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

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Abstract
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. Two retrospective observational studies are described. Non scalp cooled patients comprised 885 very thoroughly evaluated high-risk (≥4 positive lymph nodes) M0 breast cancer patients. Scalp cooled M0 patients (n=303) were collected in a registry of patients undergoing scalp cooling. Information on (scalp) skin metastases was obtained from patient files. 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 synchronal with metastases elsewhere or in a later stage. After a median follow-up of 26 months, six scalp cooled patients (2%) developed skin metastases, none of which were on the scalp skin. 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.

1. Introduction

Patients who are treated with chemotherapy report that they experience hair loss to be one of the most distressing side effects.[1, 2] Since 1970 scalp cooling has sparsely been practiced to reduce chemotherapy-induced hair loss and nowadays it's use increases all over the world.

Scalp cooling is applied continuously from 30 minutes before the start of chemotherapy until 90 minutes after stopping the infusion. The temperature of the scalp skin decreases to a mean of 15-18°C. Scalp cooling causes vasoconstriction and a decreased biochemical activity, which may protect hair root cells from extensive damage. In general, it is effective in half of the patients[3, 4] and overall well tolerated.[5]

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.

2. Methods

Patients without scalp cooling were studied in the database of the so-called 'N4+study'.[6] 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 five 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.[6] During long-term follow-up the occurrence of recurrence or distant metastases were systematically recorded.

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

	No scalp cooling (n=885)	Scalp cooling (n=303)
Characteristics		
N4+	100%	8%
Surgery	100%	Unknown
Age (years)	<56	Mean 54
Chemotherapy		
FEC	+/- 50 %[a]	11%
FEC+CTCar	+/- 50 %[a]	0
AC	0	56%
CMF	0	8%
FAC	0	6%
Paclitaxel	0	1%
Docetaxel	0	1%
Unknown	0	17%
Outcomes		
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

[a] Exact percentages unknown, while only access to data of patients with skin metastases from the N4+study

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.[7]

Retrospective systematic research in patient files was performed in 395 scalp cooled breast cancer patients from four Dutch hospitals (1997-2005). Five patients had incomplete data and were excluded. The patients had a 30 minutes pre-infusion and 90 minutes post-infusion cooling time using the Paxman cooling machine. 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).

3. Results

3.1. 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).

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[a]
2	1996 High-dose	1999 Skin (thorax), 2002 Bone+Lung (c), 2004 Skin (scalp)	2004[a]
3	1997 Conventional	1999 Skin (scalp)+Bone+Liver (c)	2002[a]
4	1997 Conventional	2001 Lymph, 2002 Skin (scalp), 2002 Liver, 2002 Lung	2002[a]

5-fluorouracil,epirubicin, cyclophosphamide (FEC), 4xFEC+ 1xcyclophosphamide, thiotepa,carboplatin (CTC)+ autologous stem cell transplantation,
[a]deceased

3.2. 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 N0 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.

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[a]
2	2004 6x FEC/ 2x	2005 Chest wall	2005 Pleuritis carcinomatosa (c)	2005[a]
3	1997 7x? / 5x	2003 Abdomen	2001 Ovarium, 2001 liver, 2001 bone	2003[a]
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[a]
6	2002 7x paclitaxel/ 7x	2003 Chest wall	2004 Endometrium, 2004 cervix	2004[a]

c: concurrent with skin metastasis, fu: in follow up, ?: type of chemotherapy unknown,
C: cyclophosphamide, M: methotrexate, F: 5-fluorouracil, E: epirubicin, A: doxorubicin
[a] deceased

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.

4. Discussion

We describe the incidence of scalp skin metastases in two cohorts of M0 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, which is in accordance with a 3% incidence in a report of Mo breast cancer patients from the Munich Cancer Registry (MCR) (n= 33.771, 56% adjuvant chemotherapy).[8] 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 M0 patients, but also with a 1.1% incidence (all stage II or III disease) among 553 scalp cooled M0 patients. [9] 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, which was not shown in the MCR data. [8] Also no differences have been reported when comparing the incidence of scalp skin metastases in other non-scalp cooled and scalp cooled cohorts. [9-11]

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 breast cancer patients have been described with scalp skin metastases as the presenting sign after adjuvant treatment; however this was not related to scalp cooling treatment. [12]

Also brain and skull metastases were all detected concurrent with metastases elsewhere. Only Spaeth et al. compared the incidence of these metastases and found no

difference between scalp cooled and non-scalp cooled patients.[10] This is in line with a mathematical model that predicted no substantial decrease of brain temperature during scalp cooling.[13] For this reason, the presence of bone metastases should not be a restriction for scalp cooling, as it is in some hospitals nowadays. Even more because skin metastases do not occur more often in patients with bone metastases. The current study also shows that N4+ in early breast cancer does not need to be a restriction.

Maybe the risk of scalp skin metastases is somewhat underestimated, because scalp cooling was prematurely ceased in half of the 303 M0 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[3], and in 5-10% because of intolerance[4], but in the large majority before the third cycle of chemotherapy.[3, 5, 14] 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.[11] 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.[8] 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.[9] Nevertheless, in breast cancer the first metastasis can appear more than 10 years following diagnosis.[8] Besides, it is unknown whether hypothermia changes the process of (time to) metastases.

There are several limitations in this report of retrospective studies. Patient characteristics vary, 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.

5. Conclusion

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 literature after 40 years of scalp cooling, it has never been reported to negatively influence the course of the disease for patients with solid tumors.[4, 11] 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 study the incidence of metastases after long term follow-up in patients who were randomized between scalp cooling or no scalp cooling during adjuvant chemotherapy. Such a trial is currently running in the USA. Another approach would be to study safety of scalp cooling in an extensive database of patients treated with adjuvant chemotherapy, who are prospectively followed for several years (depending on the primary tumor site). Our ongoing scalp cooling registry[3] 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 could be verified.[13]

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