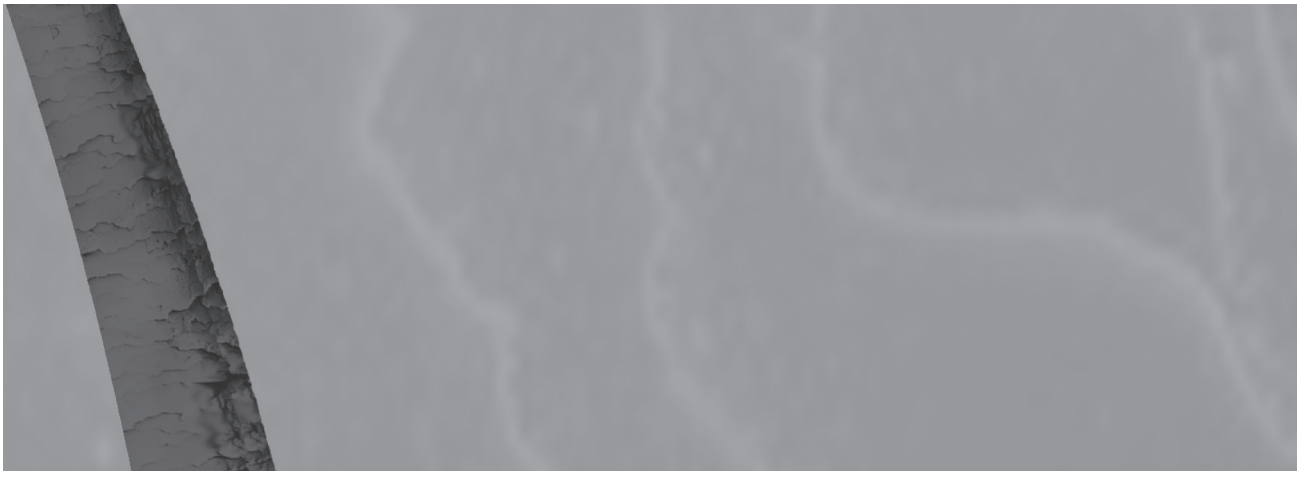
Chapter 1



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.[1] 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[2,3] 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.

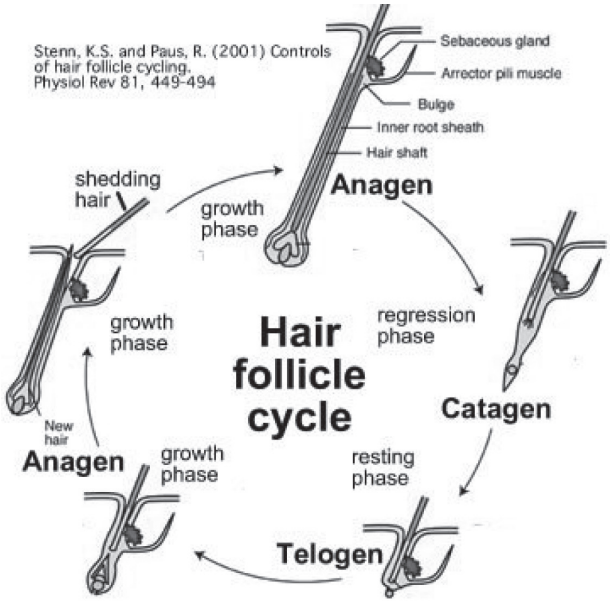


Figure 1. Hair follicle cycle.

Sensitivity to chemotherapy of each part of the follicle depends on its cycling rate. Cytotoxic agents mainly affect anagen hair follicles[1,4], because of their rapidly proliferating cells in the epithelial matrix of the bulb (Figure 2).[5] 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.[6] 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.[1] 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.[4] Hair loss usually starts one to three weeks after the first chemotherapy[1,7] 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.[4,8,9] This also leads to a greater amount of shedding hairs.

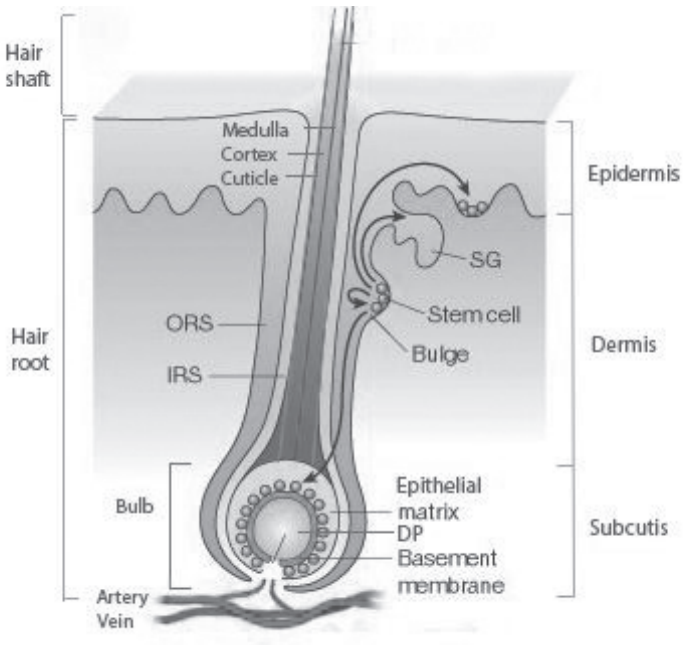


Figure 2. Hair follicle.

