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EPIDEMIOLOGY

Incidence of scalp metastases in breast cancer: a retrospective cohort study in women who were offered scalp cooling

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Abstract Scalp cooling is an intervention used to decrease the degree of chemotherapy-induced alopecia. The objective is to determine the incidence of scalp metastases among women with early breast cancer who received neoadjuvant or adjuvant chemotherapy. We conducted a retrospective cohort study of women with breast carcinoma diagnosed between June 1, 1998 and June 30, 2002. The median follow-up was 5.8 years (±1.7) for the scalp cooling group ($n = 553$) and 5.4 years (±1.7) for the non-scalp cooling group ($n = 87$). The incidence of scalp metastases was 1.1% (6 cases out of 553 patients) among women who used scalp cooling in the neoadjuvant or adjuvant setting and 1.2% also (1 case out of 87 patients) among women who did not use scalp cooling in the neoadjuvant or adjuvant setting. The incidence of scalp metastases was low and no case presented as an isolated site of relapse.

Keywords Scalp cooling · Scalp metastases · Breast cancer

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Introduction

In women with early breast cancer, chemotherapy has been shown to reduce mortality [1]. Chemotherapy is associated with various side effects such as nausea, fatigue and mucositis [2]. However, one of the chemotherapy side effects most feared by women is hair loss. Chemotherapy-induced alopecia has been shown to be distressing and one of the most troublesome chemotherapy side effect for cancer patients [3]. Even though it is usually considered to be reversible, recent data have reported persistent significant alopecia in 6.3% of women receiving docetaxel-based chemotherapy [4]. Taxane-based combination regimens are increasingly used in the adjuvant setting.

Scalp cooling is an intervention that can be used to decrease chemotherapy-induced alopecia. Cooling of the scalp is carried out using a series of cold caps placed on the head and changed at intervals to keep the scalp cold. Another method for cooling the scalp is with a machine that circulates glycol-based fluid in the cap [5, 6]. Cooling is usually started about 15 min before the start of chemotherapy and continued for a varying period of time after the end of chemotherapy (~60–90 min). Three mechanisms have been postulated to explain how scalp cooling can prevent or decrease chemotherapy-induced alopecia: cutaneous vasoconstriction leading to decrease in local concentration of chemotherapy locally, decrease in cellular

uptake of the hair follicle and reduced intra-follicular metabolic rate [7, 8].

Even though scalp cooling has shown a certain degree of efficacy in preventing hair loss, there are variations in its use around the world. In some European countries, scalp cooling is used more routinely, whereas in North America it is rarely used. In the United States, the Food and Drug Administration has stopped the approval of scalp cooling devices due to lack of documentation about their efficacy and safety [9].

To date, studies reporting on the efficacy of scalp cooling have been small. A review found seven randomized controlled trials, randomizing a total of 233 patients [10]. Overall these trials found better hair preservation with scalp cooling compared to non-scalp cooling use. However, these trials were conducted with chemotherapy combinations either not highly associated with total alopecia (e.g. CMF[1]) or with doses of drugs lower than standard doses now used.

