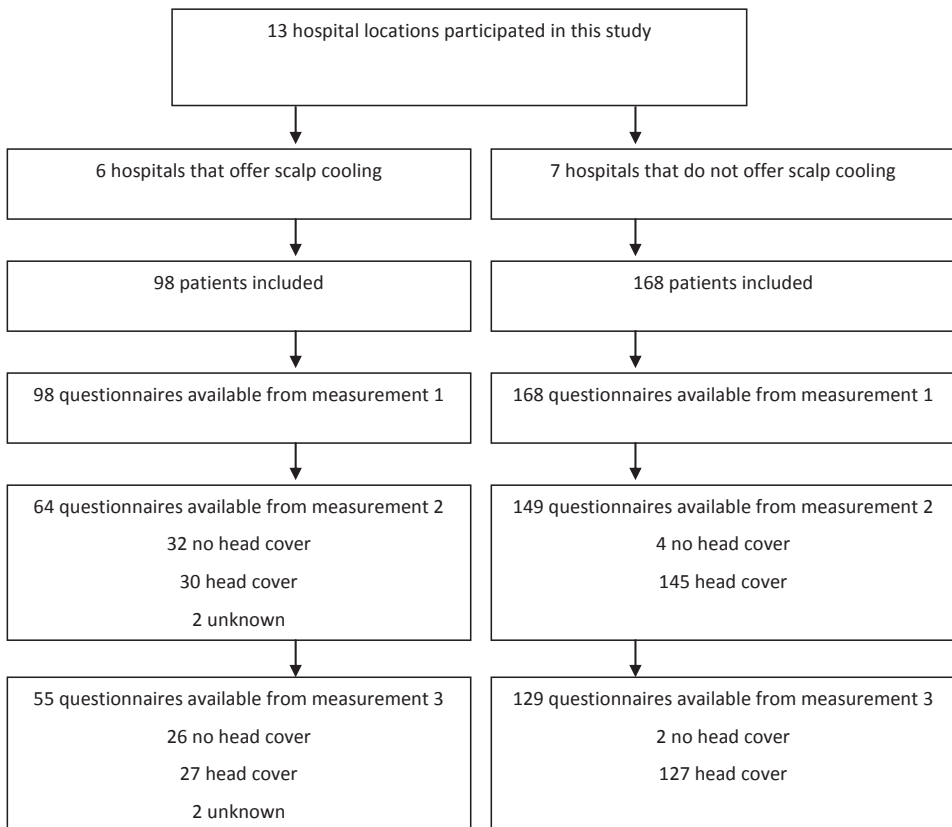
In total, 98 scalp-cooled patients and 168 non scalp-cooled patients received the first questionnaire of whom 184 (68%) fully responded at all three measurements (Figure 1).

Dropout during the study occurred due to a variety of reasons, such as logistical problems in the administration and resending of the questionnaires, but also progression of disease (switch from adjuvant to palliative treatment), or additional treatment with trastuzumab. Patient and tumour characteristics of breast cancer patients treated with or without scalp cooling did not differ significantly between both patient groups (Table 1).

### Severity of alopecia

Three weeks after the last chemotherapy, data were available of 65% of scalp-cooled patients (n=64) and 89% of non scalp-cooled patients (n=149) (Figure 1). Scalp cooling was considered effective in terms of no need of head covering in 32 of 62 evaluable patients (52%). Two patients for whom information on alopecia was missing were excluded from further analyses. All but four non scalp-cooled patients who completed the second questionnaire (n=149) reported to wear a wig or head covering. These four patients were, however, completely bald and were excluded from further analyses, because of their low number.

The mean rating of alopecia on the VAS scale among successfully scalp-cooled patients was 49 (range 17 to 97) while not successfully scalp-cooled patients had a mean score of 79



**Figure 1.** Flow-chart of the data collection process.

(range 30 to 100). Patients who did not receive scalp cooling obtained the highest rating, namely a mean of 85 (range 9 to 100). These differences in self-reported VAS scores were statistically significant for the successfully scalp-cooled group versus both other groups of patients ( $p < 0.0001$ ).

Extent of alopecia was also indicated by patients on the WHO scale. The mean WHO score among successfully scalp-cooled patients three weeks after chemotherapy was 1.4 (range 0 to 3) while not successfully scalp-cooled patients had a mean rating of 2.6 (range 2 to 3) and patients who had not received scalp cooling scored a mean of 2.9 (range 2 to 3). These three means differed significantly ( $p < 0.001$ ).

### Impact of side effects of chemotherapy and consequences of cancer

Before the onset of chemotherapy, patients expected that fear of metastases would have the highest impact on their lives, followed by alopecia and total mastectomy (Table 2). The only significant difference between the scalp-cooled and non scalp-cooled patients was seen for changes in relationship with children (42 vs. 24;  $p = 0.003$ ).

Three weeks and six months after the last chemotherapy, the actually experienced impact rankings were again highest for fear of metastases, alopecia and total mastectomy, although the order slightly changed compared to before chemotherapy (Table 3). Six months after completing chemotherapy a new prominent item (rank 2) was early hot flashes in the scalp-cooled group who needed head covering. The only significant group difference was found

**Table 1.** Socio-demographic and clinical characteristics of breast cancer patients treated with or without scalp cooling before the start of chemotherapy.

	n (%)		p-value
	Scalp cooling (n=98)	No scalp cooling (n=168)	
<b>Mean age at time of survey</b>	49.8	49.7	0.68
<b>Surgery</b>			
Mastectomy	43 (44)	94 (56)	0.16
Partial mastectomy	50 (51)	68 (40)	
<b>Lymph node dissection<sup>a</sup></b>			
Yes	79 (81)	129 (77)	0.42
No	15 (15)	35 (21)	
<b>Marital status</b>			
Married	76 (78)	124 (74)	0.31
Not married/divorced	11 (11)	29 (17)	
Living together	11 (11)	13 (8)	
<b>Education level<sup>b</sup></b>			
Low	42 (43)	91 (55)	0.16
Medium	31 (32)	42 (26)	
High	24 (25)	31 (19)	
Missing	1 (1)	4 (2)	

<sup>a</sup> including sentinel node dissection

<sup>b</sup> education: low=up to the end of high school, high=bachelor and master degree

for fatigue between the scalp-cooled patients in whom hair was preserved and the non scalp-cooled patients at three weeks following the last chemotherapy (37 vs. 59;  $p=0.01$ ).

### Health related quality of life

Before chemotherapy no statistical significant differences were found in HRQOL between patients with and without scalp cooling, except for cognitive functioning on the EORTC-QLQ-C30 (mean 85.9 vs. 80.7;  $p=0.05$ ).

Three weeks after the last chemotherapy successfully scalp-cooled patients reported statistically significant more appetite in comparison with scalp-cooled patients who needed head covering (mean 16.7 vs. 39.1;  $p=0.008$ ) (Table 4). In addition, a statistically significant

**Table 2.** Expected impact and ranking of side effects of chemotherapy and consequences of cancer one week prior to chemotherapy in patients treated with or without scalp cooling.

	Scalp cooling (n=98)		No scalp cooling (n=168)	
	Impact <sup>a</sup>	Rank	Impact <sup>a</sup>	Rank
Fear of metastases	73	1	70	1
Alopecia	70	2	65	2
Total mastectomy	58	3	56	3
Fatigue	46	4	49	4
Consciousness of one's vulnerability	45	5	45	6
Nausea	42	6	43	7
Arm problems	42	7	48	5
Changes in relationship with children	42*	8	24*	23
Vomiting	40	9	41	8
Breast changes through mastectomy	35	10	37	9
Changes in relationship with partner	35	11	31	13
Concentration problems	33	12	30	14
Mouth problems	32	13	33	10
Sleeping difficulties	32	14	30	15
Early hot flashes	32	15	31	11
Scalp cooling	31	16	-	-
Loss of appetite	30	17	27	17
Mood changes	30	18	31	12
Constipation	29	19	26	19
Changes in relationship with friends	27	20	24	20
Burning eyes	27	21	24	21
Skin problems	27	22	26	18
Change in taste	27	23	29	16
Difficulties taking care of oneself	26	24	23	24
Diarrhea	25	25	24	22
Nail problems	14	26	14	25

\* significant difference at  $<0.05$

<sup>a</sup> impact= the mean score people gave to a item (range 0-100)

difference was found for complaints about alopecia between scalp-cooled patients who required a head cover and the non scalp-cooled group (mean 43.7 vs. 25.2;  $p=0.02$ ). Overall, a trend was observed for better HRQOL in successfully scalp-cooled patients, whereas the unsuccessfully scalp-cooled group tended to have the worst HRQOL.

## Body image

Before chemotherapy, patients who were about to have scalp cooling reported more concern about body appearance (mean 3.27 vs. 3.02;  $p=0.03$ ) and a somewhat higher importance for hair (mean 4.43 vs. 4.25;  $p=0.06$ ) compared to patients who were not treated with scalp cooling (Table 5). Three weeks after completing chemotherapy, successfully scalp-cooled

**Table 4.** QLQ-C30 and QLQ-BR23 three weeks after completing chemotherapy in patients treated with and without scalp cooling.

	Scalp-cooled, no head cover (n=32)		Scalp-cooled, head cover (n=30)		No scalp cooling (n=145)	
	Mean	(sd)	Mean	(sd)	Mean	(sd)
<b>EORTC-QLQ-C30</b>						
Global health status/QOL	68.5	(21.7)	60.3	(22.2)	63.9	(21.8)
Physical function	77.9	(19.4)	70.7	(16.3)	74.4	(19.2)
Role function	62.0	(31.5)	52.2	(24.3)	56.3	(29.0)
Emotional function	72.1	(23.1)	67.8	(22.8)	70.2	(23.2)
Cognitive function	72.4	(26.6)	65.0	(28.8)	69.6	(25.6)
Social function	79.7	(24.6)	71.7	(24.0)	72.1	(26.2)
Fatigue	42.7	(28.4)	54.4	(25.3)	51.8	(26.1)
Nausea and vomiting	17.2	(18.7)	27.0	(30.3)	24.7	(29.0)
Pain	13.5	(18.7)	17.8	(25.5)	20.3	(24.1)
Dyspnea	20.8	(23.6)	27.8	(27.8)	26.6	(30.2)
Sleep disturbance	33.3	(29.3)	37.8	(28.7)	34.5	(33.1)
Appetite	16.7	(26.8)*	39.1	(36.8)*	27.1	(29.2)
Constipation	17.7	(25.4)	24.1	(23.4)	23.2	(29.4)
Diarrhea	9.4	(19.4)	8.0	(17.0)	7.5	(17.9)
Financial impact	13.5	(26.6)	18.9	(28.6)	12.9	(24.4)
<b>EORTC-QLQ-BR23</b>						
Body image	74.2	(27.9)	65.3	(23.4)	71.4	(26.8)
Sexual function	28.0	(26.0)	23.6	(20.2)	21.8	(19.7)
Sexual enjoyment <sup>a</sup>	54.2	(26.9)	48.1	(17.0)	54.5	(26.4)
Future perspective	53.8	(30.6)	52.2	(25.8)	51.0	(30.1)
Breast symptoms	31.0	(19.2)	41.0	(18.1)	39.2	(18.2)
Arm symptoms	19.0	(18.7)	21.9	(23.7)	18.0	(19.2)
Systemic therapy side effects	20.8	(22.5)	18.1	(20.1)	20.6	(18.9)
Alopecia	21.8	(31.2)	43.7	(40.0)*	25.2	(37.5)*

\*significant difference at  $<0.05$

<sup>a</sup> compliance with item sexual enjoyment is only 50%

**Table 3.** Experienced impact and ranking (rank 1 to 5) of side effects of chemotherapy and consequences of cancer three weeks and six months after completing chemotherapy in patients treated with or without scalp cooling.

	3 weeks after completing chemotherapy						6 months after completing chemotherapy					
	Scalp-cooled, no head cover			No scalp cooling			Scalp-cooled, no head cover			Scalp-cooled, head cover		
	Impact <sup>a</sup>	Rank	Impact	Rank	Impact	Rank	Impact	Rank	Impact	Rank	Impact	Rank
Alopecia	68	1	63	1	67	1	62	1	57	1	58	2
Fear of metastases	66	2	57	2	60	3	50	4	51	6	64	1
Arm problems	65	3	32	15	47	7	49	7	42	10	51	6
Total mastectomy	62	4	50	4	65	2	54	3	53	3	56	3
Consciousness of one's vulnerability	48	5	48	5	47	6	55	2	37	12	49	7
Fatigue	37*	7	56	3	59*	4	45	8	53	5	52	5
Nausea	33	9	47	6	51	5	37	13	53	4	43	9
Trouble sleeping	21	13	26	18	41	11	50	5	46	8	40	11
Early hot flashes	12	19	36	12	42	10	50	6	54	2	55	4

\*significant difference at <0.05

<sup>a</sup> impact= the mean score people gave to a item (range 0-100)

**Table 5.** Body image one week prior to chemotherapy and three weeks after chemotherapy among patients treated with and without scalp cooling.

	Before chemotherapy				3 weeks after completing chemotherapy				
	Scalp cooling		No scalp cooling		Scalp-cooled, no head cover		Scalp-cooled, head cover		
	Mean (sd)	p-value	Mean (sd)	p-value	Mean (sd)	p-value	Mean (sd)	p-value	
<b>Body image (BIS)</b> (range 0-30)									
Total score	7.71 (4.97)	0.51	7.24 (5.76)	0.51	9.13 (6.00)	0.10	12.18 (5.94)	9.74 (5.93)	0.10
<b>Concern about body image (MBA)</b> (range 1-5)									
Concern about appearance	3.27 (0.76)	0.03	3.02 (0.89)	0.03	2.97 (0.88)	0.20	3.23 (0.91)	3.08 (0.87)	0.20
Concern about body integrity	2.59 (0.89)	0.44	2.49 (1.02)	0.44	2.59 (1.00)	0.91	3.02 (0.99)	2.66 (0.96)	0.91
<b>Importance of hair for body image</b> (range 1-5)									
My hair is important to me	4.43 (0.83)	0.06	4.25 (0.83)	0.06	4.09 (0.86)	0.01	4.50 (0.63)	4.27 (0.81)	0.01
My hair is important for my appearance	4.25 (0.68)	0.15	4.09 (0.93)	0.15	3.94 (0.84)	0.07	4.40 (0.62)	4.14 (0.86)	0.07





patients reported that their hair had a significant lower importance for their body image (mean 4.09; sd 0.86) compared to scalp-cooled patients who needed head covering (mean 4.50; sd 0.63) and patients not treated with scalp cooling (mean 4.27; sd 0.81) ( $p=0.01$ ).

### Depression and anxiety

Before chemotherapy, no statistically significant differences were found in anxiety and depression between patients who were about to have scalp cooling and those who were not (depression 3.67 vs. 4.11;  $p=0.19$  and anxiety 5.69 vs. 5.22;  $p=0.83$ ). In addition, no statistically significant differences were found three weeks after the last chemotherapy between successfully and unsuccessfully scalp-cooled patients and the non scalp-cooled group (depression 3.23 vs. 4.29 vs. 4.10;  $p=0.40$  and anxiety 5.32 vs. 5.89 vs. 5.22;  $p=0.73$ ).

## Discussion

This is the first study designed to assess the effect of scalp cooling on well-being. A trend to better well-being was found in successfully scalp-cooled patients, as evidenced by a general better HRQOL and a better body image. On the other hand, unsuccessfully scalp-cooled patients reported significantly more complaints about alopecia and a tendency to less well-being compared to non scalp-cooled patients. However this was not reflected in higher anxiety or depression scores. Furthermore, this study revealed that the large majority of patients expected alopecia to be among the most distressing problems of chemotherapy and this side effect remained one of the most distressing problems three weeks as well as six months after completing chemotherapy.

It is tempting to speculate about explanations for the observed group differences in alopecia and well-being. From a psychological point of view, the uncertainty regarding hair preservation in scalp-cooled patients may cause additional distress (E. Boot, unpublished observations) and severe alopecia despite scalp cooling may lead to extra disappointment. 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.

The present study revealed only a trend towards somewhat better HRQOL and body image in the successfully scalp-cooled patients in comparison with unsuccessfully and non cooled patients. The lack of significance may be caused by insensitivity of the measurement instruments, as the applied questionnaires were not developed to measure differences in HRQOL and body image with respect to alopecia. On the other hand, the finding of significance may be caused by chance in multiple testing. In addition, it is not clear to what extent wearing wigs and head covering reduces distress. In a few previous studies HRQOL and body image have been negatively associated with alopecia, as has been shown in a recent review.<sup>29</sup>

Although patients who had chosen for scalp cooling reported more concern about their appearance before chemotherapy than non scalp-cooled patients, they did not correctly

predict the importance of hair for body image. The importance became particularly evident after having completed chemotherapy, especially in patients who ultimately had experienced alopecia despite scalp cooling. Before starting chemotherapy, the non scalp-cooled patients maybe had hope<sup>30-32</sup> but hardly expectations on preservation of their hair, because the chemotherapy schedules administered in this study nearly always cause severe alopecia. Since these patients anticipated alopecia, they might have been more prepared for this side effect and its impact on their appearance. Even though, also in the literature describing non scalp-cooled patients, it has been repeatedly reported that the experience of alopecia is very upsetting.<sup>3,32-34</sup> This stresses the need of extra support for patients experiencing alopecia<sup>30</sup>, especially since physicians and nurses tend to underestimate its impact.<sup>4,5</sup>

Before chemotherapy, a significant difference was found for the impact of chemotherapy and cancer on the relationship with children, between patients who were or were not about to have scalp cooling. Maybe particularly women with children choose scalp cooling when it is offered to them, in order to prevent their children from being confronted with their baldness. However, after chemotherapy no significant differences were observed in relationships with children between patients with or without alopecia, so probably patients' anticipated concerns about the relationship with their children were overrated. Moreover, patients reported that their young children adapted quickly to their changed appearance. As far as known, the impact of alopecia on relatives has not been studied until now.

Alopecia prevention was defined on the basis of the patient's opinion that their hair was preserved to such an extent that no wig or head covering was needed. This is justified by the fact that WHO and VAS scores, both pretending to represent the actual loss of hair, were associated insufficiently with each other and with the use of head covering and therefore appear to be less appropriate. However, it is known that the patient's decision to wear a wig or head cover will not always be directly related to the severity of alopecia; some patients with minimal alopecia nevertheless experience it as a severe burden and choose to wear a head cover, and the opposite is also true. A simple objective quantification of alopecia in order to evaluate the effectiveness of various methods of scalp cooling would be most helpful. In future studies, perhaps Cohen's trichometer might be suitable.<sup>35</sup> But, ultimately, it should be the patients' appraisal of the result of scalp cooling that must be perceived as most important.

This study has some limitations. Firstly, patient selection might have occurred, which might have biased the results on well-being, particularly in hospitals practising scalp cooling. It is not known what percentage of patients was eligible, had been offered scalp cooling and subsequently had chosen for scalp cooling. Patient characteristics in scalp-cooled and non scalp-cooled patients did not differ, however the response rate was lower in scalp-cooled patients. In addition, although the TAC regimen is tougher than AC, FEC and FAC, is not expected that the applied chemotherapy regimens will have caused differences in outcome between the subgroups of patients, because TAC was hardly administered (<5%) to breast cancer patients in the scalp cooling hospitals in 2005 and 2006. Only minimal bias may have occurred by assigning patients who stopped scalp cooling as a result of intolerance to the subgroup of unsuccessful scalp-cooled patients, because in literature this number is hardly

more than 10%.<sup>20</sup> Finally, because the non scalp-cooled group may also contain patients who would have chosen scalp cooling if it was offered in their hospital, the differences before chemotherapy might be underestimated, in particular for body image. Secondly, a limitation of the present study is the relatively large number of drop outs, which are mainly due to administrative issues. In future studies, more attention should be given to data collection in the hospitals.

Over the past decades, the impact of chemotherapy-induced side effects has changed considerably<sup>6</sup>, mainly due to changes in treatment, including symptom management. For example, medication against nausea and vomiting has improved, therefore these side effects became less important in comparison to other side effects that can not be minimised or prevented. With respect to alopecia, the quality of wigs has improved, the possibilities for head covering are meanwhile extensive and patients are nowadays regularly advised about managing alopecia before starting chemotherapy. Nevertheless, it remains an important issue for patients, which deserves attention for research.<sup>29,31,32</sup> In the prevention of alopecia, the unanswered question remains whether or not the possible positive effects for successfully scalp-cooled patients outweighs the possible negative effects when scalp cooling is unsuccessful. The answer will be mainly determined by the effectiveness of scalp cooling in a particular chemotherapy regimen. Therefore, efforts have to be undertaken to further improve the results of scalp cooling and it should not be offered to patients when the chance of hair preservation is minimal. The effectiveness of scalp cooling can only be determined when results are systematically registered, which is nowadays, as far as we know, only applied on a large scale in the Netherlands.

