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Viewpoints and debate

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

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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.

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 [1]. It is mainly used in Western Europe by breast cancer patients and prevents severe chemotherapy-induced alopecia (CIA) in half of them [2]. Scalp cooling is usually applied continuously about 30 min before, until 90 min after chemotherapy infusion [1], lowering scalp skin temperature to a mean of 18 °C (range 12–25 °C) (unpublished results).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 and 30% in retrospective patient file studies [3–5] and 3% in a German cancer registry [6] (Table 1). In addition, it varied between 9 and 32% in autopsy studies before chemotherapy was used [7–10]. These broad ranges may be caused by the distinction between true distant metastasis and local chest wall involvement, selection of microscopically confirmed metastases or may be differences in incidence determined by race [4]. Skin metastases are rarely the first presenting sign of distant metastatic breast cancer [11–15], also when patients did not undergo systemic treatment after primary local treatment [16]. The majority (53–84%) of skin metastases are detected on the trunk or near the scar of the primary neoplasm [3,12,15,17,18].

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 [6]. 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 [6].

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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 mets (%)	Syst	Duration of follow up	Chemo (%)/ Adj(%)	Type[a]	Remarks
Brownstein 1972 [12]	NR[b]	168 (?)[c]	5 (<3)	Yes	NR (included in 1948–1963)	0		[b]% M1 unknown [c]100% biopsy proven
Fisher 1982 [21]	7800	NR	2[d] (0.03)	Yes	NR	?/100	?	[d]First occurrence
Lookingbill 1990 [11]/1993 [3]	992[e,f]	71[g] (7)	18 (2)	Yes	NR (included in 1976–1986)	?/?	?	Distant ($n = 20$) or distant combined with local [e]($n = 51$) metastasis [f]% M1 unknown [g]79% biopsy proven
Spaeth 2008 (abstract) [19]	141[h,i]	NR	(<3)[j]	Yes	Median 3 yrs	100/?	Anthraand /or taxane	[h]93% breast ca [i]% M1 unknown [j]Includes also skull and brain metastases
Lemieux 2009 [22]	87 M0	NR	1[k] (1)	Yes	Median 5.4 yrs	100/100	Anthra/CMF/ taxane	[k]No scalp cooling during adjuvant treatment, developing scalp skin metastasis after 6 out of 9 systemic treatments for metastatic disease with scalp cooling
Van de Sande 2010 [20]	885 M0[l]	25 (3)	4[m] (0.5)	Yes	Mean 9.2 yrs	100/100	FEC/FEC + CTC	[l]High risk: 4 + lymph nodes [m]Scalp skin concurrent with other sites
MCR 2011	33.771 M0	929 (3)/191 (0.6) skin alone	(<0.6)[n]	No	Mean 8.2 yrs	29/100	NR	[n]Scalp skin alone

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.
[a] Anthra = anthracyclines, CMF = Cyclophosphamide, Methotrexate, 5-Fluorouracil, FEC = 5-Fluorouracil, Epirubicine, Cyclophosphamide, CTC = Cyclophosphamide, Thiotepa, Carboplatin.

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 and 3% [3,11,12,19–22], remaining low in a study population of high risk patients only [20], even in M1 patients [3,11,12] or when the study was prospective [19]. Incidence rates were not associated with time since diagnosis (110 months) [20] or receiving no adjuvant chemotherapy [12]. One study showed that also scalp skin metastases occurred at the same time or later than non-skin metastases elsewhere [20].

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% [19,22,28] (Table 2). 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 [22]. Besides, two breast cancer patients were reported in whom seven and nine years after diagnosis scalp skin metastases were detected as first metastatic site [28], 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 1970–2012 [1,29], and four additional studies [30–33]. 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 [26].

Data of >2000 Dutch scalp-cooled patients have been analysed in our studies from 2004 to 2012 [2,34–37]. 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 [38], 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 [7–10,12]. 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 [6]. 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

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

Study	*n*=	Scalp skin mets (%)	Syst	Follow up	Adj (%)	Type[a]	Remarks
Van den Hurk (1997–2005)	395	3 (0.7)[b]	Yes	Median 2.2 y	NR	Anthra/taxane/CMF	[b]1x before start chemotherapy, 2x concurrent with other sites
Spaeth 2008 (abstract) [19]	770[c]	3 (0.04)[d]	Yes	Median 3 y	NR	Anthra and/or taxane	[c]93% breast ca [d]Personal communication
Lemieux 2009 [22]	553	6 (1.1)[e]	Yes	Median 5.8 y	100	Anthra/CMF/taxane	[e]Not first metastatic site
Lemieux 2011 [28]	2	2[f]	Yes	7 + 9 y	100		[f]First and only site, stop scalp cooling after 1 or 2 cycles
Van den Hurk (2004–12) [2,34–37]	>2000[g]	1 (0.04)[h]	No	n.a.	77	Diverse	[g]87% breast ca [h]Detected after first chemotherapy
Literature (1970–2013)	2315[i]	9 (0.4)	No	n.a.	>439 (37)	Diverse	[i]At least 1287 (49%) breast ca
No mets info[n]	1204[j]	NR	No	n.a.	>237 (46)	Diverse	[j]At least 511 (42%) breast ca
No mets -FU[o]	268[k]	0	No	NR	NR	Diverse	[k]At least 190 (71%) breast ca
No mets + FU[p]	309[l]	0	No	9–46 m	133 (58)	Diverse	[l]74% breast ca
Mets[q]	307[m]	9	No	2–20 m	NR	Diverse	[m]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.

[a] Anthra = anthracyclines, CMF = Cyclophosphamide, Methotrexate, 5-Fluorouracil.

[n] No information about scalp skin metastases, references: Adams 1992, Anderson 1981, Auvinen 2010, Belpomme 1982, Benglia1986, Ciambellotti 1993, David 1987, Dean 1983, Dougherty1996, Goldhirsch 1982, Gregory 1982, Hunt1982, Kargar 2011, Keizer-Heldens 2009, Kennedy 1983, Kolen 2002, Nakazawa1985, Robinson1987, Samonigg 1984, Symonds 1986, Tierney 1992.

[o] No scalp skin metastases, follow up unknown, references: Giaccone1988, Hillen 1990, Katsimbri 2000, Macduff 2003, Massey 2004, Satterwhite 1984.

[p] No scalp skin metastases, follow up known, references: Lemenager 1997, Parker 1987, Protiere 2002, Ridderheim 2003, Ron 1997, Tollenaar 1994.

[q] Scalp skin metastases, references: Christoudoulou 2006, Kiser 1982, Middleton1985, Peck 2000, Vendelbo-Johansen 1985.

despite chemotherapy, are at risk for scalp skin metastases due to scalp cooling. If metastases develop as a result of primary resistance for chemotherapy [40], or in case of late relapses from micro-metastases in a dormant state for many years after cytotoxic treatment [41,42], 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 [39,41]. Cutaneous metastases might thus often be an indication for other distant metastases elsewhere in the body [43].

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 [23]. 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 [24]. And indeed, mostly there is some additional hair loss in the period between chemotherapy cycles [25]. Furthermore, two studies reported independently that pre-existing scalp skin metastases regressed during chemotherapy despite scalp cooling [26,27]. 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 [41,44]. 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 [13,18]. 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 [45]. But this also indicates that these metastases are mostly not clinically important [22].

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 [36] using a cancer registry and prospectively compare survival between scalp-cooled and non scalp-cooled patients.

Conflict of interest statement

None declared.

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