Because of the mechanisms of action of scalp cooling, it is hypothesized that it could also be associated with increased risk of developing scalp metastases. Autopsy series found various cancers (e.g. lung, gastric, breast) to be associated with scalp metastases [11–15]. However, these studies reported no information about use of scalp cooling. Since some of these studies were conducted before the use of chemotherapy, we can postulate that no scalp cooling was used. In the most recent review of scalp cooling [10] that included 56 studies and about 2,500 patients, scalp metastases were reported in nine patients [10]. Follow-up was short (less than 20 months except one case report who had a 7-year follow-up) and assessment of scalp metastasis was not reported in all studies [10]. Among these nine cases, two patients had haematological malignancies and the scalp recurrence was possibly the first site of relapse [16, 17], supporting the idea that scalp cooling should not be used in haematological malignancies. On the other hand, two case reports of patients who used scalp cooling despite the presence of scalp metastasis experienced regression of their metastasis, supporting the fact that a certain amount of chemotherapy reached the scalp even when cooling was used [18, 19]. In the context of women with already widespread metastatic breast cancer, a few case reports (seven cases in total) of scalp metastasis at the time they used scalp cooling have been reported [18, 20–21]. More recently, Spaeth et al. [22] reported in an abstract three cases of cutaneous/sub cutaneous scalp metastases in cohort of 770 patients who used scalp cooling (0.39%) and no case in another group of patients who did not use scalp cooling (141 patients). The majority of patients were treated for breast cancer (93%). The median follow-up was 36 months. Another group reported in an abstract form an incidence of 0.5% of scalp metastases (synchronous with other metastases) in a review of 395 scalp cooled patients [23]. Median follow-up was not reported.

Because the literature is scant about the risk of scalp metastases in association with scalp cooling in women with breast cancer, we designed a study to determine the incidence of scalp metastases among women with breast cancer. Our objective was to determine the incidence of scalp metastases in women who used scalp cooling in the neoadjuvant or adjuvant setting and compare it to that in a group of women who did not use scalp cooling.

Methods

We conducted a retrospective cohort study of women diagnosed with an invasive breast carcinoma between June 1, 1998 and June 30, 2002. Patients were included if they received chemotherapy in a neoadjuvant and/or adjuvant setting. This study was conducted in a single institution, the Centre des Maladies du Sein Deschênes-Fabia (CMS), Quebec, Canada, where scalp cooling is routinely offered to women with breast cancer.

Data on tumour characteristics and treatment received were available from the database of the CMS. Information on use of scalp cooling and presence of scalp metastases were obtained by chart review. When a patient received treatment outside the institution, we assumed that no scalp cooling was used since this technique was not widely used in other hospitals in the province. Scalp lesions were classified as "definitive" scalp metastasis if biopsy-proven, "probable" if described by the physician as scalp metastasis or if it regressed with treatment, and as "unlikely" if it was reported by physician as benign (e.g. cyst). The study was approved by the research ethics board of the institution.

Statistical methods

Descriptive statistics were used to present baseline characteristics of the population. To compare characteristics and outcomes between patients who used scalp cooling in the neoadjuvant or adjuvant setting with those who did not, *t*-tests were used for continuous data and the chi-square or Fisher test for categorical data.

Results

A total of 644 patients were identified from the database. Four patients were excluded because charts were not found

[1] Cyclophosphamide, methotrexate, 5-fluorouracil.

or did not match the hospital chart number. All other charts (640) were reviewed. Among these 640 women, 86.4% of women received scalp cooling during neoadjuvant or adjuvant chemotherapy. The median follow-up was 5.8 years (±1.7) for the scalp cooling group and 5.4 years (±1.7) for the non-scalp cooling group.

Baseline characteristics are reported in Table 1. The median age of the population was 51 years old for women with and without scalp cooling. A higher proportion of patient in the group who used scalp cooling were treated with first generation adjuvant chemotherapy (AC[2] or CMF) (61.1 vs. 43.7%, $P < 0.01$) and less frequent use of taxanes (9.4 vs. 40.2%, $P = <0.01$). Also, there were trends toward a higher proportion of stage III breast cancer (12.6 vs. 6.9%, $P = 0.06$) and more common use of both neoadjuvant and adjuvant chemotherapy (9.2 vs. 2.3%, $P = 0.06$).