## Acknowledgements


Special thanks goes to all patients who participated in the study, to nurses and doctors who performed the study and to doctors who were willing to function as an independent advisor and to answer questions of patients. Furthermore we would like to thank our colleagues from the following hospitals for their friendly cooperation; A. Schweitzer, Dordrecht; Máxima Medisch Centrum, Eindhoven; Elkerliek, Helmond; Mesos Medisch Centrum, Utrecht; St. Elisabeth, Tilburg; Twee Steden, Tilburg; Gelre, Apeldoorn; Lievensberg, Bergen op Zoom; Amphia, Breda; Catharina, Eindhoven; Sint Anna, Geldrop; Medisch Centrum Rijnmond Zuid, Rotterdam; Máxima Medisch Centrum, Veldhoven. Finally, we acknowledge the contribution of M. Mulders in the initiation of this study.

## References

1. Pickard-Holley S. The symptom experience of alopecia. *Sem Oncol Nurs.* 1995; 11: 235-8.
2. Freedman TG. Social and cultural dimensions of hair loss in women treated for breast cancer. *Cancer Nurs.* 1994; 17: 334-41.
3. Rosman S. Cancer and stigma: experience of patients with chemotherapy-induced alopecia. *Patient Educ Couns.* 2004; 52: 333-9.
4. Mulders M, Vingerhoets A, Breed W. The impact of cancer and chemotherapy: Perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nurs.* 2008; 12: 97-102.
5. Macquart-Moulin G, Viens P, Bouscary ML, Genre D, Resbeut M, Gravis G, et al. Discordance between physicians' estimations and breast cancer patients' self-assessment of side-effects of chemotherapy: an issue for quality of care. *Br J Cancer.* 1997; 76: 1640-5.
6. Carelle N, Piotto E, Bellanger A, Germanaud J, Thuillier A, Khayat D. Changing patient perceptions of the side effects of cancer chemotherapy. *Cancer.* 2002; 95: 155-63.
7. Duric VM, Stockler MR, Heritier S, Boyle F, Beith J, Sullivan A, et al. Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes AC and CMF worthwhile now? *Ann Oncol.* 2005; 16: 1786-94.
8. Griffin AM, Butow PN, Coates AS, Childs AM, Ellis PM, Dunn SM, et al. On the receiving end. V: Patient perceptions of the side effects of cancer chemotherapy in 1993. *Ann Oncol.* 1996; 7: 189-95.
9. Brown V, Sitzia J, Richardson A, Hughes J, Hannon H, Oakley C. The development of the Chemotherapy Symptom Assessment Scale (C-SAS): a scale for the routine clinical assessment of the symptom experiences of patients receiving cytotoxic chemotherapy. *Int J Nurs Stud.* 2001; 38: 497-510.
10. de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, v Beurden V, Stoter G, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. *Br J Cancer.* 1997; 76: 1055-61.
11. Tierney AJ, Taylor J, Closs SJ. Knowledge, expectations and experiences of patients receiving chemotherapy for breast cancer. *Scand J Caring Sci.* 1992; 6: 75-80.
12. Sitzia J, Huggins L. Side effects of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy for breast cancer. *Cancer practice.* 1998; 6: 13-21.
13. Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM, et al. On the receiving end - patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol.* 1983; 19: 203-8.
14. Lindley C, J.S. M, Thomason TE, Lauder D, Sauls A, Adkins S, et al. Perception of chemotherapy side effects cancer versus noncancer patients. *Cancer practice.* 1999; 7: 59-65.
15. Munstedt K, Manthey N, Sachsse S, Vahrson H. Changes in self-concept and body image during alopecia induced cancer chemotherapy. *Supp Care Cancer.* 1997; 5: 139-43.
16. Carpenter JS, Brockopp DY. Evaluation of self-esteem of women with cancer receiving chemotherapy. *Oncol Nurs Forum.* 1994; 21: 751-7.
17. Baxley KO, Erdman LK, Henry EB, Roof BJ. Alopecia: effect on cancer patients' body image. *Cancer Nurs.* 1984; 7: 499-503.
18. Hunt N, McHale S. The psychological impact of alopecia. *BMJ.* 2005; 331: 951-3.
19. Cash TF. The psychology of hair loss and its implications for patient care. *Clin Dermatol.* 2001; 19: 161-6.
20. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol.* 2005; 16: 352-58.
21. World Health Organisation. Handbook for Reporting Results of Cancer Treatment. Geneva: WHO Offset Publ. 1979.
22. Gopher D, Braune R. On the Psychophysics of Workload: Why Bother with Subjective Measures? *Human Factors.* 1984; 26: 519-32.
23. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993; 85: 365-76.

24. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, et al. The EORTC QLQ-C30 Scoring Manual (3rd edition). Brussels: European Organisation for Research and Treatment of Cancer; 2001.
25. Hopwood P, Fletcher I, Lee A, Al Ghazal S. A body image scale for use with cancer patients. *Eur J Cancer*. 2001; 37: 189-97.
26. Carver CS, Pozo-Kaderman C, Price AA, Noriega V, Harris SD, Derhagopian RP, et al. Concern about aspects of body image and adjustment to early stage breast cancer. *Psychosom Med*. 1998; 60: 168-74.
27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983; 67: 361-70.
28. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med*. 1997; 27: 363-70.
29. Lemieux J, Maunsell E, Provencher L. Chemotherapy-induced alopecia and effects on quality of life among women with breast cancer: a literature review. *Psycho Oncol*. 2008; 17: 317-28.
30. Hesketh PJ, Batchelor D, Golant M, Lyman GH, Rhodes N, Yardley D. Chemotherapy-induced alopecia: psychosocial impact and therapeutic approaches. *Supp Care Cancer*. 2004; 12: 543-9.
31. Frith H, Harcourt D, Fussell A. Anticipating an altered appearance: women undergoing chemotherapy treatment for breast cancer. *Eur J Oncol Nurs*. 2007; 11: 385-91.
32. Hilton S, Hunt K, Emslie C, Salinas M, Ziebland S. Have men been overlooked? A comparison of young men and women's experiences of chemotherapy-induced alopecia. *Psych Oncol*. 2008; 17: 577-83.
33. Boehmke MM, Dickerson SS. Symptom, symptom experiences, and symptom distress encountered by women with breast cancer undergoing current treatment modalities. *Cancer Nurs*. 2005; 28: 382-9.
34. Browall M, Gaston-Johansson F, Danielson E. Postmenopausal women with breast cancer: their experiences of the chemotherapy treatment period. *Cancer Nurs*. 2006; 29: 34-42.
35. Cohen B. The cross-section trichometer: a new device for measuring hair quantity, hair loss, and hair growth. *Dermatol Surg*. 2008; 34: 900-10.

# Chapter 9



**Scalp cooling to prevent chemotherapy-induced hair loss:  
practical and clinical considerations**

F. Mols\*, C.J.G. van den Hurk\*, A.J.J.M. Vingerhoets, W.P.M. Breed

\*Both authors contributed equally to this work.

Supp Care Cancer. 2009; 17(2): 181-189



## Abstract

### Objective

The objective of this prospective multi-centre study was to obtain insight into the severity and burden of hair loss among cancer patients treated with chemotherapy. In addition, we described the effectiveness and burden of scalp cooling, the satisfaction with wigs and with hair regrowth and body image.

### Methods

Breast cancer patients treated with (n=98) and without (n=168) scalp cooling completed questionnaires before chemotherapy, and 3 weeks and 6 months after completion of chemotherapy.

### Results

Scalp cooling was effective in preventing chemotherapy-induced hair loss in 32 of 62 available patients (52%). Even though patients knew hair loss was temporarily, it was a burden to 54% of them (n=100). Scalp cooling was a burden for only 17 out of 51 patients (33%). Most patients who used a wig or head cover were satisfied with it (82%, n=126). Patients were moderately satisfied with the regrowth of their hair after chemotherapy (Mean 11.6; sd 2.53; range 0-20). Successfully cooled patients rated their hair as less important for their body image compared to patients who did experience hair loss (p= 0.014).

### Discussion

Chemotherapy-induced hair loss is perceived as burdensome. It may be prevented by offering scalp cooling which is often an effective method to prevent this form of hair loss and is tolerated well by patients. However, if possible, scalp cooling techniques should be improved and their effectiveness should be increased because if scalp cooling is unsuccessful, patients' rate their hair loss as more burdensome compared to non-cooled patients.



## Introduction

To date, the majority of breast cancer patients are treated with surgery, often in combination with radiotherapy. These therapies are often combined with chemotherapy (Dutch guidelines; <http://www.oncoline.nl>), which may cause severe side-effects.<sup>1</sup> Patients rate hair loss as among the most severe side-effects of chemotherapy.<sup>2-10</sup> Since the 1970's preventive efforts such as tourniquet, medication and scalp cooling have been applied to prevent chemotherapy-induced hair loss.<sup>11</sup> Currently, scalp cooling is the most commonly used method.

Seven randomized clinical studies have been published which examined the effectiveness of scalp cooling.<sup>12-18</sup> These studies randomized a total of 233 patients. In six of these studies, scalp cooling was considered to be effective. The average reported success rate of scalp cooling in studies carried out before 1995, with a total number of 1563 patients, was 56% and from 1995 onwards the success rate was 73% with a total of 1047 patients included.<sup>19</sup> Despite this relatively high success rate, scalp cooling is offered very limited; e.g., in February 2008, only 36% of all Dutch hospitals offered scalp cooling, and moreover, only to a selected number of patients. Reasons for this are, among others, the underestimation of the impact of hair loss and overestimation of the burden of scalp cooling on a patient by the oncologists and nurses and the lack of knowledge on the current effectiveness of scalp cooling.

The present study is the first more systematic study that specifically addresses quality of life and scalp cooling satisfaction in a multi-centre context and has three main objectives. The first objective was to obtain insight into the severity and burden of hair loss among cancer patients treated with chemotherapy. The second objective was to describe the effectiveness and burden of scalp cooling. The third objective was to describe the satisfaction with a wig and with hair regrowth in patients who lost their hair after chemotherapy (because they did not receive scalp cooling or because scalp cooling failed). The final objective of this study was to measure the difference in body image between patients who were or were not treated with scalp cooling.

## Methods

### Setting and Participants

Breast cancer patients were enrolled in this prospective multi-centre study between October 2004 and February 2007. Thirteen hospital locations participated in this study, with six offering scalp cooling. If patients in the scalp cooling hospitals did not chose for scalp cooling, they were not included in this study.

Specialised oncology nurses informed patients about the study. Patients who decided to participate received a set of questionnaires before the start of chemotherapy, 3 weeks after the last cycle of chemotherapy and 6 months after chemotherapy. If a questionnaire was not returned, the patient received a reminder. Approval for this study was obtained from the Medical Ethics Committees of all participating hospitals. All study participants provided written informed consent.

## Inclusion and exclusion criteria

Inclusion criteria were treatment for breast cancer with one of the following intravenously chemotherapies: 4 or 6 Adriamycine (60 mg/m<sup>2</sup>) and Cyclophosphamide (600 mg/m<sup>2</sup>) treatments; 5 or 6 5-Fluorouracil (500 mg/m<sup>2</sup>), Epirubicine (90 mg/m<sup>2</sup>), and Cyclophosphamide (500 mg/m<sup>2</sup>), treatments; 5 or 6 5-Fluorouracil (500 mg/m<sup>2</sup>), Adriamycine (50 mg/m<sup>2</sup>), and Cyclophosphamide (500 mg/m<sup>2</sup>), treatments; and 5 or 6 Docetaxel (75 mg/m<sup>2</sup>), Adriamycine (50 mg/m<sup>2</sup>), and Cyclophosphamide (500 mg/m<sup>2</sup>) treatments. These chemotherapies had to be given in the adjuvant setting in a 21-day cycle. Patients treated with intravenous trastuzumab for a year following chemotherapy were excluded because of the possible influence of long-lasting intensive contact with oncology nurses and other cancer patients on the measures. Patients were excluded if they lacked basic proficiency in Dutch, if they were unable to understand the patient information folder or if they suffered from alopecia before the onset of chemotherapy.

## Measures

### Patient and tumour characteristics

The measured patient and tumour characteristics were date of birth, marital status, educational level, type of surgery and lymph node dissection.

### Severity of hair loss

The severity and importance of hair loss was measured by asking patients if they felt the need to wear a wig or other head covering. We defined the success of cooling on the basis of whether the patient reported the use of a wig or head covering. Furthermore, the severity of hair loss was reported by patients on the 4-point scale for alopecia of the World Health Organisation (WHO) with grade 0 for no hair loss, grade 1 for mild hair loss, grade 2 for pronounced hair loss and grade 3 for total hair loss (World Health Organisation, 1979). In addition, a Visual Analogue Scale (VAS) was applied ranging from 0 for no hair loss to 100 for total baldness. The severity of hair loss was measured 3 weeks after the last cycle of chemotherapy.

### Burden of hair loss

A newly developed questionnaire assessed the impact of hair loss. Part of the items were selected from questionnaires with respect to alopecia androgenetica<sup>20-22</sup>, other items were self-defined based on discussions with female cancer patients. This measure consisted of 40 statements that could be rated on a 4-point Likert scale ranging from 'not at all' to 'very much'. Higher scores indicated higher burden of hair loss. The answers on the 4-point Likert scale were divided into 2 groups, namely patients who did or did not agree with a particular statement. Patients who did not receive scalp cooling as well as scalp cooled patients who reported hair loss (defined as WHO score grade 1, 2 or 3) completed the questionnaire 3 weeks and 6 months following chemotherapy.

### Burden of scalp cooling

The burden of scalp cooling was evaluated by nine self-defined items which were based on complaints reported by patients who were treated with scalp cooling in the past. The items concerned the psychological burden, physical effects and the influence of uncertainty about

the final result of cooling. Response format was a 6-point Likert scale ranging from 'not at all' to 'a lot'. Higher scores thus indicate a higher burden of scalp cooling. The answers on the 6-point Likert scale were divided into 2 groups, namely patients who did or did not agree with a particular statement. Furthermore, patients were asked whether or not they had taken pain killers during scalp cooling.

This questionnaire was completed by 51 out of 98 scalp cooled patients. This was due to the fact that this questionnaire was added to our set of questionnaires at a later stage and only in some of the hospitals which offered scalp cooling. Since patients were asked to fill out this questionnaire after each cooling, we received a total of 153 completed questionnaires.

#### Wig use

Patients were asked what kind of head covering they used and if they wore the head covering inside the house, only outside the house or both.

A newly developed questionnaire additionally evaluated the satisfaction with wigs and head coverings and was based on consultations with an expert panel (nurses and patients). This measure consisted of 18 statements rated on a 4-point Likert scale ranging from 'not at all' to 'very much'. Higher scores indicated higher levels of satisfaction with wigs or head coverings. Patients completed the questionnaire 3 weeks and 6 months following chemotherapy.

#### Hair regrowth

Satisfaction with hair regrowth was measured by a 5-item questionnaire addressing the rapidity of regrowth, length and thickness, colour and hair style (curly or straight). The answer categories were rated on a 4-point Likert scale ranging from 'not at all' to 'very much'. Higher scores indicated higher levels of satisfaction with hair regrowth. The answers on the 4-point Likert scale were divided into 2 groups, namely patients who were or were not satisfied with hair regrowth. The questionnaire was filled out 6 months after completing chemotherapy by patients who reported a score between 1 and 3 on the WHO scale for hair loss.

#### Body image

Body image was assessed with the revised version of the Body Image Scale (BIS), consisting of 10 items rated on a 4-point Likert scale ranging from 'not at all' to 'very much'. The sum score of the 10 items ranged from 0 to 30 with higher scores representing increased symptoms or distress with regard to body image. The BIS has high reliability (Cronbach's alpha 0.93) and validity.<sup>23</sup>

Concern over body image was assessed by the Measure of Body Apperception (MBA) questionnaire.<sup>24</sup> Scores were calculated for two subscales, namely 'concern about physical appearance' and 'concern about body integrity'. These subscales both consisted of 4 items and measured personal investment in both aspects of body image, rather than assessing the body image the person currently holds.<sup>24</sup> Two self-defined items were added to the MBA to measure the importance of hair for a person's body image. Response options of the subscales and self-defined items ranged from 'strongly agree' to 'strongly disagree'.

The scores were rated on a scale from 1 to 5, with higher scores meaning more concerns or higher importance. This questionnaire was completed before chemotherapy and 3 weeks after the completion of chemotherapy.

### Statistical analyses

Statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC). Patient and tumour characteristics were compared between scalp cooled patients and not scalp cooled patients by chi-square tests for categorical variables.

From the questionnaire on the burden of hair loss, 10 statements were selected that caused the most burden to patients. We reported the number and percentage of questionnaires on which the statements were answered affirmatively. The same procedure was followed for all statements on the questionnaires; 'burden of scalp cooling', 'hair regrowth' and 'wig use'.

One week prior to chemotherapy, body image was compared between those who were going to be treated with scalp cooling and those who were not. Three weeks after chemotherapy, body image was compared between patients that were successfully cooled, not successfully cooled and patients that did not receive scalp cooling. All group comparisons were made with ANOVA's followed by Tukey's test for multiple group comparison.

## Results

### Patient and tumour characteristics

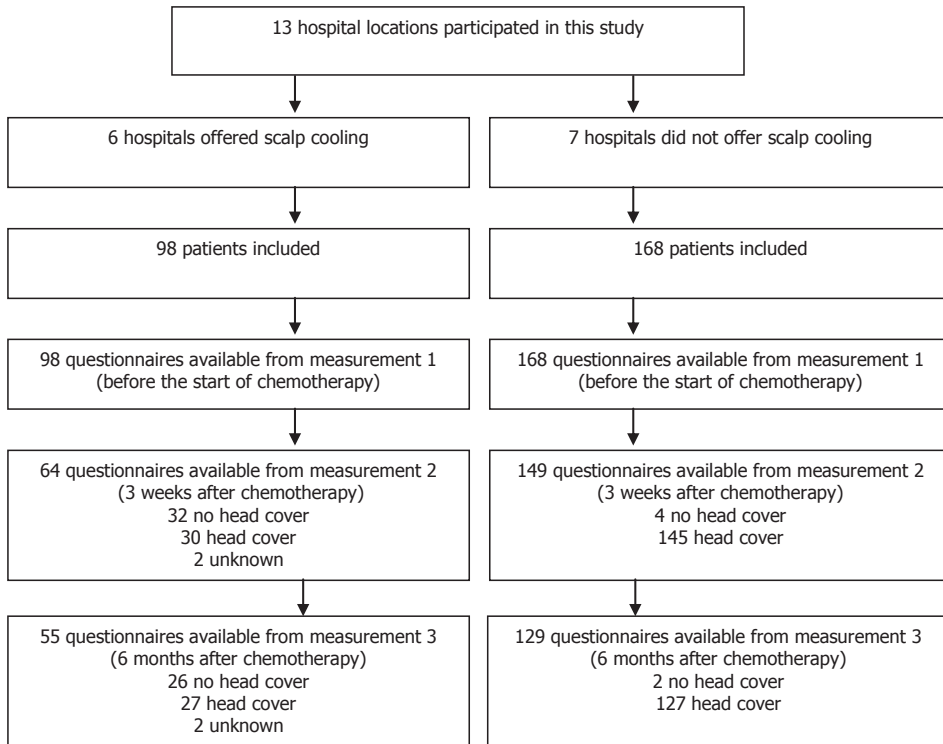
Ninety-eight patients received scalp cooling and 168 control patients were included who were treated in hospitals where no scalp cooling was available. The participants received the questionnaires at three points in time. The numbers of participants, according to measurement moment, are presented in Figure 1. In total, 184 (68%) participants responded. Dropout during the study occurred due to a variety of reasons. Most often mentioned were logistical problems.

Patient and tumour characteristics of breast cancer patients treated with or without scalp cooling are presented in Table 1. These characteristics did not differ significantly between both patient groups.

### Severity of hair loss

Three weeks after chemotherapy, data were available of 65% of cooled patients (n=64) and 89% of not cooled patients (n=149). Scalp cooling was effective in preventing chemotherapy-induced hair loss in 32 of 62 evaluable patients. Data on two patients were missing therefore they were excluded from further analyses (Figure 1). In patients who did not receive scalp cooling (n=149) all but four needed a wig or head cover. These four patients were however completely bald. Because of the low number, these four patients were excluded from further analyses.

The mean rating of hair loss on the VAS scale among successfully cooled patients was 49 (range 17 to 97) while not successfully cooled patients rated a mean of 79 (range 30 to 100). Patients who did not receive scalp cooling reported most hair loss, namely a mean of 85



**Figure 1.** Flow-chart of the data collection process. Dropout during the study occurred due to a variety of reasons. Most often mentioned were logistical problems.

(range 9 to 100). These differences in self-reported hair loss were statistically significant ( $p < 0.001$ ).

