Expert Statement on:

Scalp Cooling with Adjuvant/Neoadjuvant Chemotherapy for Breast Cancer and the Risk of Scalp Metastases

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1. Introduction

Breast cancer is a common malignancy in the western world; it is estimated that more than 180,000 women in the USA will be diagnosed in 2010 with this disease. Most of these women are treated surgically with curative intent, although neoadjuvant chemotherapy may be given first to improve surgical options. Adjuvant therapy including hormonal and chemotherapy, as well as local radiation therapy are commonly used modalities following definitive surgery to reduce the risk of local and systemic recurrence. Adjuvant chemotherapy has been shown to delay or prevent recurrence in early stage breast cancer, and recent studies as well as ongoing work is helping to define the group of patients who are most likely to benefit from this treatment. A cancer diagnosis is psychologically distressing, and decisions about adjuvant therapy compound this distress. Alopecia is a disturbing side effect of almost all effective adjuvant chemotherapy regimens. There are many toxicities associated with chemotherapy, but alopecia is the most public stigma of this treatment and, interestingly, is a real deterrent to chemotherapy for many patients (1-3). Scalp cooling to prevent chemotherapy-induced alopecia has been in use since the 1970's and offers excellent or good prevention of alopecia caused by many chemotherapeutic regimens, including those commonly used for breast cancer (4). The protection from alopecia offered by scalp cooling is a consequence of vasoconstriction resulting in reduced blood flow in the scalp, and reduced metabolic rate in the hair follicles with consequent decreased exposure to the chemotherapeutic agents. This limits the damage to dividing cells in the hair follicles.

The primary concern that has limited the use of scalp cooling devices in the United States is the possibility that scalp cooling could increase the risk for scalp metastases (4). This concern has been raised by the FDA in connection with the intended development of the DigniCap™ System, a scalp-cooling device, for introduction in the USA. Therefore Dignitana, the company behind the DigniCap™ System, has asked us to review the evidence regarding the possibility that scalp cooling used with adjuvant chemotherapy could increase the risk for scalp metastases in patients with breast cancer. There are two questions that we believe are critical to this evaluation: 1. Does adjuvant chemotherapy reduce the risk for scalp metastases in breast cancer patients? 2. Does scalp cooling increase the incidence of scalp metastases as the first sign of recurrent disease after adjuvant chemotherapy in breast cancer patients? We have reviewed the available data regarding these questions below.

2. The incidence of scalp metastases in breast cancer patients without scalp cooling

Scalp metastases are known to occur in breast cancer patients. However, the incidence of scalp metastases is not well established. In this review we have collected data from the published literature to estimate how many breast cancer patients are likely to experience scalp metastases during the course of their disease. Adjuvant chemotherapy became an established treatment modality to prevent recurrence from early stage breast cancer around 1980. However, since that time, treatment has changed considerably. Therefore, we evaluated the data from patients diagnosed and treated before 1980 separately from the data from patients diagnosed and treated after 1980. A difference in the incidence of scalp metastases prior to and after 1980 might suggest a preventive effect of adjuvant chemotherapy on the occurrence of metastases to this site. The incidence of scalp metastases as the first site of recurrence is of special importance, as if the incidence was increased in patients given adjuvant chemotherapy with scalp cooling this would raise the possibility that cooling could protect the scalp from the beneficial effects of adjuvant chemotherapy.

2.1. Incidence of scalp metastases in breast cancer patients with no adjuvant chemotherapy

2.1.1. The pattern of cutaneous metastasis was studied by Brownstein and Helwig (5) in 1972, prior to the introduction of adjuvant chemotherapy for breast cancer. In this study the clinical records of 724 male and female patients with cutaneous metastases were reviewed, including 167 women with cutaneous metastases from breast cancer. Of these 167 women, 140 had loco-regional metastases to the chest wall. Five women, or 3% of the total, had scalp metastases that developed at some point during their disease. The authors stressed that the scalp metastases in women with breast cancer usually appeared late in the disease.