Overall, the incidence of definitive or probable scalp metastases was 1.1% (7 cases out of 640 patients) of our population and these seven women received scalp cooling during the course of their disease. We found the incidence to be 1.1% (6 cases out of 553 patients) among women who used scalp cooling in the neoadjuvant or adjuvant setting. Another woman (1 case out of 87 patients) who used scalp cooling only in the metastatic setting also developed scalp metastases (1.2% of women who did not use scalp cooling in the neoadjuvant or adjuvant setting). Table 2 presents characteristics of the seven patients identified as having definitive or probable scalp metastasis. Only one patient had a biopsy. Six other patients had skin lesions that were clinically suspicious enough to reasonably believe that they had developed skin scalp metastases. Eight other patients had scalp lesions that were considered benign by the physician (e.g. eczema). The median interval between the diagnosis of breast cancer to the first distant metastasis was 29.3 months and the median interval between the first metastasis to scalp metastasis was 3.4 months. Below is a description of the seven definitive or probable cases of scalp metastases.

The first patient received CMF for a stage I breast cancer. She received adjuvant chemotherapy in a hospital that does not use scalp cooling. Two years later, she developed metastases to bones, lungs and liver and received epirubicine and used scalp cooling for six cycles out of nine (stopping the use of scalp cooling corresponded with the physician noticing a lesion on the scalp). A nodule on the scalp was found and a biopsy confirmed that it was a metastasis. The patient later received docetaxel and capecitabine (sequentially) with no scalp cooling. No other notes were reported on the scalp lesion.

[2] Doxorubicin-cyclophosphamide. CMF cyclophosphamide-methotrexate-5-fluouracil.

The second patient was diagnosed with a stage III breast cancer and had received CMF in a neoadjuvant and adjuvant setting with scalp cooling. She had refused other chemotherapy that could cause alopecia. She relapsed in the contralateral breast 8 years later and received AC with scalp cooling. The following year, she was diagnosed with metastases to lungs, bones, liver, brain, nodes, soft tissues, spleen and kidney. A clinical note reported three nodules of 5–8 mm that the patient reported having since the time of her symptoms of metastatic disease. These nodules regressed with chemotherapy (capecitabine).

The third patient was diagnosed with a stage IIIB breast cancer. She had received AC in the neoadjuvant and adjuvant setting with scalp cooling. Two years later, bones metastases were confirmed and she used anastrozole. Four months later, it was noted for the first time that the patient had a mass on her scalp that decreased in size. Later, the scalp lesion seemed to progress as the clinical notes talked about "recurring sensitive tumefaction". There is no further information about this lesion afterwards. Megestrol acetate and exemestane were then given in that order for bone metastases, soft tissue and lesions on the scalp. The patient never used scalp cooling in the metastatic setting because she only received hormone therapy after her first relapse.

The fourth patient was also diagnosed with a stage IIB breast cancer. She had received AC with scalp cooling as adjuvant therapy. Two and a half years later, bone metastases were diagnosed and docetaxel was used without scalp cooling. Two months later, a physician noticed two sensitive nodules, which regressed completely with chemotherapy.

The fifth patient was diagnosed with a stage IIA breast cancer and had received adjuvant CMF with scalp cooling. Three years later, she developed bone and lung metastases and then ones in the lymph nodes and central nervous system. Scalp cooling was used with the first two lines of chemotherapy (EC then docetaxel). Four years after the diagnosis of metastatic disease the patient showed de novo lesions on scalp and developed liver metastases. Capecitabine was started and the scalp lesions regressed.

The sixth patient was diagnosed with a stage IIIB breast cancer. She had received AC in neoadjuvant and adjuvant, but scalp cooling was used only with the neoadjuvant chemotherapy (two out of four cycles). Metastatic bone disease was diagnosed 2 years later. At that time, a 7 mm mobile nodule was found on the skin scalp and the patient said she had the lesion for about 5 months. The lesion regressed with anastrozole. Later the patient relapsed locally, and other sites of recurrence (soft tissues, peritoneal carcinomatosis and pancreas) appeared. She received CMF, docetaxel, capecitabine and megestrol acetate in that order. Scalp cooling was never used in the metastatic setting.