Extent of hair loss was also rated by patients on the WHO scale. The mean WHO score among successfully cooled patients three weeks after chemotherapy was 1.4 (range 0 to 3) while not successfully cooled patients rated a mean of 2.6 (range 0 to 3). Patients who did not receive scalp cooling reported the most hair loss, namely a mean of 2.9 (range 0 to 3).

### Burden of hair loss

Out of a list of 40 statements about the burden of hair loss to a patient, the 10 statements that were most frequently confirmed three weeks and six months following chemotherapy were reported in Table 2. On 71% of questionnaires, it was stated that hair loss made patients feel unattractive and 58% of questionnaires stated that hair loss was a problem for patients. Furthermore, 54% of questionnaires showed that, even though patients knew hair loss was temporarily, it was a burden to them.

**Table 1.** Socio-demographic and clinical characteristics of breast cancer patients treated with or without scalp cooling before the start of chemotherapy.

	n (%)		p-value
	Scalp cooling n=98	No scalp cooling n=168	
<b>Mean age at time of survey</b>	49.8	49.7	
<b>Surgery</b>			
Total mastectomy	43 (44)	94 (56)	0.1609
Breast conserving surgery	50 (51)	68 (40)	
<b>Lymph node dissection</b>			
Yes	79 (81)	129 (77)	0.4238
No	15 (15)	35 (21)	
<b>Marital status</b>			
Married	76 (78)	124 (74)	0.3060
Not married/divorced	11 (11)	29 (17)	
Living together	11 (11)	13 (8)	
<b>Education level</b>			
Low	42 (43)	91 (55)	0.1619
Medium	31 (32)	42 (26)	
High	24 (25)	31 (19)	
Missing	1 (1)	4 (2)	

**Table 2.** Ten statements that caused the most burden of hair loss 3 weeks and 6 months after chemotherapy.

Statements <sup>a</sup>	n <sup>b</sup> (%) <sup>c</sup>
1. I do not feel attractive because of my hair loss.	130 (71)
2. Hair loss was a problem for me.	106 (58)
3. Even though my hair loss was temporary, I found it a burden.	100 (54)
4. I wasn't satisfied with myself because of my hair loss.	92 (50)
5. I was very aware of myself because of my hair loss.	87 (47)
6. In the past few weeks/months I checked my hair loss in the mirror regularly.	86 (47)
7. I talked to my friends about my hair loss.	82 (45)
8. The hair loss of my eyes (eyelashes) was a burden to me.	67 (36)
9. The hair loss of my eyebrows was a burden to me.	69 (38)
10. I was looking for some elucidation about my looks because of my hair loss.	61 (33)

<sup>a</sup> Out of a list of 40 statements, 10 statements about hair loss that caused the most burden to patients are reported in this table

<sup>b</sup> n= number of questionnaires filled out by patients who did not receive scalp cooling as well as scalp cooled patients who reported hair loss, 3 weeks and 6 months following chemotherapy

<sup>c</sup> The number and percentage of patients that answered the statements confirmatively on one or more occasions

## Burden of scalp cooling

Only 51 of 98 scalp cooled patients completed the questionnaire about the burden of scalp cooling. These were the patients who underwent a maximum of six cycles of scalp cooling and were thus asked to complete a maximum of six questionnaires. Fifty-one patients filled out the questionnaire during the first cycle; 46 patients also filled out the second questionnaire; 31 patients also did questionnaire three; 16 patients did questionnaire four; 9 patients finished the fifth questionnaire and no one finished the last one. Therefore, data of 153 questionnaires were obtained.

In Table 3, we listed the statements of the questionnaire on the burden of scalp cooling and the percentage of questionnaires on which the statements were answered confirmatively. Furthermore, we added data on the number and percentage of patients who answered the statements confirmatively on one or more occasions. On 25 questionnaires (16%) it was indicated that scalp cooling was a burden, this was filled out by 17 patients on one or more occasions. The statement; "I was able to tolerate the cooling of my scalp." was answered affirmatively on 53 questionnaires (35%), by 27 patients. Twenty-one questionnaires (14%) indicated that scalp cooling gave patients (n=12) a headache. However, only nine patients occasionally took a pain killer to relief a headache (Data not shown). On 74 questionnaires (48%) it was indicated that patients thought frequently about the result of scalp cooling, this was filled out by 31 patients on one or more occasions.

## Wig use

All patients with severe hair loss induced by chemotherapy (n=175; 30 not successfully cooled and 145 not cooled) reported the use of a wig and/or other head cover. Most patients used more than one head cover; a wig was used by 81% of patients, 51% used a scarf, 23% used a

**Table 3.** The burden of scalp cooling.

Statements <sup>a</sup>	Number of questionnaires	Number of patients
	(%) <sup>b</sup>	(%) <sup>c</sup>
1. Scalp cooling was a burden to me.	25 (16)	17 (33)
2. The cooling was cold.	43 (28)	20 (39)
3. The cooling gave me a headache.	21 (14)	12 (24)
4. The 'cold cap' was heavy.	21 (14)	15 (29)
5. I was able to tolerate the cooling of my scalp.	53 (35)	27 (53)
6. I got dizzy during the cooling.	14 (9)	10 (20)
7. I felt bored during the cooling.	20 (13)	14 (27)
8. I worry a lot lately about the possibility of failure of scalp cooling.	48 (31)	22 (43)
9. Lately, I thought a lot about the result of scalp cooling.	74 (48)	31 (61)

<sup>a</sup>Statements are listed in this table in the same order of appearance as in the questionnaire

<sup>b</sup>The number and percentage of questionnaires on which the statements were answered affirmatively

<sup>c</sup>The number and percentage of patients that answered the statements confirmatively on one or more occasions

cap and 8% wore a hat. Seventy-six percent of patients who used a wig or head cover made use of it both inside and outside the house. Furthermore 37% reported to wear a wig or head cover merely outdoors and only one patient wore it just indoors.

In Table 4, we listed all 18 statements of the questionnaire on wig use and the percentage of questionnaires that were answered affirmatively three weeks and six months after chemotherapy. On 126 questionnaires (82%) it was stated that patients were satisfied with their wig; it looked a lot like their own hair (n=103; 67%), if fitted nicely round their scalp (n=119; 77%) and on only a minority of questionnaires (n=10; 1%) patients complained about irritation to the skin. However, in 91 questionnaires (59%) patients stated that they felt that their wig was expensive and that they were constantly aware of wearing it (n=96; 62%).

### Hair regrowth

Six months after chemotherapy, patients who had suffered from hair loss (n=172) were moderately satisfied with hair regrowth (Mean 11.6; sd 2.53; range 0-20). Satisfaction with hair regrowth did not differ significantly between patients who underwent scalp cooling and the control group.

**Table 4.** The burden of wearing a wig or head cover 3 weeks and 6 months after chemotherapy.

Statements <sup>a</sup>	n (%) <sup>b</sup>
1. My wig fitted nicely round my scalp.	119 (77)
2. I was constantly aware of wearing a wig/head cover.	96 (62)
3. Wearing a head cover made me feel watched by other people.	35 (23)
4. My wig caused irritation to the skin.	10 (1)
5. I was satisfied with my wig/head cover.	126 (82)
6. My wig looked a lot like my own hair.	103 (67)
7. When wearing a wig I felt just as attractive as before my hair fell out.	73 (47)
8. By wearing a wig, I felt confident about myself.	81 (53)
9. It bothered me that on some occasions, wearing a wig caused sweating.	56 (36)
10. I felt ashamed of myself when I was not wearing my wig/head cover.	53 (34)
11. My partner preferred to see me with my wig/head cover instead of without.	29 (19)
12. Wearing a wig made my head feel warm and that bother me.	51 (33)
13. With activities, like exercising, my wig was an obstruction.	54 (35)
14. I was worried about the possibility of my wig moving or falling off.	39 (25)
15. My kids preferred to see me with my wig/head cover instead of without.	50 (32)
16. My wig was expensive.	91 (59)
17. When wearing a wig, I felt more feminine compared to not wearing a wig.	85 (55)
18. My wig was easily distinguishable from my own hair.	12 (1)

<sup>a</sup> Statements are listed in this table in the same order of appearance as in the questionnaire. In this table, data were included from 3 weeks and 6 months after chemotherapy for patients wearing a wig or head cover

<sup>b</sup> The number and percentage of questionnaires on which the statements were answered affirmatively



Most patients indicated that they were satisfied with the thickness of their hair (86%, n=147) and with the speed at which their hair grows (75%, n=129). In addition, most patients were satisfied with the texture of their hair (curly or straight) (73%, n=125), the current length of their hair (72%, n=121), and the colour of their hair (57%, n=98).

### Body image

Before the initiation of chemotherapy, participants in the hospitals that offered scalp cooling reported somewhat more concern about appearance (Mean 3.27 vs. 3.02;  $p=0.03$ ) compared to patients in the hospitals that did not offer scalp cooling (Table 5). Three weeks after chemotherapy, scalp cooled patients who did not need a wig reported that their hair had a significant ( $p=0.01$ ) lower importance for their body image (Mean 4.09; sd 0.86) compared to unsuccessfully scalp cooled patients who needed a wig (Mean 4.50; sd 0.63) and patients not treated with scalp cooling (Mean 4.27; sd 0.81).

## Discussion

The aim of the present study was to obtain insight into the impact that scalp cooling to prevent hair loss during chemotherapy has on the patient. Furthermore, the objective was to evaluate the burden of hair loss, the satisfaction with wigs and with hair regrowth in patients who did lose their hair. Finally, we compared body image between patients who did and did not experience hair loss.

### The effectiveness of scalp cooling

Approximately 50% of patients that received scalp cooling did not need a wig and were therefore considered successfully cooled. This percentage seems somewhat low because the average success rate of scalp cooling in studies published after 1995 was 73%.<sup>19</sup> In the literature, wide variations of success rates of scalp cooling have been reported. The success depends upon many factors like type of applied cytotoxics, doses, number of chemotherapy courses, admission methods and scalp cooling method.<sup>14,25,26</sup> The recent, more intensive, adjuvant chemotherapy treatments in breast cancer may explain the relatively low success percentage of about 50 percent in this study. Furthermore, the definition of successfully cooled differs considerably among studies. Wearing a wig or head cover may be considered the most important criterion to determine if patients consider their scalp cooling as successful. However, graded scales, like the WHO scale are also used.<sup>19</sup> In this study, we used both methods. In addition, our relatively low success rate of scalp cooling was defined 3 weeks after the completion of chemotherapy. However, it is possible that success of scalp cooling in other studies is measured earlier (e.g. cycle 3) and not always at the end of all cycles. This could also cause a difference in success rates between other studies and our study. Another possible explanation for our rather low success rate is the fact that the present study is a multi-centre study which generally is associated with lower success rates in all kinds of evaluation studies compared to studies performed in a single centre. Also, publication bias might be a factor; it is possible that studies having achieved low success rates have not been published after 1995.

**Table 5.** Body image 1 week prior to chemotherapy and 3 weeks after chemotherapy among patients treated with and without scalp cooling.

	1 week prior to chemotherapy		3 weeks after chemotherapy		p-value	Mean (sd)	p-value	3 weeks after chemotherapy		p-value
	Scalp cooling	No scalp cooling	Scalp-cooled, no head cover	Scalp-cooled, head cover				No cooling, head cover	No cooling, head cover	
<b>Body image (BIS) (range 0-30)</b>										
Total score	7.71 (4.97)	7.24 (5.76)	7.24 (5.76)	9.13 (6.00)	0.5130	12.18 (5.94)	9.74 (5.93)	9.74 (5.93)	0.0984	
<b>Concern about body image (MBA) (range 1-5)</b>										
Concern about appearance	3.27 (0.76)	3.02 (0.89)	<b>0.0274</b>	2.97 (0.88)		3.23 (0.91)	3.08 (0.87)	3.08 (0.87)	0.2005	
Concern about body integrity	2.59 (0.89)	2.49 (1.02)	0.4393	2.59 (1.00)		3.02 (0.99)	2.66 (0.96)	2.66 (0.96)	0.9060	
<b>Importance of hair for body image</b>										
My hair is important to me	4.43 (0.83)	4.25 (0.83)	0.0551	4.09 (0.86)		4.50 (0.63)	4.27 (0.81)	4.27 (0.81)	<b>0.0141</b>	
My hair is important for my appearance	4.25 (0.68)	4.09 (0.93)	0.1494	3.94 (0.84)		4.40 (0.62)	4.14 (0.86)	4.14 (0.86)	0.0719	

### The burden of hair loss

Hair loss was rated as being a source of distress to patients and this finding confirms results reported in the literature on this topic. A number of studies have shown that a considerable number of cancer patients experience alopecia as distressing.<sup>27 9,28</sup> Furthermore, alopecia is ranked among the three most troublesome side-effects of chemotherapy, together with vomiting and nausea.<sup>2,4,8</sup>

### The burden of scalp cooling

This study showed that patients did not perceive scalp cooling as being burdensome. We found low rates of complaints which is in accordance with literature about the acceptability and tolerance of scalp cooling.<sup>17,19,29-32</sup> Twelve patients indicated that scalp cooling gave them a headache, however, only nine patients occasionally took a pain killer to relief a headache.

### The satisfaction with wigs

All respondents coped with hair loss with a strategy involving camouflaging and hiding; they wore wigs or other head covers in an attempt to hide their hair loss. Alopecia is in particular hidden outside the house, when being exposed to others with whom the patient does not wish to share the visible stigma. On the other hand, corroborating previous research<sup>33</sup>, an important minority of patients do not hide alopecia inside their own homes when being with their partner, family, and friends who know about the hair loss. Wearing a wig “repairs” your physical appearance, restores corporal integrity and prevents the patients and others of being constantly reminded of cancer. Patients in our study reported that their wigs were not easily distinguishable from their own hair which supports the idea that wigs were mostly worn to look normal, in any case not looking sick, for themselves and others.<sup>28</sup>

### The satisfaction with hair regrowth

Hair loss from chemotherapy is temporary, however how it will grow back is unpredictable, sometimes the new hair has a different colour or texture.<sup>28,34,35</sup> Six months after having completed chemotherapy patients were generally satisfied with their hair regrowth. Since nobody had experienced previous chemotherapy, they did not know what they could expect concerning the regrowth of hair. Patients who experienced severe hair loss or complete baldness have several centimetres of hair within half a year. In patients with bald spots or thinned hair (because scalp cooling was not totally preventive for hair loss and who did not shave their hair) some hair regrowth directly causes a thicker head of hair and camouflaging is not needed anymore. Patients in this study were very satisfied with the texture of their hair but were less satisfied with its colour.

### Body image

Body image did not differ between patients who did and did not lose their hair three weeks after chemotherapy. These findings confirm the results of a prior study among 77 cancer patients receiving chemotherapy, which also demonstrated that patients with alopecia had comparable scores on body image compared to those without alopecia. The negative effect of hair loss on body image may have been minimized by the process of adaptation to hair loss and possibly by the positive effects of the wig.<sup>36</sup> However, a study on changes in body image during chemotherapy among 136 women with gynaecologic malignancies who

experienced alopecia, showed that chemotherapy-induced alopecia had an adverse effect on body image.<sup>37</sup> In addition, a study among 40 cancer patients receiving chemotherapy showed a significant difference in body image between patients with alopecia and patients without alopecia.<sup>38</sup> Furthermore, a study among 29 German women with a gynaecological malignancy who lost their hair during chemotherapy found that regrowth of hair after chemotherapy did not necessarily imply recovery of the declined body image.<sup>39</sup> The studies mentioned above all used different methods to measure body image; moreover these studies did not include patients treated with scalp cooling. Comparisons with the current study are therefore problematic.

In addition, our results showed that three weeks after chemotherapy, successfully cooled patients rated their hair as less important for their body image compared to patients who did experience hair loss. These results may indicate that people only became aware of the importance of hair for their body image once they lost it.

### Limitations

This is an observational study and patient self-selection was therefore inevitable. We do not know how many patients were eligible for scalp cooling, and to how many of them it was offered and, finally, how many have accepted that offer. Dropout during the study was most often caused by logistical problems. Furthermore, the sample of scalp cooled patients was relatively small, which made sub-analyses less powerful. In addition, some of the questionnaires used in this study are relatively new and their psychometric characteristics are currently unknown. Nevertheless, the results of this study form an important contribution to the limited information available on scalp cooling to prevent chemotherapy-induced hair loss in cancer patients.

### Final remarks

In conclusion, the present study is the first more systematic study that specifically addresses scalp cooling satisfaction in a multi-centre context. This study showed that chemotherapy-induced hair loss is stressful to the majority of breast cancer patients. Hair loss may be prevented by scalp cooling although the success rate in this study was limited. Nevertheless, scalp cooling can be an effective method to prevent hair loss and is tolerated well by patients. However, scalp cooling techniques should be improved because if scalp cooling is unsuccessful, patients' rate their hair loss as more burdensome compared to patients who did not receive scalp cooling.

### Acknowledgement

We are grateful to all patients for participating in the study. We would like to thank the following hospitals for their friendly cooperation; A. Schweitzer, Dordrecht; Máxima Medisch Centrum, Eindhoven; Elkerliek, Helmond; Mesos Medisch Centrum, Utrecht; St. Elisabeth, Tilburg; Twee Steden, Tilburg; Gelre, Apeldoorn; Lievensberg, Bergen op Zoom; Amphia, Breda; Catharina, Eindhoven; Sint Anna, Geldrop; Medisch Centrum Rijnmond Zuid, Rotterdam; Máxima Medisch Centrum, Veldhoven.

## References

1. Janssen-Heijnen MLG, Louwman WJ, van de Poll-Franse LV, Coebergh JWW. Results of 50 years cancer registry in the South of the Netherlands: 1955-2004 [in Dutch]. Eindhoven: Eindhoven Cancer Registry; 2005.
2. Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM, et al. On the receiving end - patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol.* 1983; 19: 203-8.
3. Kiebert GM, Hanneke J, de Haes CJ, Kievit J, van de Velde CJ. Effect of peri-operative chemotherapy on the quality of life of patients with early breast cancer. *Eur J Cancer.* 1990; 26: 1038-42.
4. Tierney A, Taylor J. Chemotherapy-induced hair loss. *Nurs Stand.* 1991; 5: 29-31.
5. Dougherty L. Scalp cooling to prevent hair loss in chemotherapy. *Prof Nurse.* 1996; 11: 507-9.
6. de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, v Beurden V, Stoter G, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. *Br J Cancer.* 1997; 76: 1055-61.
7. Lindley C, J.S. M, Thomason TE, Lauder D, Sauls A, Adkins S, et al. Perception of chemotherapy side effects cancer versus noncancer patients. *Cancer Pract* 1999; 7: 59-65.
8. Carelle N, Piotto E, Bellanger A, Germanaud J, Thuillier A, Khayat D. Changing patient perceptions of the side effects of cancer chemotherapy. *Cancer.* 2002; 95: 155-63.
9. Lemieux J, Maunsell E, Provencher L. Chemotherapy-induced alopecia and effects on quality of life among women with breast cancer: a literature review. *Psych Oncol.* 2008; 17: 317-28.
10. Mulders M, Vingerhoets A, Breed W. The impact of cancer and chemotherapy: Perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nurs.* 2008; 12: 97-102.
11. Dean JC, Salmon SE, Griffith KS. Prevention of doxorubicin-induced hair loss with scalp hypothermia. *NEJM.* 1979; 301: 1427-9.
12. Edelstyn GA, MacDonald M, MacRae KD. Doxorubicin-induced hair loss and possible modification by scalp cooling. *Lancet.* 1977; 2: 253-4.
13. Kennedy M, Packard R, Grant M, Padilla G, Presant C, Chillar R. The effects of using Chemocap on occurrence of chemotherapy-induced alopecia. *Oncol Nurs Forum.* 1983; 10: 19-24.
14. Satterwhite B, Zimm S. The use of scalp hypothermia in the prevention of doxorubicin-induced hair loss. *Cancer.* 1984; 54: 34-7.
15. Parker R. The effectiveness of scalp hypothermia in preventing cyclophosphamide-induced alopecia. *Oncol Nurs Forum.* 1987; 14: 49-53.
16. Giaccone G, Di Giulio F, Morandini MP, Calciati A. Scalp hypothermia in the prevention of doxorubicin-induced hair loss. *Cancer Nurs.* 1988; 11: 170-3.
17. Ron IG, Kalmus Y, Kalmus Z, Inbar M, Chaitchik S. Scalp cooling in the prevention of alopecia in patients receiving depilating chemotherapy. *Supp Care Cancer.* 1997; 5: 136-8.
18. Macduff C, Mackenzie T, Hutcheon A, Melville L, Archibald H. The effectiveness of scalp cooling in preventing alopecia for patients receiving epirubicin and docetaxel. *Eur J Cancer Care.* 2003; 12: 154-61.
19. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol.* 2005; 16: 352-58.
20. Cash TF, Price VH, Savin RC. Psychological effects of androgenetic alopecia on women: comparisons with balding men and with female control subjects. *J Am Ac Dermatol.* 1993; 29: 568-75.
21. Dolte KS, Girman CJ, Hartmaier S, Roberts J, Bergfeld W, Waldstreicher J. Development of a health-related quality of life questionnaire for women with androgenetic alopecia. *Clin Exp Dermatol.* 2000; 25: 637-42.
22. Fischer TW, Schmidt S, Strauss B, Elsner P. [Hairdex: a tool for evaluation of disease-specific quality of life in patients with hair diseases]. *Der Hautarzt.* 2001; 52: 219-27.
23. Hopwood P, Fletcher I, Lee A, Al Ghazal S. A body image scale for use with cancer patients. *Eur J Cancer.* 2001; 37: 189-97.