2.1.2. Pivot et al (6) found that skin metastases occurred at some stage of disease in 249 (22%) of 1125 consecutive breast cancer patients having had surgery, radiotherapy or both – but no

adjuvant chemotherapy – as initial treatment for their disease. However, most of these skin metastases were loco-regional metastases in the chest wall. Scalp metastases were not accounted for separately among the sites of distant metastases.

Summary table for the results at a glance: Scalp metastases─ no adjuvant treatment

Study	# of pts with BC	# of pts with skin mets	# of pts with scalp mets
2.1.1.	NR	167	5 (3%)
2.1.2.	1125	249 (22%)	NR

NR: not reported

2.2. Incidence of scalp metastases in breast cancer patients receiving adjuvant chemotherapy

2.2.1. Lookingbill et al (7) investigated all patients with a malignancy whose disease had been diagnosed, treated, or followed at Milton S. Hershey Medical Center during a ten-year period starting in 1976. The use of adjuvant chemotherapy was not reported. Out of 992 women with breast cancer, 237 (24%) developed skin metastases at some time during their disease. There is no statement on the incidence of scalp metastases.

2.2.2. A large-scale investigation of cutaneous metastases was conducted by Lookingbill et al (8) in 4,020 patients with various cancers including 707 with breast cancer during a 10 year period beginning in January 1976. Out of the 707 women with breast cancer, 212 (30%) developed skin metastases over a follow-up period of about 5 years, and 18 (2.5%) developed cutaneous metastases to the scalp. The number of patients receiving adjuvant chemotherapy was not reported.

2.2.3. Krathen et al. (9) published a meta-analysis in 2003 of the incidence and location of cutaneous metastasis from various malignancies excluding melanoma, leukemia and lymphoma. A total of 20,380 patients with a variety of malignant tumors were included in the meta-analysis. There were 1903 cases of breast cancer; 457 (24%) developed cutaneous metastases at some time during their disease.

Of all 670 skin metastases from cancer of the breast, kidney, ovaries, bladder, lung, colon and rectum, and prostate, 47 (7%), occurred in the scalp. The number of scalp metastases in patients with breast cancer was not specifically accounted for, but was clearly less than 2.5% (47 out of 1903).

2.2.4. Lemieux et al (10) performed a retrospective analysis of the occurrence of scalp metastases in their patients given adjuvant or neoadjuvant chemotherapy for localised breast cancer with or without scalp cooling. There were 87 patients who had not used scalp cooling. They were followed for 5.4 years (±1.7). During that time one patient had recurrence with metastases to bones, lung, and liver. A few months later a scalp metastasis was detected.

Summary table for the results at a glance: Scalp metastases ─ adjuvant chemo probabl, no scalp cooling

Study	# of pts with BC	# of pts with skin mets	# of pts with scalp mets
2.2.1.	992	237 (24%)	NR
2.2.2.	707	212 (30%)	18 (2.5%)
2.2.3.	1903	457 (24%)	<47 (<2.5%)
2.2.4	87	NR	1 (1.2%)

NR = not reported

2.3. Incidence of scalp metastases as the first sign of recurrence

2.3.1. In the study by Pivot et al. (6) 1125 patients with recurrent breast cancer after surgery and radiotherapy were studied. 179 (16%) had loco-regional or distant skin metastases as their first metastatic site. 150 (13 %) were loco-regional metastases in the chest wall and 29 (2.6%) were distant skin metastases. The incidence of scalp metastases was not reported.

2.3.2. Dean et al (11) reference data from Fisher and The National Surgical Adjuvant Breast and Bowel Project (NSABP), who studied 7800 women with breast cancer treated with surgery alone or surgery combined with chemotherapy. Only 2 (0.025%) women experienced scalp metastasis as their first site of recurrence. Both of these patients had positive axillary lymph nodes at diagnosis and one had received adjuvant chemotherapy. Dr. Fisher (personal

communication, Oct. 2008) stated that these two patients were the only reported cases of scalp metastases over the many years of his involvement with tens of thousands of breast cancer patients enrolled on NSABP protocols.