Table 1 Baseline characteristics

	Use of scalp cooling with neoadjuvant or adjuvant chemotherapy		*P* values
	No $n = 87$	Yes = 553	
Age at diagnosis (years)	51.4 ± 9.0	51.8 ± 9.6	0.72
	%	%	
Tumour size[a]			0.49
T0	0	0.2	
T1	46.0	44.9	
T2	47.1	41.4	
T3	3.5	7.0	
T4	3.5	6.5	
Nodal status[a]			0.46
N0	34.5	42.3	
N1	65.5	57.1	
N2	0	0	
N3	0	0.4	
NX/unknown	0	0.2	
Stage[a]			0.06
I	24.1	20.8	
II	69.0	66.4	
III	6.9	12.6	
unknown	0	0.2	
Grade			0.25
I	13.9	15.4	
II	42.5	32.0	
III	31.0	39.8	
SR	12.6	12.8	
Histological type			0.40
Ductal	89.7	86.4	
Lobular	8.0	12.1	
Other	2.3	1.5	
Lymphovascular invasion			0.77
Yes	58.6	61.1	
No	41.4	38.3	
Unknown	0	0.6	
Hormone receptors			0.73
Positive	77.0	74.3	
Negative	23.0	25.5	
Unknown	0	0.2	
Chemotherapy			0.06
Neoadjuvant only	2.3	2.5	
Adjuvant only	95.4	88.3	
Both	2.3	9.2	
Type of chemotherapy			<0.01
AC or CMF	43.7	61.1	
CEF, CE, FEC ou FAC	13.8	28.0	
Taxanes-based	40.2	9.4	
Other	2.3	1.5	
Type of hormone therapy			0.37
TAM	39.1	38.0	
TAM ± AI	33.3	31.3	
Other/unknown	1.2	1.6	
Negative hormone receptor or no hormone therapy	26.4	29.1	

[a] According to the Amerian Joint Committee on cancer staging version 5; AC, doxorubicin, cyclophosphamide; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; CE, cyclophosphamide, epirubicin; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; TAM, tamoxifen; AI, aromatase inhibitors

The seventh patient was diagnosed with a stage IIIB breast cancer. She had received EC as neoadjuvant and adjuvant chemotherapy and had had scalp cooling. She developed metastases in the lungs, bones, nodes, soft tissues and adrenals, and received pegylated doxorubicin with cyclophosphamide and later CMF. She had scalp cooling for all these chemotherapy treatments. During her follow-up, a nodule of 2–3 mm was noticed on her scalp. Docetaxel was given without using scalp cooling. One month later, the scalp lesion seemed to regress. The patient developed metastases to kidneys, liver and the central nervous system and received capecitabine and later vinorelbine. The scalp lesion regressed completely.

Discussion

This is the first study designed to specifically determine the incidence of scalp metastasis in a population of women with early breast cancer who received scalp cooling for prevention of chemotherapy-induced alopecia. The incidence of scalp metastasis was low, 1.1% among women who used scalp cooling at some point during their treatment for breast cancer. In this cohort, scalp metastases never presented as the sole metastatic site. Four out of 7 women (57.1%) with scalp metastases had a stage III breast cancer as opposed to 12.0% in the whole population studied here who had stage III ($n = 76$). Stage III breast cancer are at increased risk of relapse generally compared to stage I and II. Also, none of the seven women received taxanes-based regimens in the neoadjuvant or adjuvant setting, which are known to be more effective than non-taxanes based regimens.