24. Carver CS, Pozo-Kaderman C, Price AA, Noriega V, Harris SD, Derhagopian RP, et al. Concern about aspects of body image and adjustment to early stage breast cancer. *Psych Som Med*. 1998; 60: 168-74.
25. David J, Speechley V. Scalp cooling to prevent alopecia. *Nurs Times*. 1987; 83: 36-7.
26. Adams L, Lawson N, Maxted KJ, Symonds RP. The prevention of hair loss from chemotherapy by the use of cold-air scalp-cooling. *Eur J Cancer Care*. 1992; 1: 16-8.
27. Pickard-Holley S. The symptom experience of alopecia. *Semin Oncol Nurs*. 1995; 11: 235-8.
28. Williams J, Wood C, Cunningham-Warburton P. A narrative study of chemotherapy-induced alopecia. *Oncol Nurs Forum*. 1999; 26: 1463-8.
29. Katsimbri P, Bamias A, Pavlidis N. Prevention of chemotherapy-induced alopecia using an effective scalp cooling system. *Eur J Cancer*. 2000; 36: 766-71.
30. Protiere C, Evans K, Camerlo J, d'Ingrado MP, Macquart-Moulin G, Viens P, et al. Efficacy and tolerance of a scalp-cooling system for prevention of hair loss and the experience of breast cancer patients treated by adjuvant chemotherapy. *Supp Care Cancer*. 2002; 10: 529-37.
31. Ridderheim M, Bjurberg M, Gustavsson A. Scalp hypothermia to prevent chemotherapy-induced alopecia is effective and safe: a pilot study of a new digitized scalp-cooling system used in 74 patients. *Supp Care Cancer*. 2003; 11: 371-7.
32. Massey CS. A multicentre study to determine the efficacy and patient acceptability of the Paxman Scalp Cooler to prevent hair loss in patients receiving chemotherapy. *Eur J Oncol Nurs*. 2004; 8: 121-30.
33. Rosman S. Cancer and stigma: experience of patients with chemotherapy-induced alopecia. *Pat Edu Couns*. 2004; 52: 333-9.
34. Fairlamb DJ. Hair changes following cytotoxic drug induced alopecia. *Postgr Med Journal*. 1988; 64: 907.
35. Batchelor D. Hair and cancer chemotherapy: consequences and nursing care-a literature study. *Eur J Cancer Care*. 2001; 10: 147-63.
36. Wagner L, Gorely M. Body image and patients experiencing alopecia as a result of cancer chemotherapy. *Cancer Nurs*. 1979; 2: 365-9.
37. Nolte S, Donnelly J, Kelly S, Conley P, Cobb R. A randomized clinical trial of a videotape intervention for women with chemotherapy-induced alopecia: a gynecologic oncology group study. *Oncol Nurs Forum*. 2006; 33: 305-11.
38. Baxley KO, Erdman LK, Henry EB, Roof BJ. Alopecia: effect on cancer patients' body image. *Cancer Nurs*. 1984; 7: 499-503.
39. Munstedt K, Manthey N, Sachsse S, Vahrson H. Changes in self-concept and body image during alopecia induced cancer chemotherapy. *Support Care Cancer*. 1997; 5: 139-43.



# Part IV




Cost-effectiveness





# Chapter 10



**Cost-effectiveness analysis of scalp cooling to reduce  
chemotherapy-induced alopecia**

C.J.G van den Hurk, M.E. van den Akker-van Marle, W.P.M. Breed,  
L.V. van de Poll-Franse<sup>1</sup>, J.W.R. Nortier, J.W.W. Coebergh

Acta Oncol. 2013; in press



## Abstract

### Background

Alopecia is a frequently occurring side effect of chemotherapy that often can be prevented by cooling the scalp during the infusion. This study compared effects and costs of scalp cooling with usual general oncological care, i.e. purchasing a wig or head cover.

### Material and methods

Scalp-cooled patients (n=160) were compared with non scalp-cooled patients (n=86) at 15 Dutch hospitals. Patients were enrolled prior to anthracycline and/or taxane-based chemotherapy for several types of cancer between 2007 and 2008. Cost-effectiveness of scalp cooling compared with that of usual care was determined by the ratio of costs to quality adjusted life years (QALYs). Costs for scalp cooling (machines and nursing time), hair dressers, wigs and head covers were estimated from a societal perspective. QALYs were measured using the Short Form-36.

### Results

Scalp cooling reduced the use of a wig or head cover by 40%, but wigs were still purchased unnecessarily by 38% of scalp-cooled patients. Average societal costs decreased therefore only by €269 per patient due to scalp cooling ( $p=0.02$ ). Given the eligibility for scalp cooling at the time, the insignificant difference in QALYs resulted from a balance of the benefits for those patients with successful scalp cooling and those without success. For the Dutch, given the generally accepted threshold of willingness to pay for a QALY (between €20,000 and €40,000), scalp cooling was cost-effective, therefore justifying the choice of scalp cooling or purchasing a wig or head cover.

### Conclusion

Given the right indication, cost-effectiveness might be improved further by postponing wig and head cover purchases, by improving scalp cooling efficacy, as well as using the scalp cooling capacity more intensively.

## Introduction

Chemotherapy frequently induces alopecia, making cancer visible to the outside world. It is often considered an inevitable side effect of chemotherapy, a temporary burden that should be taken for granted. It has however a negative impact on the well-being of many cancer patients<sup>1-3</sup>, which -according to some- has been underestimated or ignored by both oncology nurses and medical doctors.<sup>4,5</sup>

During the last 5 years prevention of chemotherapy-induced alopecia (CIA) has become a topic of supportive care. Of the ±91,000 patients newly diagnosed with cancer in the Netherlands in 2009, 27% received chemotherapy as part of their primary treatment (source: Netherlands Cancer Registry, unpublished data). From 2000 to 2008, the proportion of breast cancer patients who received chemotherapy as part of initial treatment increased by 40%<sup>6</sup>; the proportion even doubled for patients with gastro-intestinal and lung cancer (source: Eindhoven Cancer Registry, unpublished data). The administration of chemotherapy is still increasing. Although the incidence of severe CIA is generally lower in the case of targeted therapies and oral chemotherapy, these agents are often combined with regular cytotoxic drugs that do cause CIA.

Scalp cooling is the most effective method to prevent CIA. In currently used chemotherapies scalp cooling equipment prevents severe hair loss in about half of the patients.<sup>7-9</sup> Prevention of CIA by pharmaceutical agents is not very promising as a clinical application in the near future<sup>10-12</sup>; neither are new non-pharmaceutical methods such as electrogenesis or laser therapy.<sup>13,14</sup> The use of scalp cooling has increased world wide and CIA does not seem to be inevitable anymore.

Medical oncologists have to choose whether they want to offer scalp cooling as a service to patients at risk of severe CIA. Effectiveness and safety, but also costs and attribution of costs play a role in this decision. As part of an introduction program for scalp cooling we therefore compared costs and effects of scalp cooling with those of usual care, i.e. in the Netherlands the choice of purchasing a wig or head cover, when cancer patients are faced with CIA.

## Material and methods

### Patients and setting

In this non randomised prospective study scalp-cooled patients (n=160) were compared with non scalp-cooled patients with the same chemotherapy regimens (n=86). While the effectiveness of scalp cooling has been proven, also in trials<sup>7,8</sup>, it would be unethical to randomise patients. Patients were eligible if they received a chemotherapy schedule with the potential of inducing severe CIA and therefore scalp cooling was commonly applied. Patient characteristics were well balanced except for the proportion of patients receiving 5-fluorouracil, epirubicine and cyclophosphamide (FEC) (Table 1). From January 2007 to December 2008, patients were included from 15 hospitals, two of which did not offer scalp cooling. Patients in the scalp cooling hospitals who did not choose scalp cooling could participate in the non scalp-cooled group.

Scalp cooling was performed using the Paxman system (type PSC1 or PSC2) with a standardised cooling time: from 30 minutes before the chemotherapy infusion to 90 minutes after stopping the infusion.

Approval for this study was obtained from the Medical Ethics Committees and all participating patients signed forms of informed consent.

## Measures

Patients received four sets of questionnaires (see sections below) with return envelopes and were asked to complete them at home before the start of chemotherapy and three weeks, six and twelve months after completing chemotherapy. Patients were eligible for analysis if they completed at least the first and second questionnaire.

**Table 1.** Socio-demographic and clinical characteristics of patients treated with or without scalp cooling (n=246).

	Scalp-cooled n=160 (%)	Non scalp- cooled n=86 (%)	p-value
<b>Mean age</b> (range) years	52 (29-75)	51 (28-77)	0.4
<b>Gender</b>			0.07
Male	6 (4)	0	
Female	152 (96)	86 (100)	
Missing	2		
<b>Cancer</b>			0.001
Breast	152 (95)	77 (90)	
Ovary	0	8 (9)	
Gastro-intestinal	3 (2)	0	
Lung	3 (2)	1 (1)	
Prostate	2 (1)	0	
<b>Chemotherapy<sup>a</sup></b>			0.0006
FEC	101 (66)	39 (45)	
Paclitaxel combination	4 (3)	7 (8)	
Docetaxel mono/ combination	8 (5)	1 (1)	
AC+Paclitaxel	11 (7)	11 (13)	
FAC	12 (8)	4 (5)	
FEC+Docetaxel	6 (4)	7 (8)	
TAC	5 (3)	14 (16)	
Other	6 (4)	3 (4)	
Missing	7		
<b>Chemotherapy setting</b>			0.3
Adjuvant	131 (86)	78 (91)	
Palliative	22 (14)	8 (9)	
Missing	7		

<sup>a</sup> F=5-Fluorouracil, E=Epirubicin, C=Cyclophosphamide, A=Doxorubicine, T=Docetaxel

## Costs

CIA-related costs were estimated from the start of chemotherapy until twelve months after completion. At that time, the hair has grown to such an extent, that the majority of patients are satisfied and stop wearing a wig or head cover.<sup>15</sup> In order to estimate from the societal perspective, we took into account all health effects and changes in resource use caused by scalp cooling. Because of the short time line, costs were not discounted. Costs were converted to the 2010 price level, using the general Dutch consumer price index.<sup>16</sup>

Patients reported the cost of wigs and head covers from the start of chemotherapy until six months after completing chemotherapy. It was assumed that patients did not buy additional wigs or head covers after that time. Costs of hair dressers were estimated for all patients up to twelve months following chemotherapy. Other (health) care requirements (e.g. informal care) and productivity (e.g. return to work) were assumed to be unaffected by scalp cooling.

Hospital costs included time spent by nurses and equipment needed for scalp cooling. In each hospital a maximum of ten oncology nurses (range 2-10) completed a questionnaire. Nurses reported the time required to provide information about CIA and the performance of scalp cooling, i.e. fitting and cleaning the cap. Nursing time was valued at gross wages.<sup>17</sup> Equipment costs were collected for two years and included the machine, caps, coolant and maintenance costs. The economic lifetime of the machine and caps was assumed to be 10 years<sup>17</sup>. Annual costs were divided by the annual number of sessions. The sessions were recorded by a data manager for all chemotherapy patients treated with scalp cooling in day care during the 2-year study period, including use by non study participants. Scalp cooling is currently not used during clinical chemotherapy treatment.

Additional space required for storage of the equipment was negligible. Also electricity, costs of cleaning the cap and use of disposable gauze bandages for hygienic application of the cool cap's chin strap were too minimal to take into account. No extra treatment chairs or beds were required for scalp cooling in the day care units.

## Quality of Life

Utilities represent the valuation of quality of life (QoL) of the patients, on a scale from zero (as bad as death) to one (perfect health). Quality Adjusted Life Years (QALYs) takes into account both the quantity and quality of life generated by health care interventions.

Patients reported general health related QoL using the Short Form-36 (SF-36). From the SF-36 we derived SF-6D scores which were used to calculate utilities.<sup>18</sup> Together with the EQ-5D, HUI and QWB the SF-36 derived SF-6D is one of the methods used for economic evaluations from a societal perspective.<sup>19,20</sup> The utilities provide societal valuation and offer the possibility of comparison of the impact with other medical interventions.

As sensitivity analysis we also obtained valuations by the patients themselves using a Visual Analogue Scale (VAS), ranging from 0 (worst imaginable QoL) to 100 (perfect QoL). The VAS values were transformed to a utility scale, using the power transformation  $1 - (1 - \text{VAS}/100)^{1.61}$ .<sup>21</sup> QALYs were calculated from the area under the utility curves for the entire study period.

## Statistics

Socio-demographic and clinical characteristics were compared between scalp-cooled and non scalp-cooled patients using the Chi-square test. Cost analyses were performed with Stata 9.2 (StataCorp, College Station, TX, USA). To reduce possible bias in these analyses due to missing data, multiple imputation by chained equations was used<sup>22</sup>, with 10 iterations for the switching regression model. For each missing utility or cost measure, an imputation regression model was used that included age, gender, chemotherapy type, number of chemotherapy sessions, setting (adjuvant or palliative), number of scalp cooling sessions, SF36 and VAS for QoL and cost measurements at all moments. Differences in QALYs or use of head covering and costs between scalp-cooled and non scalp-cooled patients were analysed using the bootstrap method.

Base case cost-utility analysis was determined comparing societal costs from the start until 12 months after the stop of chemotherapy and QALYs based on the SF-36. Sensitivity analyses were performed using VAS for QoL and costs of the equipment. Costs of equipment were halved, reflecting doubling the number of scalp-cooled patients who use the machine in a hospital.

The societal Willingness To Pay (WTP) for a QALY is an indicator of cost-effectiveness, comparing WTP \* QALYs gained versus costs. Then the probability that a strategy is cost-effective is graphed as a function of WTP in an acceptability curve.<sup>23</sup> Cost-effectiveness is plausible when the probability that scalp cooling is effective (y-axis) exceeds 0.5. The Dutch economic threshold for WTP is assumed to be between €20,000 and €40,000 per QALY.<sup>24,25</sup>

## Results

### Costs

The average societal costs decreased €269 (95% CI €46 - €493;  $p=0.02$ ) per scalp-cooled patient compared to usual care (Table 2).

Patient's costs associated with wigs, other head covers and hair dressers were missing for respectively 5%, 5% and 10% of them. Non scalp-cooled patients spent significantly more money (mean difference €534, 95%CI €314 - €754;  $p<0.001$ ) on wigs and head covers and less on hair dressers (mean difference €82, 95%CI €46 - €119;  $p<0.001$ ) from the start of chemotherapy to six months after its completion (Table 2). Overall, the mean price for a wig was €616 (range €43 - €3,000), €265 was the standard refund by health insurance companies in 2007 and 2008, being about 45% of wig costs. Purchasing a wig was reported by 52% of scalp-cooled patients versus 77% of non scalp-cooled patients: health insurance companies saved refund for wigs in about 25% of the chemotherapy patients who were at risk of severe CIA. As several patients had more than one wig during the follow-up period, the mean costs per patient could be higher than the mean price for a wig, as is the case in the non scalp-cooled group (mean costs per patient €946).

When addressing only patients who purchased a wig, scalp-cooled patients bought a mean number of 1.8 wigs versus 2.0 for non scalp-cooled patients, mean prices per wig were respectively €541 and €653.



Table 2. Mean cost per scalp-cooled and non-scalp-cooled patients from the start of chemotherapy until 12 months after completion of chemotherapy.

Cost item per patient	Scalp-cooled n= 160		Non Scalp-cooled n= 86		Mean Difference		p-value <sup>c</sup>
	% <sup>b</sup>	Mean costs (sd) (€)	% <sup>b</sup>	Mean costs (sd) (€)	Costs (€)		
<b>Wig<sup>a</sup></b>							
- before start chemotherapy	46	460 (657)	71	946 (844)	-486		<0.001
- during chemotherapy	30	144	50	322	-178		
- 3 wks - 6 mo after chemotherapy	36	219	66	426	-208		
<b>Head cover<sup>a,d</sup></b>	19	97	20	198	-100		
- before start chemotherapy	49	49 (87)	79	97 (153)	-48		0.48
- during chemotherapy	25	12	48	27	-14		
- 3 wks - 6 mo after chemotherapy	35	22	64	49	-27		
<b>Total wig and/or head cover</b>	23	14	34	21	-7		
		509 (673)		1043 (895)	-534		0.005
<b>Hair dresser</b>	92	191 (187)	89	109 (102)	82		0.002
- during chemotherapy	42	32	19	12	20		
- 3 wks - 6 mo after chemotherapy	71	66	53	23	44		
- 6 - 12 mo after chemotherapy	83	93	85	72	18		
<b>Total patient</b>		700 (693)		1152 (909)	-452		<0.001
<b>Total scalp cooling hospital</b>	100	183 (135)	0	0	183		<0.001
- equipment costs	100	94	0	0	94		
- nursing costs	100	89	0	0	89		
<b>Total societal cost</b>		883 (678)		1152 (909)	-269		0.02

wk= weeks, mo= months

<sup>a</sup> measured until 6 months after chemotherapy<sup>b</sup> percentage of patients who reported costs<sup>c</sup> bootstrap method, correcting for non-response using multiple imputation<sup>d</sup> wig excluded

Eligibility for scalp cooling varied between hospitals regarding types of cancer and chemotherapy. Non scalp-cooled patients represented 56% of those treated in the two hospitals that did not offer scalp cooling.

One hundred and eight nurses completed the questionnaire on time expenditure. Nurses spent a mean of 10 minutes per patient on information about scalp cooling, which amounted to €5 per patient. Mean nursing time was 36 minutes per patient (range 9-81) and was assessed at €18 per scalp cooling session. Time needed to plan the cooling sessions was negligible (mean 10 minutes per week, range 0-35 minutes).

Nurses performed 1862 scalp cooling sessions per year. The 13 hospitals used six 2-person scalp cooling machines and 17 single-person machines. The mean costs of equipment amounted to €21 per cooling session, with a mean of 144 sessions per hospital per year. Patients underwent a mean of 4.2 scalp cooling sessions.

The mean costs of scalp cooling were €183 per patient per hospital, whereby €94 were equipment costs (machine including caps, coolant and maintenance) and €89 nursing costs.

### Quality of Life

For the four measurements in time, SF-6D scores were missing for respectively 6%, 4%, 19% and 26% of the patients. VAS scores were missing for 1%, 2%, 15% and 22% of the patients. According to the SF-6D and VAS, there was no significant difference in QALYs between scalp-cooled and non scalp-cooled patients (Table 3).

### Cost-effectiveness

The probability that scalp cooling was cost-effective compared to no scalp cooling depended on the WTP (Figure 1). For low values of the maximum WTP for a QALY (up to €34,000), the probability of being cost-effective was in favour of scalp cooling (above 0.5). For higher values of the WTP this probability decreased and chemotherapy without scalp cooling became preferable (below 0.5). Since the turning point of cost-effectiveness was within the acceptable range of the WTP for a QALY in the Netherlands, both strategies are acceptable from the societal point of view.

### Sensitivity analyses

When using VAS for QoL valuation, the difference between scalp-cooled and non scalp-cooled patients was somewhat more pronounced in favour of non scalp-cooled patients than for the SF-6D (Table 3). Therefore, the line of the acceptability curve decreases (Figure 1), indicating that scalp cooling is less likely to be cost-effective.

When the number of patients using the scalp cooling equipment in a hospital is doubled, equipment costs would amount to €12 euro per session and mean costs for the hospital would become €136 per scalp-cooled patient. In this sensitivity analysis, the difference in societal costs became €316 for scalp-cooled versus non scalp-cooled patients (95%CI €93 to €540,  $p=0.01$ ). Then the turning point of the probability that scalp cooling is cost-effective (i.e. 0.5) is about €40,000 per QALY. That is the upper value of the Dutch economic threshold for WTP, indicating that scalp cooling could be considered cost-effective (Figure 1).