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.[10] 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[1,5] with fewer cells per unit length[11] (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.[1]

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[5], presumably by their slower growth rate and enhanced repair mechanisms.[6] The normal hair growth rate usually returns within several weeks[1,12] to several months[8] 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.[1] When hair grows again, about

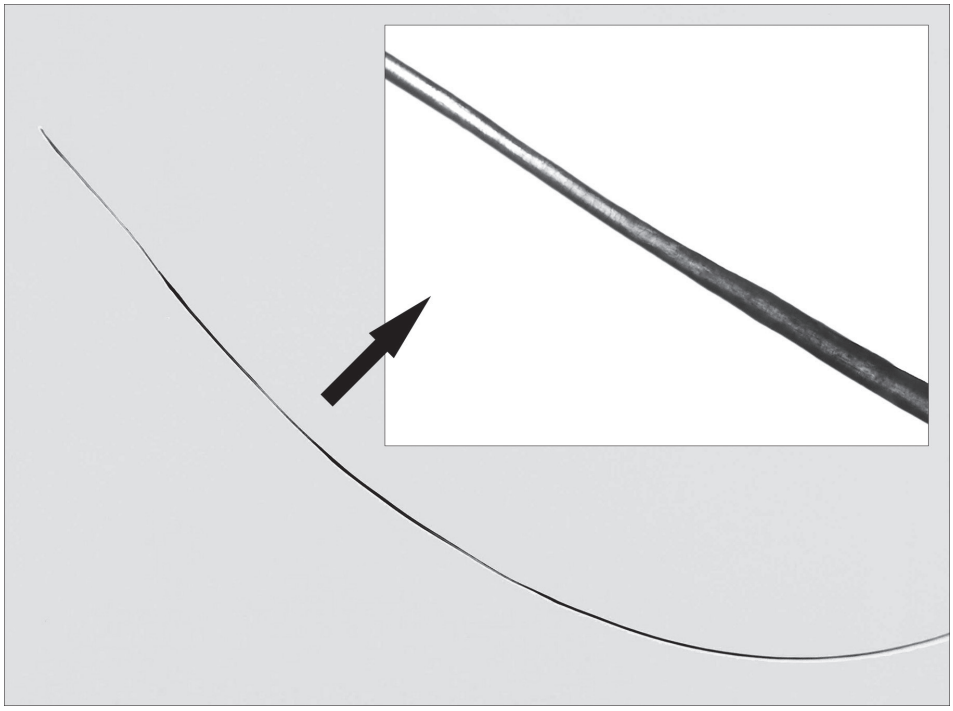


Figure 3. Diminished hair shaft diameter after chemotherapy with scalp cooling (photo: H. Snijders).

65% of the patients experience a change from their previous hair color or texture (dryness, curling, straightening)[7], 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.[6]

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[13], 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 (M0) 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.[13] 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.[14]

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.[15] So there are about 8300 M1 patients, of whom about 1000 had metastases at diagnosis.[13] Approximately 60% of the remaining 7300 patients will receive palliative chemotherapy within 20 months[16], 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%.[17] 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.[18] 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.[19-21] 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.[6]

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.[1,19,22] Cisplatin, 5-fluorouracil, methotrexate, mitoxantrone, vinorelbine, gemcitabine, carboplatin,[1,22] and pegylated liposomal doxorubicin[20,21] 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.[1,7] 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.[6] 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.[6]

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%.[12] Busulphan is the most commonly implicated agent, but it has also been described following cyclophosphamide, thiotepa, melphalan, etoposide, carboplatin, docetaxel, paclitaxel[12], and in the sequential scheme of 5-fluorouracil, epirubicin, cyclophosphamide (FEC) followed by docetaxel.[23]

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.[24] It has been repeatedly reported that for a majority of patients the experience of alopecia is distressing.[25-29] 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.[30,31] When ranking side effects of cancer treatment, patients indicate CIA as one of the most feared sequelae of chemotherapy[32-34] and rank it among the five most troublesome.[35-38] The impact of CIA on body image is the most often studied QoL aspect, but outcomes are inconclusive.[7]

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.[39] 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.[25,39,40] 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 dissapeared, 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.[3] 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.[41,42] 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).[43] 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.[44-46] 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.[47,48] The majority of patients tolerate scalp cooling very well, head aches and coldness are the most frequent complaints[49], 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

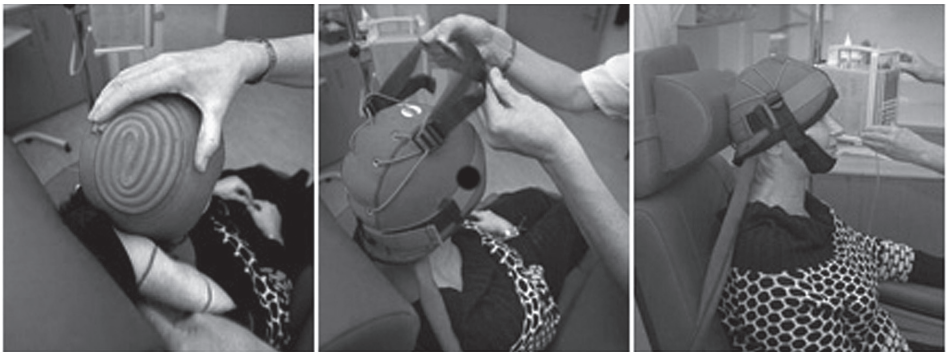


Figure 4. Scalp cooling (photo: M. Molle, Volkskrant).

scalp cooling[49], 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. Contra-indications 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[50-56], supported by studies with historical controls.[57] 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[57], 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.[58,59] 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.[35] In 2005 a review was published, underscoring the effectiveness of scalp cooling.[49] 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). 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.

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