Summary table for the results at a glance─ Scalp metastases as first site of recurrence, no scalp cooling

Study	# of pts with BC	# of pts with distant skin mets as first metastatic site	# of pts with scalp mets as first metastatic site
2.3.1.	1125 (recurrent)	29 (2.6%)	<29 (<2.6% of recurrent)
2.3.2.	7800 (all)	NR	2 (0.025%)

NR: not reported

3. The incidence of scalp metastases in breast cancer patients treated with chemotherapy together with scalp cooling

Grevelman and Breed (4) reviewed the literature on scalp metastases in connection with scalp cooling in patients with a variety of malignancies. They found that only 24 out of 58 studies reported data on scalp metastases after chemotherapy and scalp cooling. In 16 studies of those 24 studies it was specifically mentioned that no patients developed scalp metastases. However, the follow-up time was relatively short in most studies. There is a need for additional review and analysis aimed particularly at breast cancer patients.

3.1. Incidence of scalp metastases in breast cancer patients without or with metastatic disease with scalp cooling

In a prospective multicenter study Spaëth et al. (12) followed 911 cancer patients from year 2002 to year 2006 to examine the efficacy and safety of scalp cooling in connection with chemotherapy. Of the 911 patients there were 876 women, most of them with localised or advanced breast cancer treated with adjuvant or palliative chemotherapy. 770 patients chose

scalp cooling and 141 chose to have chemotherapy without scalp cooling. During follow-up of at least 2 years, one cutaneous scalp metastasis and two subcutaneous scalp metastases were reported in the patients who used scalp cooling, and no scalp metastases among the patients who did not use scalp cooling. This brief report does not give any indication of what kind of primaries the three patients had, or if the chemotherapy was given as adjuvant treatment or as palliative treatment for advanced disease. Because the majority of patients chose to use scalp cooling, the incidence of scalp metastases is essentially the same between the two allocated patient groups.

Summary table for the results at a glance ─ Scalp metastases after scalp cooling in a mixed population of patients with early and late stage breast cancer

Study	# of pts with BC	# of pts with scalp mets after scalp cooling	# of pts with scalp mets without scalp cooling
3.1.	<876	≤3 out of <770	0 out of <141

3.2. Incidence of scalp metastases in breast cancer patients with adjuvant chemotherapy and scalp cooling

3.2.1. Protiere et al (13) investigated 77 breast cancer patients who received adjuvant chemotherapy together with scalp cooling. 28 patients who did not use scalp cooling served as a control group. In addition there was a reference group of 109 similar patients given adjuvant treatment without being offered scalp cooling. No scalp metastases occurred in the patients having had scalp cooling during a median follow-up of 44 months, range 23-63 months. The authors do not mention anything about scalp metastases in the control or reference group.

3.2.2. Thirty-five patients with breast cancer treated with adjuvant chemotherapy with scalp cooling following definitive surgery were investigated in the study performed by Tollenar et al (14). During a mean follow-up period of 46 months, no scalp metastases occurred.

3.2.3. 19 patients were treated with adjuvant chemotherapy and scalp cooling, and 16 with adjuvant chemotherapy without scalp cooling in a study conducted by Ron et al (15). After a

median follow-up of 14 months (up to 2.5 years for several patients) no scalp metastases were observed.

3.2.4. Twenty-four patients with breast cancer were treated with adjuvant chemotherapy together with scalp cooling (16). No scalp metastases were detected. However, the follow-up time was not specified.

3.2.5. Lemieux et al (10) reported a retrospective analysis of scalp metastases in patients who were treated with adjuvant or neoadjuvant chemotherapy for localised breast cancer with or without scalp cooling. 553 patients used scalp cooling, and 87 patients did not. Follow-up was 5.8 years (±1.7) and 5.4 years (±1.7), respectively. Six patients in the scalp cooling group developed scalp metastases together with or after the diagnosis of metastases to bone and other sites. Among the 87 patients who had been treated without scalp cooling, one patient developed metastases to bones, lung, and liver. A few months later a scalp metastasis was diagnosed.