**Table 3.** Mean utility and quality adjusted life years (QALYs) in scalp-cooled and non scalp-cooled patients.

Measure	Scalp-cooled n= 160	Non scalp-cooled n= 86	Difference	p-value <sup>a</sup>
<b>SF-6D</b>				
Average utility				
During Chemotherapy	0.59	0.59	-0.003	
3 wk - 6 mo after Chemotherapy	0.58	0.59	-0.006	
6 - 12 mo after Chemotherapy	0.58	0.60	-0.02	
QALYs <sup>b</sup>	0.78 (sd 0.16)	0.79 (sd 0.13)	-0.008	0.68
<b>VAS</b>				
Average utility				
During Chemotherapy	0.86	0.88	-0.02	
3 wk - 6 mo after Chemotherapy	0.84	0.88	-0.04	
6 - 12 mo after Chemotherapy	0.83	0.88	-0.05	
QALYs <sup>b</sup>	1.13 (sd 0.28)	1.17 (sd 0.22)	-0.04	0.40

wk= weeks, mo= months

<sup>a</sup> bootstrap method, correcting for non-response using multiple imputation

<sup>b</sup> mean duration study period 487 days for scalp cooling group and 484 days for group without scalp cooling  
SF-6D= health related quality of life, VAS= visual analogue scale for quality of life, QALYs= quality adjusted life years, sd= standard deviation

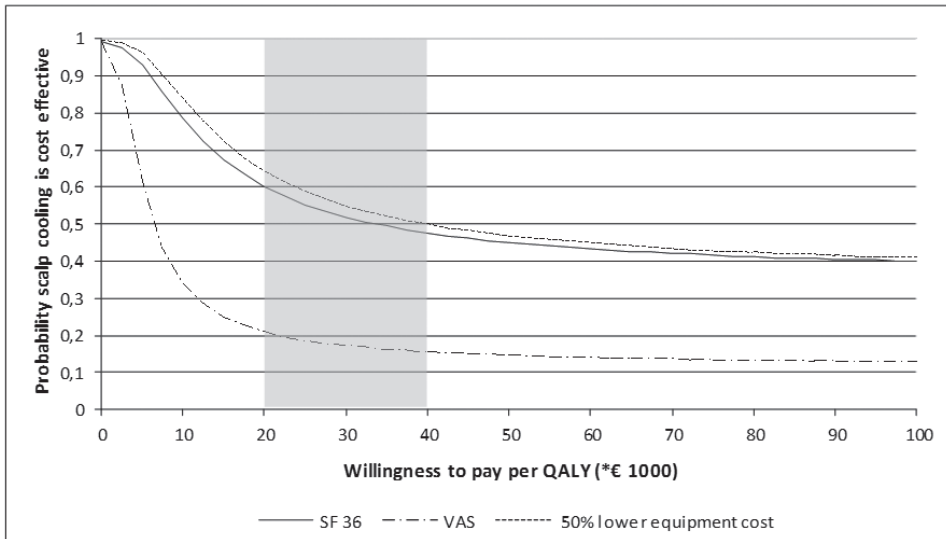
## Discussion

Given the indications for treatment with chemotherapy and scalp cooling at the time of this study, scalp cooling appeared to be less expensive than usual care, i.e. purchasing a wig or head cover. Societal savings were €269 per scalp-cooled patient, but there was no significant difference in QALYs compared to non scalp-cooled patients. Using scalp cooling saved €452 for patients, but entailed €183 extra costs per patient for hospitals. All in all, it seems justified to offer both options to the patient.

Assuming 24,500 patients a year with chemotherapy as part of their primary treatment (source: Netherlands Cancer Registry), whereby half would be faced with severe CIA, and half of them would choose scalp cooling, then total savings based on about 6,000 patients per year in the Netherlands would amount to €1,500,000.

To our knowledge, cost-effectiveness of scalp cooling has never been investigated. Only one Willingness To Pay study on CIA found that lung cancer patients were willing to pay €83 per 3-weekly chemotherapy cycle to reduce the risk of CIA from 40% to 5%.<sup>26</sup> The WTP depended on the perceived impact of CIA and was higher among females with a higher income.

Cost-effectiveness of scalp cooling can easily be improved by decreasing the costs of anticipated head cover purchase.<sup>27</sup> Secondly, costs will be reduced when a higher proportion of patients is satisfied with the scalp cooling result and thus do not feel the need to wear head covering, which is now e.g. about 50% among patients with FEC chemotherapy.<sup>28</sup> Therefore, scalp cooling should not be offered to patients with chemotherapy schedules in



**Figure 1.** Plausibility of cost-effectiveness of scalp cooling versus no scalp cooling related to societal Willingness To Pay.

which scalp cooling is ineffective, i.e. TAC chemotherapy.<sup>28</sup> Furthermore, research should be performed to further improve the efficacy of scalp cooling, e.g. by optimizing scalp cooling times and temperature. Third, savings on nursing staff might be obtained when nursing assistants or volunteers would be trained to apply scalp cooling.

Societal costs may also be reduced if the purchase of machines is aligned to the number of cooling sessions. A hospital that owns one machine can treat at least one patient a day, but in this study on average fewer than three patients a week underwent scalp cooling.

More intense usage of scalp cooling lowered the costs for the machine per session from €24 to €12, but will increase the costs of nursing time. However, while in one hospital nurses spent extra time due to additional methods of fitting the cap -which are not used in any other hospital- nursing time per patient has been somewhat overestimated in this study. The occupation of a bed or chair may become an important additional cost aspect for the cost-effectiveness of scalp cooling, whereas occupation grades of day care units rise. Consequently, cost limits for planning scalp cooling is important, e.g. by shortening the post-infusion cooling time.<sup>29</sup>

For patients who had purchased a wig, somewhat higher prices per wig were found in the non scalp-cooled patient group, as also a somewhat higher mean number of wigs per patient. This might be explained by scalp-cooled patients who buy the wig as a precaution and therefore might spend somewhat less money, but also do not buy an additional wig when scalp cooling is successful.

Health-related QoL as measured with a generic questionnaire was comparable for scalp-cooled and non scalp-cooled patients. The benefits for successful scalp-cooled patients were

probably balanced by those without success<sup>1</sup>, which is 50% of those on FEC chemotherapy. Results can be improved when optimal temperatures and cooling times per chemotherapy type are known.

We used the SF-36 derived SF-6D questionnaire as we expected it to be more sensitive in measuring the effects of scalp cooling than for example the EQ-5D, although no Dutch tariff is available for this questionnaire. We do not expect that using the EQ-5D would have changed our results. On the one hand the EQ-5D does result in lower valuations than the SF-6D<sup>30</sup>, but on the other hand Dutch valuations are higher than UK valuations<sup>31</sup>, which may offset each other. Furthermore, as both the SF-6D valuations and the VAS results did not differ between both groups, it is not to be expected that the results would have been different when using the EQ-5D or other generic QoL measures.

This non-randomised study has some limitations. Firstly the approach to the supply of wigs and head covering differs between countries. Therefore, our cost-effectiveness model may have to be adapted according to the local situation. Secondly, there are missing data, especially at six and twelve months after completing chemotherapy. Missings were equally distributed among scalp-cooled and non scalp-cooled patients, and we do not expect patients with missing data to have had a worse or better general QoL, because of the fairly homogenous group of patients. Missing imputation was used to account for the missings. Third, differences in wig purchasing between scalp-cooled and non scalp-cooled patients might be somewhat biased by the inclusion of 44% of the non scalp-cooled patients in hospitals that offered scalp cooling. Since these patients did not choose to prevent alopecia by scalp cooling, they might have been less concerned about their appearance. Therefore their QoL might be less influenced by hair loss and they might spend less on head covers and wigs, which might have resulted in an underestimation of the cost-effectiveness of scalp cooling.

This is a first effort to study cost-effectiveness of scalp cooling, which will be subject to change in the near future, while there is certainly much room for improvement. Costs will decrease when scalp-cooled patients delay wig purchase and when patients are more accurately selected for scalp cooling. A high success rate of scalp cooling is needed to attain adequate cost-effectiveness, which will differ per patient group with a certain chemotherapy type and dosage. The rather low costs may be an extra incentive for oncological professionals to offer scalp cooling as a generally highly appreciated service to their patients.

## Acknowledgements

Special thanks go to all patients who participated in the study, to M. Peerbooms and A. Willemse who assisted in data collection and control, A. Krol, MD, PhD, at the Leiden University Medical Center, who was willing to function as an independent advisor and to answer questions of patients. Furthermore, we thank the nurses and doctors who performed the study in the following hospitals: A.Schweitzer, Dordrecht; AvL/NKI, Amsterdam; Elkerliek, Helmond; Gelre, Apeldoorn; Havenziekenhuis, Rotterdam; Leids Universitair Medisch Centrum; Máxima Medisch Centrum, Eindhoven; Medisch Centrum Alkmaar; Mesos Medisch

Centrum, Utrecht; Refaja, Stadskanaal; St. Lucas, Winschoten; Slingeland, Doetinchem; Spaarne, Hoofddorp; Twee Steden, Tilburg; Ziekenhuis Zevenaar.

This study was supported by ZonMw (grant number 945-07-002), the Netherlands organisation for health research and development. Author LP was supported by a Cancer Research Award from the Dutch Cancer Society (#UVT-2009-4349).

## References

1. Hurk van den CJ, Mols F, Vingerhoets AJ, Breed WP. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psycho-oncology*. 2010; 19: 701-9.
2. Carelle N, Piotto E, Bellanger A, Germanaud J, Thuillier A, Khayat D. Changing patient perceptions of the side effects of cancer chemotherapy. *Cancer*. 2002; 95: 155-63.
3. Munstedt K, Manthey N, Sachsse S, Vahrson H. Changes in self-concept and body image during alopecia induced cancer chemotherapy. *Support Care Cancer*. 1997; 5: 139-43.
4. Mulders M, Vingerhoets A, Breed W. The impact of cancer and chemotherapy: Perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nurs*. 2008; 12: 97-102.
5. Macquart-Moulin G, Viens P, Bouscary ML, Genre D, Resbeut M, Gravis G, et al. Discordance between physicians' estimations and breast cancer patients' self-assessment of side-effects of chemotherapy: an issue for quality of care. *Br J Cancer*. 1997; 76: 1640-5.
6. Sukel MP, van de Poll-Franse LV, Nieuwenhuijzen GA, Vreugdenhil G, Herings RM, Coebergh JW, et al. Substantial increase in the use of adjuvant systemic treatment for early stage breast cancer reflects changes in guidelines in the period 1990-2006 in the southeastern Netherlands. *Eur J Cancer*. 2008; 44: 1846-54.
7. Breed WPM, Hurk van den CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss; scalp cooling potentials and limitations. *Exp Rev Dermatol*. 2011; 6: 109-25.
8. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol*. 2005; 16: 352-58.
9. Auvinen PK, Mahonen UA, Soininen KM, Paananen PK, Ranta-Koponen PH, Saavalainen IE, et al. The effectiveness of a scalp cooling cap in preventing chemotherapy-induced alopecia. *Tumori*. 2010; 96: 271-5.
10. Wang J, Lu Z, Au JL. Protection against chemotherapy-induced alopecia. *Pharma Res*. 2006; 23: 2505-14.
11. Hussein AM. Chemotherapy-induced alopecia: new developments. *South Med J*. 1993; 86: 489-96.
12. Trueb RM. Chemotherapy-induced alopecia. *Sem Cut Med Surg*. 2009; 28: 11-4.
13. Benjamin B, Ziginas D, Harman J, Meakin T. Pulsed electrostatic fields (ETG) to reduce hair loss in women undergoing chemotherapy for breast carcinoma: a pilot study. *Psych Oncol*. 2002; 11: 244-8.
14. Shiao TK, Shiao TK, Shiao JC. Successful treatment of chemotherapy-induced alopecia with LaserCap: a case report. *Hair Transplant Forum International*. 2010; 156.
15. Hurk van den CJG, Breed WPM, Mols F. Chemotherapy-induced hair loss. In: Preedy Ve, ed. *Handbook of Hair in Health and Disease*. Wageningen, The Netherlands: Wageningen Academic Publishers 2012:403-16.
16. Statistics Netherlands. Consumer price index. April 2010 [Available from: [www.cbs.nl](http://www.cbs.nl), cited 2010 Sept 09]
17. Oostenbrink JB, Bouwmans CAM, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek. Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. 2004 [in Dutch].
18. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care*. 2004; 42: 851-9.
19. Brazier JE, Rowen D, Mavranzeouli I, Tsuchiya A, Young T, Yang Y, et al. Developing and testing methods for deriving preference-based measures of health from condition-specific measures (and other patient-based measures of outcome). *Health Tech Assess*. 2012; 16: 1-114.
20. McDonough CM, Tosteson AN. Measuring preferences for cost-utility analysis: how choice of method may influence decision-making. *PharmacoEcon*. 2007; 25: 93-106.
21. Stiggelbout AM, Eijkemans MJ, Kiebert GM, Kievit J, Leer JW, De Haes HJ. The 'utility' of the visual analog scale in medical decision making and technology assessment. Is it an alternative to the time trade-off? *Int J Tech Assess Health Care*. 1996; 12: 291-8.

22. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics Med.* 1999; 18: 681-94.
23. Fenwick E, Marshall DA, Levy AR, Nichol G. Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. *BMC health serv res.* 2006; 6: 52.
24. Council for Public Health and Health Care (Raad voor de Volksgezondheid en Zorg). *Sensible and sustainable care.* 2006.
25. Smulders YM, Thijs A. [The cost per year of life gained: trends and internal contradictions]. *NTvG.* 2006; 150: 2467-70.
26. Bernard M, Brignone M, Adehossi A, Pefoura S, Briquet C, Chouaid C, et al. Perception of alopecia by patients requiring chemotherapy for non-small-cell lung cancer: a willingness to pay study. *Lung Cancer.* 2011; 72: 114-8.
27. Hurk van den CJG, Akker van den -van Marle ME, Breed WPM, Poll van de-Franse LV, Nortier JWR, Coebergh JWW. Impact of scalp cooling on chemotherapy-induced alopecia, wig use and hair growth of patients with cancer. *J Oncol Nurse* (in press). 2013.
28. Hurk van den CJ, Peerbooms M, van de Poll-Franse LV, Nortier JW, Coebergh JW, Breed WP. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - results of the Dutch Scalp Cooling Registry. *Acta Oncol.* 2012; 51: 497-504.
29. Hurk van den CJ, Breed WP, Nortier JW. Short post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia. *Supp Care Cancer.* 2012; 20: 3255-60.
30. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Econ.* 2004; 13: 873-84.
31. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ.* 2006; 15: 1121-32.





# Chapter 11



Discussion



In this thesis we addressed various aspects of the safety and effectiveness of scalp cooling to prevent hair loss caused by chemotherapy in patients with cancer. In addition we studied the impact of chemotherapy-induced alopecia (CIA) on Quality of Life (QoL) and we performed a cost-effectiveness analysis of scalp cooling for certain regimens. In this chapter, the results of these studies will be placed in a broader perspective and some issues and implications will be discussed, including some directions for further implementation and future research.

To summarize, our research showed that:

- Scalp cooling seems to be indicated for a broad variety of currently used chemotherapies in cancer patients with solid tumors (chapter 5).
- In general, 50% of the patients are satisfied with the scalp cooling result (chapter 5), significantly reducing CIA and wig and head cover use (chapter 7). However, results can and need to be further improved in the near future by fine-tuning indications and methods through future studies, which also improves cost-effectiveness (chapter 10).
- Methods of scalp cooling can be optimized, as shown by shortening the post-infusion cooling time (PICT) for 3-weekly docetaxel from 90 to 45 minutes (chapter 6).
- The incidence of (scalp) skin metastases in breast cancer is very low (chapter 2 and 3) and the risk of leaving metastasis untreated by scalp cooling in breast cancer patients has been refuted (chapter 4).
- Breast cancer patients often reported a negative impact of CIA on QoL (chapter 8 and 9), although scalp cooling did not improve general QoL (chapter 8 and 10).
- Scalp cooling is cost-effective and can easily become more cost-effective (chapter 10).

## Safety of scalp cooling

Among medical professionals treating patients with cancer, safety of scalp cooling has been a major area of concern. The ultimate answer to this question would be to perform a randomized controlled trial in patients at risk for scalp skin metastases, with versus without scalp cooling during a chemotherapy schedule for which CIA can be prevented. However, we did and still do not consider this to be feasible with the aim to evaluate safety. Therefore we performed a retrospective analysis on the pattern of metastases in a large cohort of patients with metastatic breast cancer, who had not received scalp cooling (Chapter 2). Skin metastases were prevalent in 3% of these 33,771 patients from the Munich Cancer Registry, whereas skin metastases alone occurred late in follow-up and only in 0.6%. Exclusive occurrence of a scalp skin metastasis could indicate an increased risk of scalp cooling. In the Munich registry the location of the skin metastases was not registered, but from other series it appears that a scalp skin metastasis as the only site of relapse is extremely rare. We analysed the incidence of skin metastases after a median follow-up of 110 months in 885 Dutch patients with high-risk, early stage breast cancer, who had received a conventional or intensified dose adjuvant chemotherapy (Chapter 3). Twenty-five of these patients (3%), all of whom did not receive scalp cooling, developed skin metastases, four of them (0.5%) on the scalp. In these four patients the scalp skin metastases were always accompanied by metastases at other sites.

To assess the risk in patients who received scalp cooling, a patient file investigation was done in 390 patients with breast cancer in four Dutch hospitals (Chapter 3). After a median follow-up of 26 months two (0.5%) scalp-cooled patients developed scalp skin metastases. Both patients already had metastases at other sites before the start of chemotherapy (M1). A relation of the occurrence of scalp skin metastases with scalp cooling was unlikely.

For breast cancer patients we conclude that the scalp apparently is not a good seeding ground for metastases despite the intense vascularisation. As we did not find a difference in the incidence of scalp skin metastases in patients treated with or without adjuvant chemotherapy (Chapter 4), it seems unlikely that micro-metastases are effectively eliminated by adjuvant chemotherapy on that location. In thousands of patients with solid tumors who have been treated with scalp cooling in the adjuvant setting, an unfavourable outcome due to scalp skin metastases has never been reported.

Another safety aspect is the risk for metastases in the skull and brain or primary brain tumors. A model from the Technical University in Eindhoven showed that during scalp cooling the temperature decreased in the outer part of the skull, but only minimal in the outer part of the brain.<sup>1</sup> These temperatures have however never been measured in vivo. The skull contains bone marrow that possibly could host disseminated tumor cells. So if temperatures would significantly decrease by scalp cooling, the cytotoxic effect could in theory be less effective. However, in one systematic cohort study after scalp cooling it was concluded that there was no increase in scalp skin, skull or brain metastases.<sup>2</sup>

Unpublished results of our research group showed that general body temperature did not decline during four hours of scalp cooling, indicating no risk for an overall decreased cytotoxic effect.

In some hospitals the presence of bone metastases in the palliative setting or more than four positive lymph nodes after staging of early breast cancer-reflecting a high risk for micro metastases- are restrictions for scalp cooling in breast cancer patients. In our opinion there are no data to support these restrictions. Skin metastases do not occur more often in patients with bone metastases and the temperature of the skull decreases minimally during scalp cooling. Besides, in high risk (N4+) breast cancer patients, the incidence of scalp skin metastases turns out to be very low (Chapter 3).

Theoretically, frost bite could be a side-effect of scalp cooling, but the scalp skin temperature never decreases to such an extent that this could happen; Accordingly to this fact it has never been reported when using scalp cooling machines.

## Effectiveness and determinants of scalp cooling

Results of scalp cooling have been described from 1411 patients treated in 28 hospitals in the Netherlands, as they are recorded in the Dutch Scalp Cooling Registry (Chapter 5). Besides type of chemotherapy, higher dose, shorter infusion time, older age, female gender and non-West-European type of hair significantly increased the proportion head cover use. Hair wetting, length, quantity and chemical manipulation (dyeing, colouring, waving) and previous

treatment with chemotherapy did not influence the degree of head covering among the patients. However, confirmation of these findings is certainly warranted.

Overall, about 50% of the scalp-cooled patients treated with anthracyclines did not wear a wig or head cover during their last chemotherapy session (Chapter 5). Three-weekly docetaxel monotherapy resulted in a better outcome: 60-90% did not wear a head cover, depending on the dose. These data on docetaxel monotherapy are promising, also for men with advanced prostate cancer who are candidates for palliative chemotherapy. Nevertheless, the added value of scalp cooling is probably higher for anthracyclines, as these might more often cause severe hair loss without scalp cooling (95%<sup>3</sup> vs 70%<sup>4</sup>). For most types and doses of chemotherapy the incidence of CIA without scalp cooling is still lacking, it varies tremendously and is underestimated in phase II and III trials.<sup>4</sup> On the contrary the incidence is often overestimated by Medical Doctors (MDs) from their clinical point of view.<sup>3</sup> Hence, the overall real effectiveness of scalp cooling will at least be somewhat lower than the currently reported 50%.

The at present frequently used combination of docetaxel, doxorubicin and cyclophosphamide (TAC) did not result in a decrease of hair loss after scalp cooling (Chapter 5). Therefore, if patients with early stage breast cancer for whom adjuvant chemotherapy is indicated want to have a reasonable chance not to loose their hair, they should not be treated with the combination of an anthracycline and a taxane, but in a sequence. The recently updated guideline on the treatment of breast cancer in the Netherlands contains several sequential schedules for the indication of adjuvant chemotherapy: FEC x3 followed by docetaxel monotherapy x3, or AC x4 followed by docetaxel monotherapy x4, or paclitaxel monotherapy x12.<sup>5</sup> Data on the results of scalp cooling with weekly paclitaxel are limited due to the logistic burden, but it seems that about 80% of the patients wear no head covering (Chapter 5).