Table 2 Characteristics for patients with scalp metastasis

Patient number	Age at diagnostic	Stage	Histology	Grade	LVI	Metastatic sites[b]	Use of scalp cooling in adjuvant/neo adjuvant?
1	57	I	Ductal	Poorly differentiated	No	1,2,3,7	No[a]
2	44	IIIA	Ductal	Poorly diferentiated	Yes	1,2,3,4,5,6,7	Yes
3	41	IIIB	Ductal	Well differentiated	No	2,6,7	Yes
4	50	IIB	Ductal	Poorly differentiated	Yes	1,2,3,7	Yes
5	62	IIA	Ductal	Moderately differentiated	No	2,3,4,5,7	Yes
6	38	IIIB	Ductal	Moderately differentiated	Yes	2,6,7	Yes
7	54	IIIB	Adeno-squamous	Unknown	Yes	1,2,3,4,5,6,7,9	Yes

LVI, lymphovascular invasion, [a]scalp cooling used for chemotherapy given at relapse, [b]1 lung, 2 bone, 3 liver, 4 CNS, 5 lymph nodes, 6 soft tissues, 7 scalp, 8 bone marrow, 9 other

Scalp metastases were first reported in the 1930's [11, 14]. Scalp metastases have been described with a variety of cancers, including lung, gastric and breast cancers. During the 1930's, no chemotherapy was used and we can therefore assume that scalp cooling was not used either.

It is hypothesized that scalp cooling could favour the development of scalp metastases because its mechanisms of action. With the exception of one woman (who used scalp cooling only for metastatic disease), our results show that all other women who developed a biopsy-proven or a clinical suspicion of scalp metastasis had received scalp cooling in either the neoadjuvant/adjuvant setting. There are two cases report in the literature of women who already had scalp metastases and still used the cold cap. Their scalp metastases responded to treatment even with the use of scalp cooling, demonstrating that a certain amount of chemotherapy still reached the scalp [18, 19]. The clinical implication of scalp metastases is unknown but in our study, the lesions were small and did not seem to be problematic to women.

The safety of cryotherapy (use of cold), which is also being used to reduce other side-effects, has not been questioned. For example ice chips can be chewed to reduce the incidence of mucositis. More recently, gloves have been tested to prevent nail toxicity associated with docetaxel [24].

Our study has several strengths. First, this is the study with the longest follow-up. Secondly, it is the largest sample size of all published studies on scalp metastases. Lastly, data were available on patients' characteristics (e.g. staging) and cancer evolution, making possible to know when scalp metastases appeared in relation to other metastases.

This study also has some limitations. Firstly, all the charts reviewed came from a single institution. Secondly, scalp examination during medical visits was not conducted systematically, so it is possible that other women developed scalp metastasis but were not diagnosed as such. However, this would mean that scalp metastases would not be clinically important if not detected by the patient or their physician. Thirdly, of all the patients who potentially had scalp metastasis (seven), only one patient was biopsy-confirmed. Therefore, it cannot be excluded that the other six lesions were benign and because they fluctuated they were identified as malignant. Fourthly, the control group was small: only 87 women compared to the 553 who received scalp cooling. Therefore, comparisons between the two groups are limited. Lastly, we had no control group (a group of women who did not receive chemotherapy in the neoadjuvant/adjuvant setting).

Conclusion

This study found a low incidence of scalp metastases in women with breast cancer and in none of the case it was the first isolated site of relapse. All women with scalp metastases have received scalp cooling at some point during their treatment and women with stage III breast cancer were at higher risk of developing scalp metastases, a population which is at increased risk of relapse in general. These biopsy-confirmed lesions and suspicious scalp lesions were all found in women who also had metastases in at least another site. However, with these results, we cannot exclude that possibility that scalp cooling contributed to scalp metastases and were favoured by scalp cooling. Further research is needed to definitively establish the relationship between scalp cooling and scalp metastases and the strength of the association.

