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

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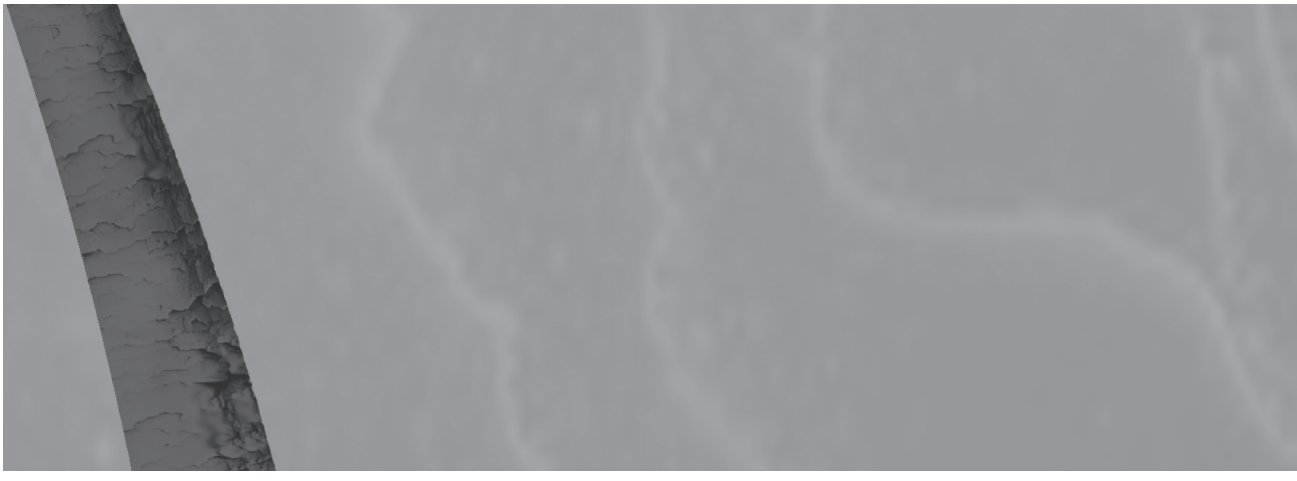
Chapter 11



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.[1] 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.[2]

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%[3] vs 70%[4]). 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.[4] On the contrary the incidence is often overestimated by Medical Doctors (MDs) from their clinical point of view.[3] 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.[5] 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.[6] 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.[6] 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 anthracylines 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[7], which is undesirable for comparing and pooling data.[8] 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.[9-11] 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[8]- 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).12 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[13], 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 indispensible.

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

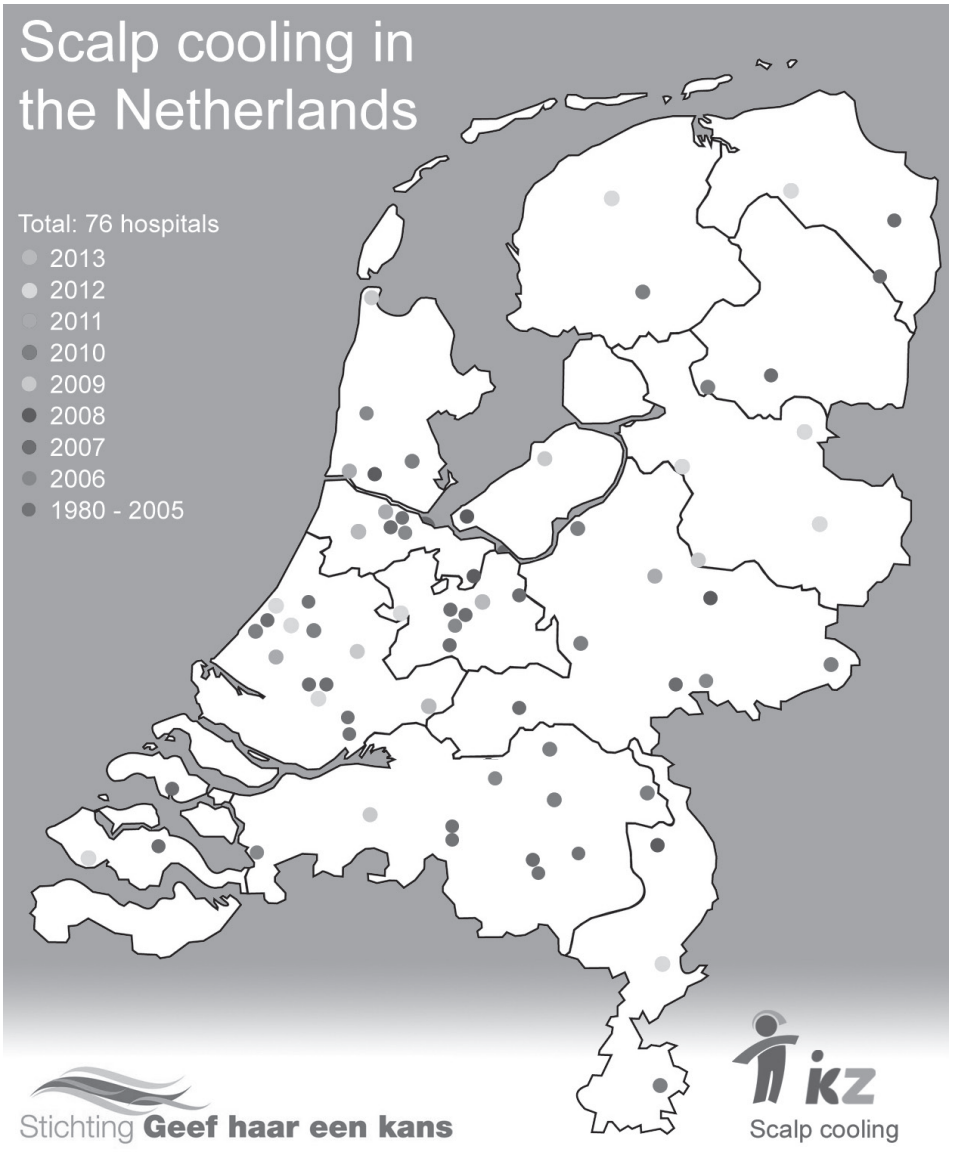


Figure 1. Map of Dutch scalp cooling hospitals 2005 - 2013.

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[14], elderly and men with cancer[15] 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.[16] It is noteworthy that for women who wear a scarf for religious reasons, hair is an important aspect in family life.[17,18]

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.[19] 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/ 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 5ºC 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 d yed, 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[8] 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 ↓	*Cell membrane* if active transport: cytotoxic influx ↓ *Intracellular* cell mitosis ↓ toxic reactions ↓	*Cell membrane* if active transport: cytotoxic outflow ↓ *Intracellular* 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.[7]).
↓ 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[1] 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.[8]

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.19 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.

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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