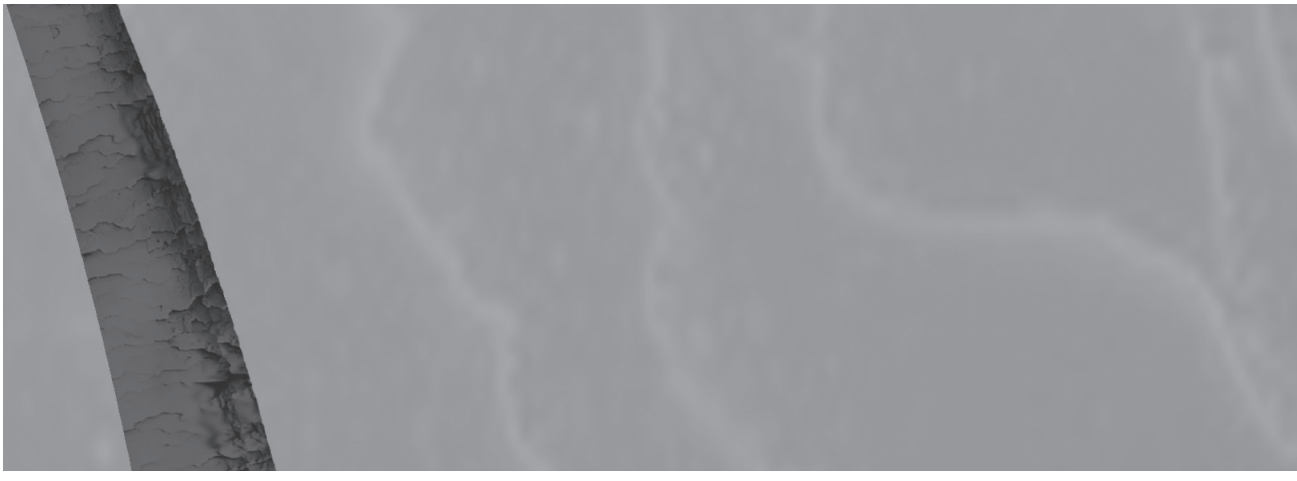
Summary



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 Almost all previous studies evaluated solely effectiveness of scalp cooling, often for small groups of patients and outdated types of chemotherapy.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.