For 3-weekly docetaxel chemotherapy the rather arbitrarily chosen PICT of 90 minutes can be shortened to 45 minutes with the same effectiveness of scalp cooling (Chapter 6). At present we are shortening this PICT further to 20 minutes in a randomized controlled trial.

Lack of evidence on the effectiveness of scalp cooling is one of the most important reasons for the moderate application in daily practice in the Netherlands. Scalp cooling has been reported to be effective in 6 out of 7 randomized controlled trials.<sup>6</sup> However, these trials were underpowered and currently outdated, because of the used chemotherapy regimens. The non-randomized studies with control groups mostly reported multiple combinations of also outdated chemotherapies.<sup>6</sup> Therefore, new non-randomized studies with adequate control groups and randomized trials with schedules causing substantial hair loss are needed for the interest of the patients.

In chapter 7, scalp cooling resulted in a 40% reduction of wig and head cover use for patients treated with anthracyclines or taxanes. The degree of CIA was evaluated using three subjective scales. We found high correlation between the WHO score for alopecia and a Visual Analogue Scale (VAS), but only moderate correlation with the use of a wig or head cover. So, perception of the amount of hair loss does not correspond well with the patients' need for head covering. In our opinion, patients' satisfaction with the result should be added

as an important value for evaluating scalp cooling. Internationally, a broad diversity of scalp cooling evaluation methods is used<sup>7</sup>, which is undesirable for comparing and pooling data.<sup>8</sup> Therefore, we recently initiated the development of a common internationally validated, patient reported questionnaire to measure severity of CIA, as well as its impact on QoL. For research purposes we now use the Hair Check device, an additional objective measure for hair quantity.<sup>9-11</sup> It is however too time consuming to use in daily clinical practice.

At last, not only quantity but also quality of hair after scalp cooling is important and showed to be satisfactory (Chapter 7). Most patients reported their hair to have become somewhat dryer and static, but changes in colour or texture –like in non scalp-cooled patients<sup>8</sup>- have never been reported. We found no association of dyeing, colouring or waving hair and the result of scalp cooling (Chapter 5). Therefore, patients are advised to treat their hair with care, but in our opinion they can colour or wave it between chemotherapy sessions (using least aggressive products), otherwise an undesirable hair dress arises.

### The impact of CIA on QoL

Breast cancer patients who received chemotherapy, with or without scalp cooling, expected and perceived CIA as one of the most burdensome side-effects of cancer treatment, even after six months (Chapter 8). Repeatedly patients state that they thought to be prepared, but when hair loss actually occurred, it was even more impressive than they ever expected. A self-developed questionnaire showed that even though patients knew that CIA was temporary, half of them reported the hair loss to be a problem and a burden (Chapter 9). The majority also reported that they did not feel attractive because of CIA.

Despite this reported high impact, we observed only a trend towards a better QoL and body-image when scalp cooling was successful (Chapter 8). In the cost-effectiveness study of chapter 10, even no difference in QoL was observed between scalp-cooled and non scalp-cooled patients. Apparently, the currently used validated QoL questionnaires are not sensitive enough to distinguish the impact of CIA on general QoL, not even when CIA is part of the questionnaire (EORTC-BR23).<sup>12</sup> Besides, in the cost-effectiveness study the benefits for successful scalp-cooled patients are probably balanced by those without success. Wig use might mitigate the burden of CIA, but will never fully compensate the loss.

Additional distress seemed to be caused when patients lost their hair despite scalp cooling (Chapter 8). Therefore, it should not be offered when the chance for hair preservation is low and extra attention should be paid to patients to cope with CIA when scalp cooling is unsuccessful.

In chapter 9, one third of the scalp-cooled breast cancer patients reported that the cooling was a burden to them. The psychological aspect in these was the uncertainty about the final scalp cooling result, mentioned by two third of the women. Until we know whether scalp cooling will be effective for an individual patient, they all have to be prepared for potential hair loss. MDs and nurses play an important role in preparing for and coping with CIA. However, they often only reveal it during the information conversation about chemotherapy, but refrain from discussing it when it actually happens. The impact of CIA is probably still

underestimated by many MDs and nurses<sup>13</sup>, because patients do not often mention the issue during a consult or in aftercare.

The physical aspect of the burden of scalp cooling concerned that half of the patients reported to tolerate it, but they mentioned coldness (39%), headaches (24%), dizziness (20%) and a heavy cool cap (29%) (Chapter 9). For this study it is unknown how many patients stopped scalp cooling because of intolerance, but in our other studies and in the literature it is mostly below 5%. In chapter 6, patients reported a mean of 7.9 on a Visual Analogue Scale (VAS) for tolerability (range 0-10, 10 being very well acceptable), 80% reported no headache and 13% a moderate headache. Therefore, we hold to the general conclusion that scalp cooling as performed nowadays is well tolerated by patients.

### Cost-effectiveness

Scalp cooling appeared to be €269 less expensive than usual care, i.e. purchasing a wig or head cover, when measured among mainly breast cancer patients (Chapter 10). However, scalp cooling did not add to the Quality Adjusted Life Years (QALYs) in comparison with non scalp-cooled patients. Overall, scalp cooling was cost-effective and it seems justified to offer both, scalp cooling and usual care, to the patient. Cost-effectiveness can however be improved easily, first by reducing wig purchasing: 38% of the scalp-cooled patients who bought a wig did not use it (Chapter 7). Further improvement is also possible by adapting indications for scalp cooling, e.g. not offering it to patients for whom scalp cooling has no added value (as for TAC chemotherapy) and only start scalp cooling if the patient is really motivated to try it. Besides, cost-effectiveness improves by obtaining better scalp cooling results, and therefore research is indispensable.

One drawback of the study, which will decrease cost-effectiveness, is not having taken into account the time for occupying a bed or chair in the hospital. This aspect was not an issue during the inclusion period. However, as time pressure on day care units increases, it might become more of an issue for scalp cooling.

At the end, the rather low costs may be an extra incentive for oncological professionals to offer scalp cooling as a generally highly appreciated service to their patients.

In the Netherlands, at present the service of scalp cooling is paid by the hospital while insurance companies save money because of fewer reimbursements for wigs. More equal distribution of costs and benefits would be achieved when including scalp cooling in the DOT (Diagnose behandel combinatie Op weg naar Transparantie). However, then scalp cooling is required to be standard care and has to be incorporated in the protocols, which does not apply for most Dutch hospitals yet.

### Directions for further implementation of scalp cooling in the Netherlands - Give him/her and hair a chance

In the Netherlands, the number of scalp cooling hospitals has increased rapidly since 2006 (Figure 1), but it is still not offered in about 20% of the hospitals that provide chemotherapy. This figure is comparable to the UK (no scalp cooling: 22%) and Scandinavian countries (no scalp cooling: Finland 0%, Norway 22%, Sweden 54%). In the rest of Europe and other parts



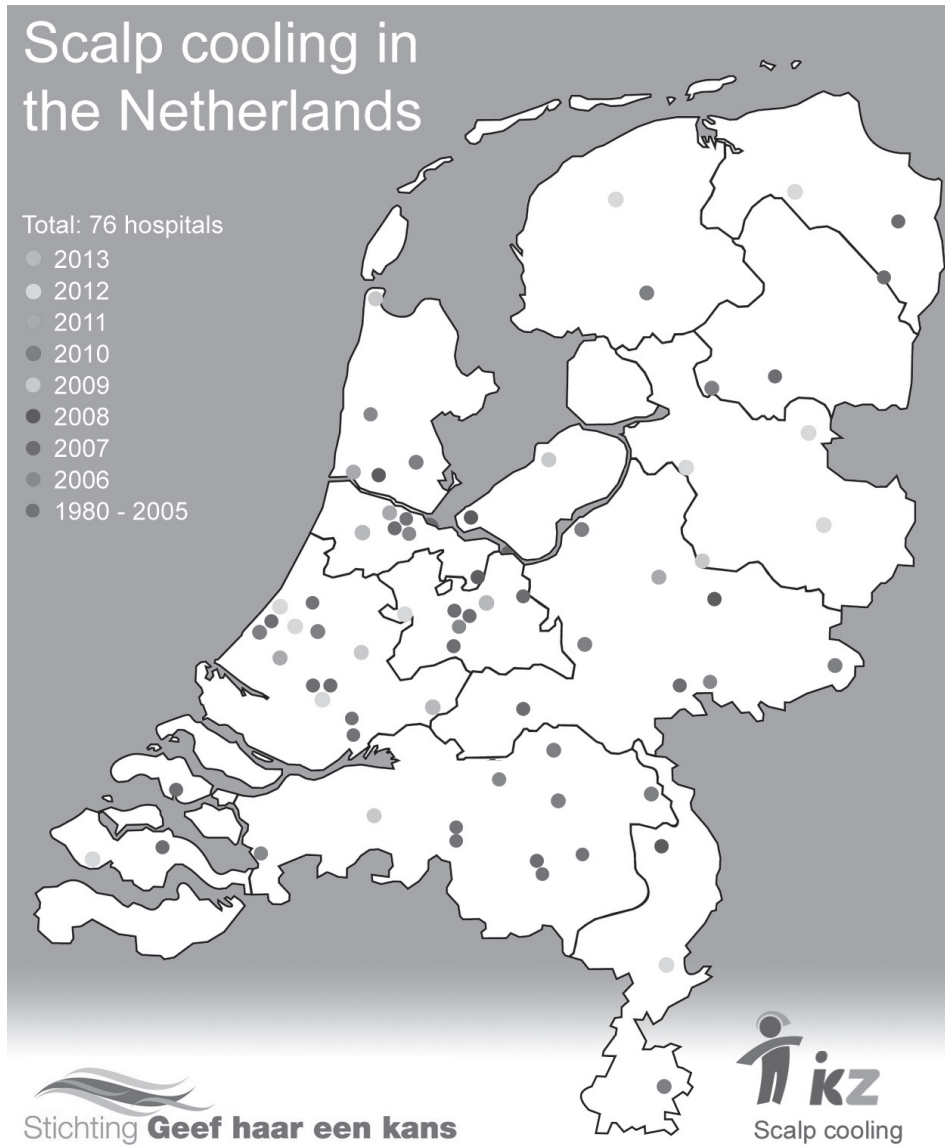


Figure 1. Map of Dutch scalp cooling hospitals 2005 - 2013.

of the world scalp cooling is minimally offered. In 2010, there were about 900 scalp cooling machines in use across 20 countries, which has increased to about 1800 in 35 countries in 2013.

Currently scalp cooling is offered to only a small proportion of patients in Dutch hospitals receiving chemotherapy with a high chance of severe hair loss. Even in chemotherapy schedules in which very good hair preservation can be obtained, like with docetaxel monotherapy, it is often not offered. Data of the cost-effectiveness study showed that in current practice 52% of the patients were good candidates for scalp cooling ( $n=1898$ ), but 66% of them ( $n=1250$ ) were not treated with scalp cooling. In 48% of these 1250 non scalp-cooled patients it had not been offered, and the reason why was unknown. Most of the remaining patients had rejected scalp cooling. In chapter 10 we report that the scalp cooling device is on average used for less than three patients per week. However, in other hospitals -e.g. the Albert Schweitzer hospital in Dordrecht and the Medical Centre Alkmaar- a number of machines are in use daily, treating several patients a day.

The restricted application of scalp cooling has various reasons (Textbox 1). Cooling capacity might be too low and time constraints might be an important reason. However, in the more than 75 Dutch hospitals in which scalp cooling is performed, potential logistic problems have frequently be solved by changes in planning or by transferring the patient to another room during the PICT. The extra nursing time could be compensated when scalp cooling would be reimbursed by health insurance companies or when volunteers are instructed to (partly) take care of the procedure.

Scalp cooling restrictions can induce undertreatment and limit the patients' well-being by causing unnecessary CIA. Health care professionals should not select patients based on their own opinions on CIA and scalp cooling. Our studies showed that the large majority of scalp-cooled patients were women with breast cancer. It seems that it is offered on a regular basis to this patient group only, and not or to a lesser extent to patients with other cancers who are facing CIA, like in ovarian, colorectal, prostate, lung and endometrial cancer. Also adolescents with solid tumors<sup>14</sup>, elderly and men with cancer<sup>15</sup> are overlooked. In chapter 6 we showed that 37% of the included 129 scalp-cooled patients were men, which is about 50% in the currently ongoing PICT trial. It suggests that in these studies it has more actively been offered to them.

Undertreatment with scalp cooling also seems to occur for immigrants. In our cost-effectiveness study only four of the 160 scalp-cooled patients were of non Caucasian origin (Chapter 10). Based on cancer registry data, we expected this to be 10 out of 160 patients.<sup>16</sup> It is noteworthy that for women who wear a scarf for religious reasons, hair is an important aspect in family life.<sup>17,18</sup>

Patient information on scalp cooling from oncologists and oncology nurses will likely be decisive for most patients. Therefore, patients facing CIA should receive the right information on the possibility, effectiveness, possible side-effects and potential risk of scalp cooling for their specific situation in order to make an informed treatment decision. If the patient is

a good candidate for scalp cooling, the decision will finally depend on how important the preservation of hair is for a patient and how he or she can cope with the uncertainty on the result and the risk of scalp cooling.

In one of our studies a substantial proportion of oncologists and oncology nurses reported that they consider their knowledge about scalp cooling to be insufficient to fully inform the patient.<sup>19</sup> Besides, patient information about scalp cooling is still hardly addressed for example in leaflets of the Dutch Cancer Society or in the automatically generated patient information about side-effects of chemotherapy called 'SIB op Maat' in the Netherlands. For these reasons we have compiled extensive information under the name 'Standard for CIA' to increase the knowledge on scalp cooling amongst MDs and nurses. In addition, websites with information for oncological care givers and patients has been developed ([www.hoofdhuidkoeling.nl/](http://www.hoofdhuidkoeling.nl/) [www.geefhaareenkans.nl/](http://www.geefhaareenkans.nl/)), as well as patient leaflets. To implement the patient information we want to closely cooperate with patient organisations.

**Textbox 1.** Reasons for restrictions in offering scalp cooling by nurses and MDs.

**Logistics/ context**

- Cooling capacity is too low
- Time constraints in logistics or nursing time
- Scalp cooling is not incorporated in the protocol and therefore not in standard care
- Not broadening indications after starting scalp cooling for only a restricted patient group
- No financial incentive

**Knowledge**

- Underestimation of the impact of CIA
- Overestimation of the burden of scalp cooling
- Lack of knowledge about the current situation in literature and in the Netherlands

**Safety/effectiveness**

- Uncertainty about the risk of scalp skin metastases
- Difficulties in explaining the risk of scalp skin metastases to patients
- Effectiveness is regarded insufficient, too less added value compared to no scalp cooling

**Awareness/ attitude**

- Own opinion about CIA and scalp cooling
- Differences in opinion about scalp cooling in the oncological team
- Difficulties in explaining whether several patients are good candidates for scalp cooling and others are not
- Patients do not ask for scalp cooling

## Directions for future research (Textbox 2)

### Effectiveness

We already mentioned the need for new non-randomized studies with adequate control groups and randomized trials on effectiveness and a common internationally validated evaluation method for CIA. Furthermore, in order to improve effectiveness and minimize the burden of scalp cooling, studying the optimal temperature is in our opinion the most important factor. Also because cold-sensation is besides headaches the major complaint during scalp cooling. However, when it shows that the temperature needs to be lowered, we do not expect the tolerance to be much affected, as reported by volunteers in whom wetting the hair caused a 5°C lower scalp skin temperature (I. Muhanna et al., unpublished data). The second most important associated factor to be studied is PICT, which may imply shortening the discomfort and the extra time in the hospital.

Scalp cooling research on dose-response relationship (cooling temperature and time) needs to be conducted more efficiently, firstly by using a research model in which the patient is its own control. The advantages are the small number of patients needed to draw conclusions

### Textbox 2. Remaining research topics.

#### **Effectiveness**

- Real effectiveness of scalp cooling, i.e. compared to CIA in non scalp-cooled patients
- Dose-effect relation regarding scalp cooling time and temperature
- Determinants of the scalp cooling result, like: age, gender, chemotherapy type, dose and infusion time, alopecia-inducing chemotherapy ever before, the hair length and quantity, the type of hair determined by ethnical background, hair dyed, waved or coloured, use of water or hair conditioner before the start of scalp cooling
- Effect of cytotoxics and hypothermia on damage and survival of hair matrix cells
- Clinically feasible quantitative measure for CIA
- Clinically feasible scalp skin temperature measure

#### **Safety**

- Survival and pattern of metastases of scalp-cooled versus non scalp-cooled patients
- Skull and brain temperature during scalp cooling

#### **Quality of life**

- Common internationally validated questionnaire examining CIA and its impact on QoL
- Impact of CIA on beloved ones, male patients, return to work or when wearing a head cover for religious reasons
- Pattern of hair loss during scalp cooling
- Quality and growth of hair during and after scalp cooling

and the elimination of many potential confounding factors. In this model a small part at one side of the scalp would be treated differently (e.g. cooling temperature or time) and hair loss is compared with the remaining part of the scalp. One practical application would be evaluation of the effectiveness of wetting the hair during scalp cooling, which is done in some Dutch and many foreign hospitals. Secondly, pre-clinical research may accelerate clinical research by generating and testing hypotheses, as recently started in a collaborative initiative with Huddersfield University (UK). Keratinocyte cell lines are exposed to cytotoxics using different temperatures and exposure times.

Why does scalp cooling succeed in one patient and fails in another patient with the same clinical characteristics? Is it the proportion of anagen hairs, rate of cytotoxic clearance, or maybe internal temperature regulation towards the scalp skin? We do not know yet.

Inter-individual differences in biological availability of cytotoxics is common knowledge, but pharmacokinetics in hair matrix cells have not been unravelled<sup>8</sup> and might be important for PICTs. We neither know how hypothermia may influence these pharmacokinetics. As shown in chapter 5, cytotoxic damage of hairs seems to be more extensive using shorter infusion times. So peak plasma concentration may be more important for the damage than the exposure time?

To improve effectiveness it is helpful to know which scalp cooling working mechanism is most important (Figure 2). Possibly it is the reduced exposure of hair matrix cells by vasoconstriction and a reduced perfusion? Or is it mainly about the lower metabolism in the cells? Or do we overlook an additional mechanism, like e.g. a stress reaction of the cells due to the cold? It is also unknown to what extent cell activity has to be reduced and whether cytotoxic damage or recovering after damage are most important for hair matrix cells to survive chemotherapy. Recovering may start as soon as scalp skin temperature is rising again, which would be an indication for shortening PICTs.

Hypothermia		
Perfusion ↓ ▼	Metabolism ↓ ▼	Metabolism ↓ ▼
Concentration of cytotoxics in hair matrix cells ↓	<i>Cell membrane</i> if active transport: cytotoxic influx ↓  <i>Intracellular</i> cell mitosis ↓ toxic reactions ↓	<i>Cell membrane</i> if active transport: cytotoxic outflow ↓  <i>Intracellular</i> repair mechanisms ↓
▼ Hair matrix cell † ↓	▼ Hair matrix cell † ↓ (damage ↓)	▼ Hair matrix cell † ↑ (repair ↓)
▼ Hair loss ↓	▼ Hair loss ↓	▼ Hair loss ↑

**Figure 2.** Proposed working mechanism of scalp cooling (Adapted from Breed et al.<sup>7</sup>).  
↓ decrease, † death, ↑ increase

## Safety

In order to provide more conclusive knowledge on the safety of scalp cooling, data are needed from large patient groups treated with adjuvant chemotherapy, which are prospectively followed for several years (depending on the primary tumor site). Especially in breast cancer, first recurrence of the disease may occur more than ten years after initial diagnosis. Our ongoing scalp cooling registry offers possibilities for monitoring this issue, when linked with the cancer registry. The most important outcome measure would be survival after chemotherapy with and without scalp cooling, although this knowledge may become outdated when regimens have changed. It would also be interesting to use information on patterns of metastases, which is however not yet available in the Dutch cancer registry.

Another challenge for research is to measure skull and brain temperature during scalp cooling. Then the reliability of Janssen's mathematical model<sup>1</sup> could be verified. There is however, to our knowledge, no appropriate measurement method available yet.

## Continuation, differentiation and patient information

Due to the changing chemotherapy regimens and protocols and the improvement of scalp cooling techniques, continuation of our registry is of utmost importance for decision making for patients who are facing CIA. Besides, it offers practical information since we can compare results, scalp cooling methods and indications between hospitals. Optimization of cooling methods will have to be evaluated for the different types of chemotherapy, while they have distinct mechanisms of action and therefore CIA can not be perceived as one entity.<sup>8</sup>

Anno 2013, cancer treatment is heading towards an individualised approach, which might also apply for scalp cooling. But this is only possible if we are able to identify specific patient characteristics to better predict whether scalp cooling will be effective in a certain situation and if we are able to improve and refine scalp cooling techniques.