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References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early

breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687–1717. doi:10.1016/S0140-6736(05)66544-0
2. Carelle N, Piotto E, Bellanger A et al (2002) Changing patient perceptions of the side effects of cancer chemotherapy. Cancer 95:155–163. doi:10.1002/cncr.10630
3. Lemieux J, Maunsell E, Provencher L (2008) Chemotherapy-induced alopecia and effects on quality of life among women with breast cancer: a literature review. Psychooncology 17:317–328. doi:10.1002/pon.1245
4. Sedlacek SM (2006) Persistent significant alopecia (PSA) from adjuvant docetaxel after doxorubicin/cyclophosphamide (AC) chemotherapy in women with breast cancer. Breast Cancer Res Treat. Abstract no 2105
5. Anonymous (2008) http://www.dignitana.se/
6. Anonymous (2008) http://www.paxman-coolers.co.uk/pages/index.asp
7. Edelstyn GA, MacDonald M, MacRae KD (1977) Doxorubicin induced hair loss and possible modification by scalp cooling. Lancet 2:253–254. doi:10.1016/S0140-6736(77)92877-X
8. Hillen HFP, Breed WPM, Botman CJ (1990) Scalp cooling by cold air for the prevention of chemotherapy-induced alopecia. Neth J Med 37:231–235. doi:10.1017/CHOL9780521223546
9. Camp-Sorrell D (1991) Scalp hypothermia devices: current status. ONS News 6:1–5
10. Grevelman EG, Breed WP (2005) Prevention of chemotherapy-induced hair loss by scalp cooling. Ann Oncol 16:352–358. doi:10.1093/annonc/mdi088 Review. 60 refs
11. Gates O (1937) Cutaneous metastases of malignant disease. Am J Cancer 30:718–730
12. Reingold IM (1966) Cutaneous metastases from internal carcinoma. Cancer 19:162–168. doi:10.1002/1097-0142(196602)19:2<162::AID-CNCR2820190204>3.0.CO;2-A
13. Brownstein MH, Helwig EB (1972) Metastatic tumors of the skin. Cancer 29:1298–1307. doi:10.1002/1097-0142(197205)29:5<1298::AID-CNCR2820290526>3.0.CO;2-6
14. Fay T (1938) Correlation of body segmental temperature and its relation to the location of carcinomatous metastasis. Surg Gynecol Obstet 66:512–514
15. Lookingbill DP, Spangler N, Helm KF (1993) Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. J Am Acad Dermatol 29:228–236. doi:10.1016/0190-9622(93)70173-Q
16. Witman G, Cadman E, Chen M (1981) Misuse of scalp hypothermia. Cancer Treat Rep 65:507–508
17. Forsberg SA (2001) Scalp cooling therapy and cytotoxic treatment. Lancet 357:1134. doi:10.1016/S0140-6736(00)04293-8
18. Christodoulou C, Tsakalos G, Galani E et al (2006) Scalp metastases and scalp cooling for chemotherapy-induced alopecia prevention. Ann Oncol 17:350. doi:10.1093/annonc/mdj008
19. Satterwhite B, Zimm S (1984) The use of scalp hypothermia in the prevention of doxorubicin-induced hair loss. Cancer 54:34–37. doi:10.1002/1097-0142(19840701)54:1<34::AID-CNCR2820540109>3.0.CO;2-W
20. Middleton J, Franks D, Buchanan RB et al (1985) Failure of scalp hypothermia to prevent hair loss when cyclophosphamide is added to doxorubicin and vincristine. Cancer Treat Rep 69:373–375
21. Vendelbo Johansen L (1985) Scalp hypothermia in the prevention of chemotherapy-induced alopecia. Acta Radiol Oncol 24:113–116. doi:10.3109/02841868509134372
22. Spaeth D, Luporsi E, Coudert B et al (2008) Efficacy and safety of cooling helmets for the prevention of chemotherapy-induced alopecia: a prospective study of 911 patients (pts). PASCO 26:517s
23. van den Hurk C, Coebergh JWW, van de Poll-Franse LV et al (2008) Some aspects of scalp cooling in breast cancer patients receiving chemotherapy. EJC suppl 6:201
24. Scotte F, Tourani JM, Banu E et al (2005) Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. J Clin Oncol 23:4424–4429. doi:10.1200/JCO.2005.15.651