The Dutch scalp cooling network has expanded from 4 hospitals in 2005 to more than 75 hospitals in 2013 (Figure 1). This increase is the result of clinical research performed since 2005, cooperation of and registration by many MDs and nurses, and donation of more than 100 scalp cooling machines by the Roparun Foundation. For the future there is an urgent need to improve the results, to increase the knowledge on scalp cooling among MDs and nurses and to improve patient's familiarity on the usefulness of scalp cooling.<sup>19</sup> Hopefully this leads to a more frequent use and better acceptance by the medical community for the benefit of patients treated with chemotherapy schedules for which scalp cooling has been proven to be effective.

## References

1. Janssen FE. Modelling physiological and biochemical aspects of scalp cooling. Eindhoven: Technical University Eindhoven; MSc Thesis 2007.
2. Spaeth D, Luporsi E, Weber B, Guiu S, Braun D, Rios M, et al. Efficacy and safety of cooling helmets (CH) for the prevention of chemotherapy-induced alopecia (CIA): A prospective study of 911 patients (pts). *J Clin Oncol*. 2008; 26.
3. Geerts P, Hendriks M, van den Hurk C, Dercksen M, Breed W. Hair preservation in FEC-chemotherapy; not an exception. 2013; (Submitted).
4. Hurk van den CJ, Breed WP, Nortier JW. Short post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia. *Supp Care Cancer*. 2012; 20: 3255-60.
5. Oncoline. Guideline mamma carcinoma 2012 [Richtlijn mammacarcinoom 2012]. [Available from: <http://www.oncoline.nl/mammacarcinoom>]
6. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol*. 2005; 16: 352-58.
7. Breed WPM, Hurk van den CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss; scalp cooling potentials and limitations. *Exp Rev Dermatol*. 2011; 6: 109-25.
8. Paus R, Haslam IS, Sharov AA, Botchkarev VA. Pathobiology of chemotherapy-induced hair loss. *Lancet Oncol*. 2013; 14: e50-9.
9. Cohen B. The cross-section trichometer: a new device for measuring hair quantity, hair loss, and hair growth. *Dermatol Surg*. 2008; 34: 900-10; discussion 10-1.
10. Vleut RE, van Poppel, J.E.A.M., Dercksen, M.W., Peerbooms, M., Houterman, S., Breed, W.P.M. Hair Mass Index, obtained by cross-section trichometry: an objective and clinically useful parameter to quantify hair in chemotherapy induced alopecia. *Supp Care Cancer*. 2012; 21: 1807-14.
11. Hendriks MAE, Geerts PAF, Dercksen PAF, van den Hurk CJG, Breed WPM. Evaluation of Cohen's Cross-Section Trichometer for Measuring Hair Quantity. *Dermatol Surg*. 2013; 38: 631-4.
12. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *JNCI*. 1993; 85: 365-76.
13. Mulders M, Vingerhoets A, Breed W. The impact of cancer and chemotherapy: Perceptual similarities and differences between cancer patients, nurses and physicians. *Eur J Oncol Nurs*. 2008; 12: 97-102.
14. Atay S. Symptom characteristics and clustering in children and adolescents undergoing or being off cancer chemotherapy. *J Buon*. 2011; 16: 751-8.
15. Hilton S, Hunt K, Emslie C, Salinas M, Ziebland S. Have men been overlooked? A comparison of young men and women's experiences of chemotherapy-induced alopecia. *Psych Oncol*. 2008; 17: 577-83.
16. Visser O, van der Kooy K, van Peppen AM, Ory FG, van Leeuwen FE. Breast cancer risk among first-generation migrants in the Netherlands. *Br J Cancer*. 2004; 90: 2135-7.
17. Erol O, Can G, Aydinler A. Effects of alopecia on body image and quality of life of Turkish cancer women with or without headscarf. *Supp Care Cancer*. 2012; 20: 2349-56.
18. Can G, Demir M, Erol O, Aydinler A. A comparison of men and women's experiences of chemotherapy-induced alopecia. *Eur J Oncol Nurs*. 2013; 17: 255-60.
19. Peerbooms M, Breed WPM, van den Hurk CJG. Familiarity, opinions, experiences and knowledge about scalp cooling - A Dutch survey among breast cancer patients and oncological professionals. 2013; (submitted).
20. Brownstein MH, Helwig EB. Metastatic tumors of the skin. *Cancer*. 1972; 29: 1298-307.
21. Dean JC, Griffith S, Cetas TC, Mackel CL, Jones SE, Salmon SE. Scalp hypothermia: a comparison of ice packs and the kold kap in the prevention of doxorubicin-induced alopecia. *JCO*. 1983; 1: 33-7.
22. Lookingbill DP, Spangler N, Sexton FM. Skin involvement as the presenting sign of internal carcinoma. A retrospective study of 7316 cancer patients. *J Am Ac Dermatol*. 1990; 22: 19-26.

23. Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. *J Am Ac Dermatol.* 1993; 29: 228-36.
24. Lemieux J, Amireault C, Provencher L, Maunsell E. Incidence of scalp metastases in breast cancer: a retrospective cohort study in women who were offered scalp cooling. *Br Ca Res Treat.* 2009; 118: 547-52.
25. Sande van de MAE, Hurk van den CJG, Breed WPM, Nortier JWR. Hoofdhuidmetastasen bij hoogrisico borstkankerpatienten. *Ned Tijdschr Geneesk.* 2010; 154: A2134 [article in Dutch].
26. Lemieux J, Desbiens C, Hogue JC. Breast cancer scalp metastasis as first metastatic site after scalp cooling: two cases of occurrence after 7- and 9-year follow-up. *Br Ca Res Treat.* 2011; 128: 563-6.
27. Hurk van den CJG, Peerbooms M, Komen M, Nortier JWR, Smorenburg CH, Breed WPM. Multicenter results of scalp cooling to prevent chemotherapy-induced alopecia in 1500 breast cancer patients. *Suppl Cancer Res.* 2011; 71: 1s-653s Page 594s.
28. Hurk van den CJ, Mols F, Vingerhoets AJ, Breed WP. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psych Oncol.* 2010; 19: 701-9.
29. Hurk van den CJG, Akker van den -van Marle ME, Breed WPM, Poll van de-Franse LV, Nortier JWR, Coebergh JWW. Impact of scalp cooling on chemotherapy-induced alopecia, wig use and hair growth of patients with cancer *J Oncol Nurse* (accepted for publication). 2013.
30. Hurk van den CJ, Peerbooms M, van de Poll-Franse LV, Nortier JW, Coebergh JW, Breed WP. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - results of the Dutch Scalp Cooling Registry. *Acta Oncol.* 2012; 51: 497-504.





**Now this is not the end  
It is not even the beginning of the end  
But it is, perhaps, the end of the beginning**

W.S. Churchill, 20th November 1942



# Summary





---

## Summary

### Chapter 1 Hair loss and scalp cooling.

Various cytotoxics cause severe alopecia, it is estimated to affect more than 15,000 Dutch cancer patients per year. Hair loss has high impact on the majority of these patients, they describe it as stigmatizing and a constant reminder of cancer disease.

Hair matrix cells and cancer cells are rapidly dividing and therefore susceptible for damage by cytotoxics. Until now, scalp cooling is the only effective method to prevent severe hair loss. The rationale behind scalp cooling is vasoconstriction and a reduced biochemical activity. It is continuously applied 30 minutes before, during and in general 90 minutes after the cytotoxics infusion. It can be applied in all patients with solid tumors, however this thesis focuses on breast cancer patients.

Despite the fact that scalp cooling has been practiced for more than 40 years, still remarkably little research has been conducted, in particular in comparison with prevention of other side-effects of cancer treatment. Almost all previous studies evaluated solely effectiveness of scalp cooling, often for small groups of patients and outdated types of chemotherapy.

## PART I Safety

In **part I** we focus on the safety of scalp cooling in the adjuvant treatment setting. Scalp cooling induces a risk if it would protect micro-metastases in the scalp skin besides protection of hair matrix cells. The incidence of *skin* metastases and *scalp skin* metastases has been compared between scalp-cooled and non scalp-cooled breast cancer patients.

In **chapter 2** data from the Munich Cancer Registry showed a decreased general incidence of metastases in 33,771 non scalp-cooled patients without metastases at diagnosis in the period 1978-2003. However, in this period also unfavourable changes were exhibited in the pattern of metastases and no improvement was observed in survival of the patients after occurrence of metastases. The proportion of patients with *skin metastases* was 3% and it did not vary over the years, despite changes in type of systemic therapy. In 20% of the patients with *skin metastases alone* it was diagnosed more than 10 years after initial diagnosis. So safety of scalp cooling for this patient group should be studied using long follow-up times.

The incidence of *scalp skin metastases* appeared to be approximately 0.5% in Dutch cohorts of 885 non scalp-cooled and 390 scalp-cooled breast cancer patients (**chapter 3**). Scalp skin metastases always occurred at the same time or later than metastases elsewhere and are therefore not the lethal factor. Our studies as well as the literature showed that the incidence of scalp skin metastases is comparable for scalp-cooled (0.04-1%) and non scalp-cooled (0.03-3%) breast cancer patients (**chapter 4**). In thousands of patients with solid tumors, an unfavourable development of the disease due to scalp cooling has never been reported. It is therefore unlikely that the local efficacy of chemotherapy is decreased to such an extent, that the extremely low baseline risk increases.

## PART II Effectiveness

In **part II** effectiveness of scalp cooling was studied with respect to the purchase and use of wigs and head covers. Furthermore, factors associated with the scalp cooling result were studied.

Data from the Dutch Scalp Cooling Registry showed that overall 50% of the 1,411 scalp-cooled patients from 28 Dutch hospitals did not wear a head cover during their last chemotherapy session (**chapter 5**). However, satisfaction with the result varied from 8% of the patients after TAC chemotherapy (combination of Docetaxel, Doxorubicine and Cyclophosphamide) up to 95% after paclitaxel treatment. Moreover, type of chemotherapy, higher dose, shorter infusion time, older age, female gender, and non-West-European type of hair significantly increased the proportion of head cover use. Hair length, quantity and chemical manipulation (dyeing, waving, coloring), wetting hair before scalp cooling, and previous treatment with chemotherapy did not influence the results. Confirmation of our findings is certainly warranted. Only then more patient-tailored information can be provided and maybe scalp cooling techniques can be modified to further improve the effectiveness.

A randomized trial showed that the post-infusion cooling time (PICT) for 3-weekly docetaxel chemotherapy can be shortened from 90 to 45 minutes with the same effectiveness of scalp cooling (except TAC) (**chapter 6**). Scalp cooling was well tolerated: patients reported a Visual Analogue Scale score of 79 (range 0 not acceptable – 100 very well acceptable) and no head ache in 80% of the scalp cooling sessions.

Scalp cooling resulted in a 40% reduction of wig and head cover use and a significant decrease in severity of chemotherapy-induced alopecia (CIA) between scalp-cooled and non scalp-cooled patients (**chapter 7**). Among scalp-cooled patients who purchased a wig as a precaution, only 62% actually used it, which implicates unnecessary costs for patients and health insurance companies. The majority of patients reported that hair started to grow again three to six weeks after the last chemotherapy. One out of four scalp-cooled patients mentioned that hair kept growing also during chemotherapy. After half a year most of them were satisfied with their hair style.

## PART III Quality of life

In **part III** the impact of CIA on the well-being of scalp-cooled and non scalp-cooled breast cancer patients was studied. Scalp cooling was effective in 52% of the patients.

Alopecia was considered among the most distressing problems before initiating chemotherapy, and three weeks and six months after chemotherapy (**chapter 8**). Besides, scalp cooling not only tended to contribute to the health related quality of life (QoL) and body image of successfully scalp-cooled patients, but also seemed to cause additional distress when patients lost their hair despite scalp cooling. Therefore, extra attention should be paid to patients when scalp cooling is unsuccessful and again it stresses the need for improvement of the results.

Although patients knew that CIA was temporary, half of them reported that it was a burden and/or a problem. The majority also reported that they did not feel attractive anymore

because of the hair loss (**chapter 9**). Scalp cooling was a burden to 33% of the patients. They often mentioned the uncertainty about the final scalp cooling result and to a lesser extent coldness, headaches, dizziness or a heavy cool cap. Patients would therefore benefit from additional support regarding the uncertainty about hair loss and research on the optimum scalp cooling temperature. Most patients who used a wig or head cover were satisfied with it, but also many patients were constantly aware of it. Satisfaction with growth of the hair was moderate.

## PART IV Cost-effectiveness

Scalp cooling is cost-effective, as is purchasing a wig or head cover. This justifies the choice between both options (**chapter 10**). Average societal costs –incorporating scalp cooling, hair dressers, wigs and head covers- decreased €269 per scalp-cooled patient compared to non scalp-cooled patients. However, scalp cooling did not yield advantages in quality adjusted life years (QALYs). Cost-effectiveness can be improved by postponing wig and head cover purchases, by improving scalp cooling results, and by using the scalp cooling capacity more intensively.

### In conclusion

In **chapter 11** the findings of the studies presented in this thesis are discussed, placed into perspective and future directions for research have been drawn.

Scalp cooling seems to be safe in the adjuvant treatment setting, is effective for half of the patients, is cost-effective and overall well tolerable. However, real effectiveness remains unknown while the proportion of patients developing severe hair loss without scalp cooling is unknown. Effectiveness has to be and will be improved, preferably by examining optimal scalp skin temperatures and cooling times, with special attention for the patient's tolerance. Other niches to be studied are the impact of hypothermia on pharmacokinetics and –dynamics and the mechanisms of damage and repair at the hair matrix level.

The impact of CIA is high for many patients, but scalp cooling seems not to improve QoL when measured by general, validated questionnaires. Moreover, in each scalp cooling study different outcome parameters are used, which is undesirable for comparing the results. Therefore, a common internationally validated questionnaire should be developed to define the patient-reported amount of hair loss and its impact on QoL.

Finally, the safety of scalp cooling could be additionally studied by linking the scalp cooling registry to the cancer registry and evaluating the incidence of metastases and survival in comparison with non scalp-cooled patients.

At the time of starting this PhD project, four Dutch hospitals applied scalp cooling, which nowadays has increased to over 75. Though, in many hospitals scalp cooling eligibility criteria are too restricted, inducing undertreatment of several patient groups. All patients facing severe alopecia should receive patient-tailored information about the possibility, effectiveness, possible side-effects and potential risk of scalp cooling in order to make an informed treatment decision.





# Samenvatting





## Samenvatting

### Hoofdstuk 1 Haarverlies en hoofdhuidkoeling.

Diverse soorten chemotherapie veroorzaken ernstige haaruitval (alopecia). Naar schatting gaat het om meer dan 15.000 kankerpatiënten per jaar in Nederland. Haarverlies heeft grote impact op het merendeel van deze patiënten. Ze beschrijven haarverlies als 'stigmatiserend'; het herinnert hen dagelijks, steeds opnieuw, aan het hebben van de ziekte kanker.

Haarwortelcellen delen zich -evenals tumorcellen- snel, waardoor deze erg vatbaar zijn voor schade door chemotherapie. Tot nu toe is hoofdhuidkoeling de enige effectieve manier om ernstig haarverlies te voorkomen. Hoofdhuidkoeling berust enerzijds op bloedvatvernauwing, zodat minder schadelijke stoffen de haarwortelcellen bereiken. Anderzijds zorgt de lagere temperatuur van de hoofdhuid voor een lagere activiteit van de haarwortelcellen, waardoor er waarschijnlijk minder schadelijke stoffen in deze cellen terecht komen. Hoofdhuidkoeling wordt toegepast vanaf 30 minuten vóór aanvang van de chemotherapie tot en met 90 minuten ná het stoppen van het infuus. Deze koeltechniek kan gebruikt worden voor alle patiënten die een tumor hebben in een weefsel of orgaan; Dat wil zeggen dat de kanker niet mag zijn ontstaan in het beenmerg, bloed of in de lymfebanen. In dit proefschrift wordt de nadruk gelegd op hoofdhuidkoeling bij patiënten met borstkanker.

Ondanks het feit dat hoofdhuidkoeling al meer dan 40 jaar wordt toegepast, is er opmerkelijk weinig onderzoek naar verricht, met name in vergelijking met het voorkómen van andere bijwerkingen ten gevolge van kankerbehandelingen. In nagenoeg alle voorgaande studies wordt enkel de effectiviteit van hoofdhuidkoeling bestudeerd; vaak met kleine aantallen patiënten en verouderde typen chemotherapie.

### DEEL I Veiligheid

In **deel I** beschrijven we de veiligheid van hoofdhuidkoeling voor behandelingen met chemotherapie die gericht zijn op genezing (adjuvante of curatieve chemotherapie). Hoofdhuidkoeling zou een risico kunnen zijn indien naast de haarwortelcellen ook uitgezaaide tumorcellen (metastasen) in de hoofdhuid beschermd zouden worden tegen chemotherapie. Daarom is een vergelijking gemaakt tussen het optreden van uitzaaiingen in de *huid* en in de *hoofdhuid* bij borstkankerpatiënten die wél en géén hoofdhuidkoeling kregen.

In **hoofdstuk 2** werd een groep van 33.771 borstkankerpatiënten uit de kankerregistratie van München bestudeerd die geen uitzaaiingen hadden bij diagnose en bij wie de behandeling gericht was op genezing. Deze patiënten kregen geen hoofdhuidkoeling. In de periode 1978-2003 werd een afname gezien van het percentage patiënten dat uitzaaiingen kreeg na afronding van alle behandelingen (operatie, chemotherapie, bestraling, hormonale therapie). Echter werd in deze periode geen verbetering van de overleving gezien indien patiënten in de loop van de tijd alsnog uitzaaiingen kregen. Dat was het gevolg van een ongunstige verandering in de plek waar de uitzaaiingen in het lichaam gevonden werden. Het percentage patiënten met uitzaaiingen in de *huid* -verspreid over het lichaam- was 3% en varieerde niet in de loop van de jaren, ondanks veranderingen in chemotherapie en hormonale therapie. Nieuwe therapieën lijken dus geen grote invloed te hebben gehad op uitzaaiingen in de huid. Bij 20% van de patiënten die enkel een uitzaaiing in de huid hadden, werd deze gevonden

meer dan 10 jaar na het stellen van de diagnose borstkanker. Borstkankerpatiënten moeten dus lange tijd gevolgd worden om het risico van hoofdhuidkoeling volledig uit te kunnen sluiten.

De kans op het ontwikkelen van een uitzaaïing in de *hoofdhuid* was 0,5% voor zowel 885 patiënten die geen en 390 patiënten die wel hoofdhuidkoeling ondergingen (**hoofdstuk 3**). Uitzaaïingen in de hoofdhuid werden altijd gelijktijdig of later ontdekt dan uitzaaïingen elders in het lichaam, waardoor deze niet bepalend waren voor het verdere verloop van de ziekte. Onze studies, maar ook eerder gepubliceerde onderzoeken, laten zien dat de kans op het optreden van uitzaaïingen in de *hoofdhuid* vergelijkbaar is bij borstkankerpatiënten die wel (0,04-1%) of geen (0,03-3%) hoofdhuidkoeling kregen (**hoofdstuk 4**). Nooit werd een negatief verloop van de ziekte gerapporteerd na behandeling met hoofdhuidkoeling bij duizenden patiënten met tumoren in een weefsel of orgaan. Het is daarom onwaarschijnlijk dat het effect van chemotherapie in de hoofdhuid dusdanig wordt verminderd dat daardoor het toch al extreem lage risico van uitzaaïingen in de hoofdhuid toeneemt.

## DEEL II Effectiviteit

In **deel II** werd de effectiviteit van hoofdhuidkoeling bestudeerd, gebaseerd op het al dan niet aanschaffen en gebruiken van een pruik of hoofdbedekking. Daarnaast werden factoren onderzocht die van invloed zouden kunnen zijn op het resultaat van hoofdhuidkoeling.

Onze registratiedatabase met patiënten uit 28 Nederlandse ziekenhuizen liet zien dat 50% van de 1.411 patiënten die hoofdhuidkoeling kregen geen pruik of hoofdbedekking nodig hadden na afloop van de chemotherapie (**hoofdstuk 5**). De tevredenheid van de patiënten met het eindresultaat varieerde echter per type chemotherapie: van 8% na behandeling met TAC (een combinatie van docetaxel, doxorubicine en cyclofosfamide) tot 95% na behandeling met paclitaxel. Verder leek een hogere dosering, kortere infusietijd, hogere leeftijd, vrouwelijk geslacht en niet-West-Europees haartype te zorgen voor een minder goed eindresultaat van hoofdhuidkoeling. De lengte en dichtheid van het haar, evenals voorgaande behandeling met chemotherapie leken daarentegen geen invloed te hebben op het resultaat. Dat gold eveneens voor permanenten, bleken en kleuren en/of het nat maken van het haar voor de start van hoofdhuidkoeling. Aangezien deze factoren voor het eerst zijn bestudeerd, moeten de bevindingen nog wel bevestigd worden in andere studies. Pas dan kan meer gepersonaliseerde patiënteninformatie worden verstrekt of kan de methodiek van hoofdhuidkoeling eventueel worden aangepast om de resultaten verder te verbeteren.

In een andere studie werd door middel van loting bepaald of bij een patiënt hoofdhuidkoeling werd voortgezet tot 90 of 45 minuten na afloop van het chemotherapie-infuus (**hoofdstuk 6**). Deze studie werd uitgevoerd onder patiënten die elke drie weken chemotherapie met docetaxel kregen toegediend, met uitzondering van TAC. De effectiviteit van hoofdhuidkoeling bleek voor beide groepen gelijk, zodat patiënten met hoofdhuidkoeling bij dit type chemotherapie voortaan drie kwartier eerder naar huis kunnen gaan. Daarnaast vorderden deze patiënten de hoofdhuidkoeling goed: ze rapporteerden op een Visueel Analoge Schaal (een horizontale lijn van 100 millimeter) een score van 79 (0 was niet te verdragen en 100 zeer goed te verdragen). Verder rapporteerden deze patiënten dat ze tijdens 80% van de

hoofdhuidkoelingsessies geen last hadden gehad van hoofdpijn. Bij 13% was sprake van 'minimale' hoofdpijn en bij de overige 7% van sessies werd 'matige' of 'ernstige' hoofdpijn gemeld.

Een derde studie liet zien dat door toepassing van hoofdhuidkoeling het gebruik van een pruik of hoofdbedekking afnam met 40% in vergelijking met patiënten die geen hoofdhuidkoeling kregen. Tevens vond een beduidende verlaging van de mate van haaruitval plaats (**hoofdstuk 7**). Van de patiënten die hoofdhuidkoeling kregen en uit voorzorg een pruik aanschaffen, maakte 38% uiteindelijk geen gebruik van deze pruik. Hierdoor maken patiënten, maar ook zorgverzekeraars, onnodige kosten. Het merendeel van de patiënten rapporteerde dat het haar weer begon te groeien tussen drie en zes weken na de laatste chemotherapie. Bij één op de vier patiënten die hoofdhuidkoeling kregen bleek het haar ook tijdens de chemotherapie te blijven groeien. Na een half jaar waren de meeste patiënten weer tevreden met hun kapsel.

### DEEL III Kwaliteit van leven

In **deel III** werd de invloed van haaruitval op het welbevinden van borstkankerpatiënten met en zonder hoofdhuidkoeling bestudeerd. Hoofdhuidkoeling was effectief bij 52% van de patiënten. Daardoor was het mogelijk drie groepen patiënten met elkaar te vergelijken: succesvolle of niet-succesvolle hoofdhuidkoeling, en een groep zonder hoofdhuidkoeling.

Haaruitval werd door patiënten bestempeld als één van de meest belastende bijwerkingen, zowel voorafgaand als drie weken en zes maanden na afloop van de chemotherapie (**hoofdstuk 8**). Daarnaast leek hoofdhuidkoeling niet alleen bij te dragen aan de kwaliteit van leven en het lichaamsbeeld van patiënten bij wie hoofdhuidkoeling succesvol was, maar het leek ook extra ongerief te veroorzaken indien patiënten het haar hadden verloren ondanks hoofdhuidkoeling. Daarom dient extra aandacht besteed te worden aan het omgaan met haarverlies bij niet-succesvol gekoelde patiënten. Daarnaast benadrukt het het belang om de resultaten van hoofdhuidkoeling verder te verbeteren.

Ondanks het gegeven dat patiënten vooraf wisten dat haaruitval door chemotherapie een tijdelijk karakter heeft, rapporteerde de helft van de patiënten dat het haarverlies een last en/of een probleem voor hen was (**hoofdstuk 9**). Het merendeel rapporteerde ook dat ze zich niet meer aantrekkelijk voelden door het haarverlies. Voor 33% van de patiënten was hoofdhuidkoeling een last. Als reden hiervoor werd vaak de onzekerheid ten opzichte van het eindresultaat genoemd en in mindere mate ook koude, hoofdpijn, duizeligheid of het gewicht van de koelkap. Patiënten zouden dus gebaat zijn bij begeleiding betreffende mogelijk haaruitval en onderzoek naar de optimale temperatuur van hoofdhuidkoeling. De meeste patiënten die een pruik of hoofdbedekking gebruikten waren er tevreden over, maar velen waren zich ook continu bewust van het feit dat ze iets op het hoofd droegen. Patiënten die haaruitval hadden gehad, waren na afloop van de chemotherapie matig tevreden met hun haargroei.

## DEEL IV Kosteneffectiviteit

In **deel IV** wordt de kosteneffectiviteit van hoofdhuidkoeling beschreven. Hoofdhuidkoeling blijkt kosteneffectief te zijn, evenals de aanschaf van een pruik of hoofdbedekking. Hierdoor is het gerechtvaardigd om beide opties aan te bieden aan de patiënt (**hoofdstuk 10**). Bij patiënten die hoofdhuidkoeling kregen, daalden de gemiddelde maatschappelijke kosten met €269 per patiënt in vergelijking met patiënten die geen hoofdhuidkoeling kregen. Deze besparing was inclusief kosten voor hoofdhuidkoeling (machine en tijdsinvestering voor verpleegkundigen), kapperskosten, pruiken en hoofdbedekkingen. Hoofdhuidkoeling droeg echter niet bij aan de voor kwaliteit gecorrigeerde levensjaren, de zogenaamde QALYs. De kosteneffectiviteit van hoofdhuidkoeling kan verder worden verhoogd door de aanschaf van een pruik of hoofdbedekking uit te stellen totdat daadwerkelijk haarverlies optreedt, door het verbeteren van de resultaten van hoofdhuidkoeling en door het frequenter gebruiken van de koelmachines.

## Conclusies

In **hoofdstuk 11** worden de resultaten van de studies in dit proefschrift bediscussieerd en worden aanbevelingen gedaan voor toekomstig onderzoek. Hoofdhuidkoeling lijkt veilig voor patiënten die adjuvant of curatief worden behandeld met chemotherapie. Voor patiënten die levensverlengende (palliatieve) chemotherapie krijgen, is veiligheid van hoofdhuidkoeling doorgaans geen punt van discussie. Hoofdhuidkoeling is effectief voor de helft van alle patiënten, het is kosteneffectief en het wordt door de meeste patiënten goed verdragen. Echter blijft de werkelijke toegevoegde waarde van hoofdhuidkoeling per type chemotherapie onduidelijk, aangezien het nog altijd onbekend is welk deel van de patiënten zonder hoofdhuidkoeling ernstige haaruitval krijgt.

Ook kan en dient de effectiviteit van hoofdhuidkoeling verder verbeterd te worden. Dit kan bereikt worden door het bestuderen van de optimale hoofdhuidtemperatuur en koeltijden, waarbij speciale aandacht dient te zijn voor de verdraagbaarheid van hoofdhuidkoeling door de patiënt. Een ander hiaat in onze kennis is de invloed van koude op de (ver)werking van chemotherapie in de haarwortelcellen. Vooruitgang kan het best bewerkstelligd worden door een combinatie van celstudies in het laboratorium en het bestuderen van de optimale werking van hoofdhuidkoeling met medewerking van patiënten.

Haaruitval door chemotherapie heeft grote invloed op het welbevinden van veel kankerpatiënten, maar hoofdhuidkoeling lijkt niet bij te dragen aan verbetering van de kwaliteit van leven wanneer dit gemeten wordt met vragenlijsten over de algemene kwaliteit van leven. Daarnaast evalueren onderzoekers het resultaat van hoofdhuidkoeling op verschillende manieren, waardoor uitkomsten moeilijk te vergelijken zijn. Het is daarom wenselijk om een internationale, patiënt-gerapporteerde vragenlijst te ontwikkelen. Deze vragenlijst zou de mate van haaruitval moeten meten én de invloed van haaruitval op de kwaliteit van leven.

Tot slot zou de veiligheid van hoofdhuidkoeling verder onderzocht kunnen worden door de registratiedatabase voor hoofdhuidkoeling te koppelen aan de kankerregistratie, zodat uitzaaiingen en de overleving van patiënten op lange termijn bestudeerd kunnen worden.

Op het moment dat dit promotieonderzoek van start ging, werd hoofdhuidkoeling toegepast in vier Nederlandse ziekenhuizen. Dit aantal is sindsdien opgelopen tot meer dan 75. In veel ziekenhuizen wordt hoofdhuidkoeling uitsluitend aangeboden aan enkele specifieke patiëntengroepen, waardoor vele andere patiëntengroepen worden uitgesloten die in principe ook in aanmerking zouden kunnen komen voor deze behandeling. Alle patiënten voor wie hoofdhuidkoeling geschikt is, zouden informatie op maat moeten krijgen over de mogelijkheid, effectiviteit, eventuele bijwerkingen en het risico van hoofdhuidkoeling, opdat zij goed geïnformeerd zelf een beslissing over deze behandeling kunnen nemen.





# Curriculum Vitae





## About the author

Corina J.G. van den Hurk was born in Geffen, the Netherlands, on the 7th of February 1978. She finished secondary education at the Titus Brandsma Lyceum in Oss in 1996. She continued to study occupational therapy at the Hogeschool van Amsterdam, where she received her bachelor degree in 2000. Thereafter, she studied health science at Maastricht University, with a master degree in movement science and epidemiology. After graduating in 2003 she worked as a cancer registrar at the former Comprehensive Cancer Centre East in Nijmegen. Thereafter she registered and analysed data for a project on quality of care in breast cancer at the Comprehensive Cancer Centre South in Eindhoven. She started research on scalp cooling at Leiden University Medical Centre and the Comprehensive Cancer Centre South in 2005. From 2009 to 2013 she was also assistant coordinator of the EU-FP7 project EUROpe against Cancer: Optimisation of the Use of Registries for Scientific Excellence in research (EUROCOURSE).



# List of publications





## List of publications

1. Peerbooms M., Breed, W.P.M., **Hurk van den, C.J.G.** Familiarity, opinions, experiences and knowledge about scalp cooling - A Dutch survey among breast cancer patients and oncological professionals. 2013; (submitted)
2. **Hurk van den, C.J.G.**, Sande van de, M.A.E., Breed, W.P.M., Nortier, J.W.R. Adjuvant chemotherapy in breast cancer patients without and with scalp cooling: very low incidence of scalp skin metastases in retrospective studies. 2013; (submitted)
3. Daanen, H.A.M., Peerbooms, M., **Hurk van den, C.J.G.**, Os van, B., Levels, K., Teunissen, L.P.J., Breed, W.P.M. Core temperature affects scalp skin temperature during scalp cooling. 2013; (submitted)
4. **Hurk van den, C.J.G.**, Poll van de-Franse, L.V., Breed, W.P.M., Coebergh, J.W.W., Nortier, J.W.R. Scalp cooling to prevent alopecia after chemotherapy can be considered safe in patients with breast cancer. *Breast*. 2013; (in press)
5. Mols, F., Beijers, T., Lemmens, V.E.P.P, **Hurk van den, C.J.G.**, Vreugdenhil, G., Poll van de-Franse, L.V. Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: Results from the population-based PROFILES registry. *J Clin Oncol*. 2013; (in press)
6. **Hurk van den, C.J.G.**, Akker van den-van Marle, M.E., Breed, W.P.M., Poll van de-Franse, L.V., Nortier, J.W.R., Coebergh, J.W.W., 2012. Cost-effectiveness of scalp cooling to reduce chemotherapy-induced alopecia. *Acta Oncol*. 2013; (in press)
7. **Hurk van den, C.J.G.**, Akker van den-van Marle, M.E., Breed, W.P.M., Poll van de-Franse, L.V., Nortier, J.W.R., Coebergh, J.W.W., 2012. Impact of scalp cooling on chemotherapy-induced alopecia, wig use and hair growth of patients with cancer. *J Oncol Nurse*. 2013; (in press)
8. Komen, M.M.C., Smorenburg, C.H., **Hurk van den, C.J.G.**, Nortier, J.W.R. Factors influencing the effectiveness of scalp cooling in the prevention of chemotherapy-induced alopecia: review of the literature. *Oncologist*. 2013; (in press)
9. Znaor, A., **Hurk van den, C.J.G.**, Primic-Zakelj, M., Agius, D., Coza, D., Demetriou, A., Dimitrova, N., Eser, S., Karakilinc, H., Zivkovic, S., Bray, F., Coebergh, J.W., Cancer incidence and mortality patterns in South Eastern Europe in the last decade: Gaps persist compared with the rest of Europe. *Eur J Cancer*. 2013; 49: 1683-91.
10. Hendriks, M.A.E., Geerts, P.A.F., Dercksen, M.W., **Hurk van den, C.J.G.**, Breed, W.P.M. The usefulness of Cohen's cross-section trichometer for measuring hair quantity. *Dermatol Surg*. 2012; 38: 631-4.
11. **Hurk van den, C.J.G.**, Breed, W.P.M., Nortier, J.W.R. Short post-infusion scalp cooling times in the prevention of docetaxel-induced alopecia. *Supp Care Cancer*. 2012; 20, 3255-60.
12. **Hurk van den, C.J.G.**, Peerbooms, M., Poll van de-Franse, L.V., Nortier, J.W.R., Coebergh, J.W.W., Breed, W.P.M.. Scalp cooling hair preservation and associated characteristics in 1411 chemotherapy patients - Results of the Dutch Scalp Cooling Registry. *Acta Oncol*. 2012; 51, 497-504.
13. **Hurk van den, C.J.G.**, Eckel, R., Poll van de-Franse, L.V., Coebergh, J.W., Holzel, D., Nortier, J.W., Breed, W.P., Engel, J., 2011. Unfavourable pattern of metastases in M0 breast cancer patients during 1978-2008: a population-based analysis of the Munich Cancer Registry. *Br Ca Res Treat*. 2011; 128, 795-805.
14. Komen, M.M.C., Smorenburg, C.H., **Hurk van den, C.J.G.**, Nortier, J.W.R., 2012. Scalp cooling for Chemotherapy-induced alopecia. [article in Dutch] *Ned Tijdschr Geneesk*. 2011;155(45):A3768.
15. **Hurk van den, C.J.G.**, Breed, W.P.M., Mols, F. Chemotherapy-induced hair loss. (in: *Handbook of Hair in Health and Disease*, edited by Professor V.R. Preedy. Wageningen Academic Publishers, 2012; p. 403-16. ISBN: 978-90-8686-174-3).
16. Breed, W.P.M., **Hurk van den, C.J.G.**, Peerbooms, M. Presentation, impact and prevention of chemotherapy-induced hair loss; scalp cooling potentials and limitations. *Expert Review Dermatol*. 2011; 6, 109-25.
17. Sande van de, M.A.E., **Hurk van den, C.J.G.**, Breed, W.P.M., Nortier, J.W.R. Allow scalp cooling during adjuvant chemotherapy in patients with breast cancer; scalp metastases rarely occur. [article in Dutch] *Ned Tijdschr Geneesk*. 2010; 154, A2134.



18. **Hurk van den, C.J.G.**, Mols, F., Vingerhoets, A.J.J.M., Breed W.P.M. Impact of alopecia and scalp cooling on well-being among breast cancer patients. *Psych Oncol.* 2010; 19: 701–9.
19. Mols, F., **Hurk van den, C.J.G.**, Vingerhoets, A.J.J.M., Breed, W.P.M. Scalp cooling to prevent chemotherapy-induced hair loss: practical and clinical considerations. *Supp Care Cancer.* 2009; 17(2):181-9
20. **Hurk van den, C.J.G.**, Poll van de-Franse, L.V., Tutein-Nolthenius-Puylaert, M.C.B.J.E., Roukema, J.A., Sangen van der, M.J.C., Nieuwenhuijzen, G.A.P., Eijnden van den-van Raaij, A.J.M., Coebergh, J.W.W. Compliance with the breast cancer guidelines in the region of the Comprehensive Cancer Centre South, 2003/04. [article in Dutch] *Ned Tijdschr Geneeskd.* 2006; 150: 963-8.

# Dankwoord





## Dankwoord

Wat zijn er in mijn leven veel bijzondere en mooie mensen op mijn pad gekomen. Wat een rijkdom!

Veel dank ben ik verschuldigd aan de wijzen en geleerden die me meenamen in de wereld van kanker, geneeskunde, epidemiologie en de wetenschap in het algemeen.

Hans, graag onderschijf ik de heldenstatus die je eerder toegedicht kreeg, want in de veelheid aan taken van je 24/7 overvolle agenda wist je zelfs voor mij altijd tijd vrij te maken. Je hield me op het wetenschappelijke pad als ik de missionarisweg insloeg en stond me bij in de voortdurende zoektocht naar financiering. Ik waardeer het ten zeerste dat je met ons aan de wieg van hoofdhuidkoeling in Nederland hebt willen staan.

Jan-Willem, aan je hand lopend door Europees KankerRegistratie-land, luisterend naar wijze lessen en de meest uiteenlopende, buitengewone verhalen, kregen wij een bijzondere band. Ik wens en weet dat deze nooit verloren zal gaan. Dank je wel voor je continue bron van inspiratie.

Lonneke, vrouw aan de top en -nog veel belangrijker- een topvrouw! Je stond me met raad en daad bij op wetenschappelijk en persoonlijk vlak. Dank je wel voor je altijd opgetogen motivatie en voor alle kansen en perspectieven die je me steeds opnieuw weer biedt. Ik hoop in de toekomst nog vele projecten samen met jou tot een goed einde te brengen.

Wim, het verdriet van jouw patiënten om haaruitval heeft je vele jaren geleden in zijn macht gekregen en nooit meer los gelaten. Als eenzame strijder aan het front werd je door veel collega's vriendelijk afgewimpeld als je ze probeerde te overtuigen van het nut van hoofdhuidkoeling. Alle eer voor jou als we kijken waar we nu staan en een blik in de toekomst werpen. Dank je wel voor je onuitputtelijke inzet.

En wat ben ik bevoorrecht dat ik mag werken bij het IKZ: een fijne sfeer, de juiste spirit, een super plek om jezelf te kunnen ontplooiën. Dank je wel geweldige collega's van de afdeling onderzoek en daar buiten! In het bijzonder dank aan Floor, Sandra en Mijke die me altijd hebben bijgestaan om alle ballen in de lucht te kunnen houden. En last but not least, onze Janny! Heel veel dank voor je voortdurende steun en vertrouwen, dank voor alles wat je deed en doet met hart en ziel.

Dank je wel verpleegkundigen, voor de plezierige samenwerking. Wat heb ik een onverminderd respect voor jullie gave om te geven.

Dank je wel patiënten die aan de studies en projecten deelnamen. Patiënten die mij door enkele woorden in een persoonlijk gesprek meer hebben geleerd dan een vragenlijst ooit duidelijk zal kunnen maken.

Thanks to the national and international co-authors, medical doctors and scientists who inspire me and make me even more enthusiast about our collaborative scalp cooling research.

Thanks to the manufacturers and importers of scalp cooling machines for the kind cooperation.

Dank aan al degenen die hoofdhuidkoeling een warm hart toedragen en hoofdhuidkoeling op de kaart hebben gezet in Nederland: samen Geven we Haar Een Kans!

Dank je wel mijn paranymfen, Marieke en Manon, dat jullie naast me willen staan op de voor mij zo bijzondere dag van mijn promotie.

Dank je wel familie van den Hurk en familie van Erp, voor regelmatige knappe staaltjes Brabantse gezelligheid.

Dank je wel vriendinnen en vrienden uit (de tijd in) Geffen, Vorstenbosch, Rosmalen, Maastricht en Amsterdam. Zonder jullie gezelligheid, onzinnige of goede gesprekken zou mijn leven geen leven zijn. Laten we samen verder genieten van de mooie dingen van het leven!

Dank je wel familie Hollander en familie Vogels voor een tweede warm thuis in heden en verleden.

Ik ben een gelukkig mens. Het geluk begon al bij mijn geboorte, met mijn pap en mam. Dit proefschrift draag ik aan hen op omdat ik meer dan ooit besef wat zij mijn hele leven voor me hebben gedaan en nog altijd doen. De geborgenheid en er altijd voor elkaar zijn in ons gezin zijn goud waard, dank je wel voor alles en nog veel meer Rianne, Marco, Robert, Sharon en de lieve mini's.

Jeroen en Daan, mijn schatjes, jullie brengen warmte in hoofdhuid-coole tijden en maken dat ik nooit vergeet wat echt belangrijk is in dit leven. Ik rij elke ochtend met plezier naar Eindhoven, maar sjees ook met een dikke vette glimlach terug naar huis. Jullie maken mijn geluk compleet! 😊