Summary table for the results at a glance ─ Scalp metastases after adjuvant chemo and scalp cooling

Study	# of pts with BC	# of pts with scalp mets with scalp cooling	# of pts with scalp mets without scalp cooling
3.2.1.	77+(28+109)	0 out of 77	Probably 0 out of (28+109)
3.2.2.	35	0 out of 35	- (uncontrolled)
3.2.3.	19+16	0 out of 19	0 out of 16
3.2.4.	24	0 out of 24	- (uncontrolled)
3.2.5	553+87	6 out of 553 (1.1%)	1 out of 87 (1.2%)

3.3. Incidence of scalp metastases in breast cancer patients with metastatic disease

3.3.1. There are several studies on scalp cooling in patients with advanced breast cancer. Parker (17) has reported the results from 12 patients with metastatic breast cancer divided in two groups - use of scalp cooling and no use of scalp cooling. Patients were treated with CMF

combination chemotherapy every 3 weeks, with 12 months of follow-up. No scalp metastases were seen during follow-up.

3.3.2. Christodoulou et al (18) treated 30 patients with advanced breast cancer with alopecia-causing agents together with scalp cooling. No scalp metastases were detected during the treatment or follow-up period.

3.3.3. Christodoulou et al (19) also reported a series of 227 breast cancer patients treated with chemotherapy together with scalp cooling during a 7 year period from 1998 to 2005. Scalp metastases were found in two patients. These two patients had multiple metastatic sites from their advanced disease (Dr. Christodoulou; personal communication, October 2008). Interestingly one patient with breast cancer and scalp metastases that was to be treated with weekly docetaxel decided to have scalp cooling with her chemotherapy. The scalp metastases responded to treatment and her hair was preserved.

3.3.4. Giaccone et al (20) treated 19 patients with breast cancer, most of which had recurrent disease with chemotherapy together with scalp cooling. There were 13 patients with breast cancer in the control group who did not use scalp cooling. There were no scalp metastases in the patients using scalp cooling. However, the length of the follow-up time was not given. The authors do not mention anything about any occurrence of scalp metastases in the control group.

3.3.5. In study from 1985, 61 evaluable patients with metastatic breast cancer received chemotherapy with scalp cooling (21). One patient with established liver metastases had a scalp metastasis detected 2.5 months after the start of treatment. Follow up ranged from 2 to 20 months.

3.3.6. Eighty-eight women with metastatic breast cancer were treated with chemotherapy with scalp cooling (22). No scalp metastases developed during the median follow-up of 9 months (range 4-12 months). The authors conclude that “in our experience we have been using the cold cap for about 15 years and no increase in the rate of scalp metastases has been observed”.

3.3.7. Thirty-six patients with metastatic breast cancer were treated with palliative chemotherapy with scalp cooling (16). Scalp metastases were detected in four patients. The follow-up time was not specified.

3.3.8. A post-marketing surveillance was conducted in Scandinavian hospitals where the DigniCap™ is used (Dignitana, company information 2008). A total of 2,249 patients were identified who had received chemotherapy with scalp cooling using the DigniCap™ System. 202 women had breast cancer, and all but one had advanced disease. Follow-up time was more than a year in most patients. During follow-up one patient with widespread metastatic disease also developed a metastasis to the scalp.

Summary table for the results at a glance ─ Scalp metastases after palliative chemo and scalp cooling

Study	# with BC	Scalp mets after scalp cooling, #	Scalp mets without scalp cooling, #
3.3.1.	6+6	0 out of 6	0 out of 6
3.3.2.	30	0 out of 30	-
3.3.3.	227	2 out of 227 (0.9%)	-
3.3.4.	19+13	0 out of 19	0 (?) out of 13
3.3.5.	61	1 out of 61 (1.6%)	-
3.3.6.	88	0 out of 88	-
3.3.7.	36	4 out of 36 (11%)	-
3.3.8.	202	1 out of 202 (0.5%)	=

4. Discussion

The possibility that scalp cooling protects the scalp from the beneficial effects of adjuvant chemotherapy has been a concern that has limited the use of these devices in the United States. However, a thorough review of the literature reveals little evidence to support this concern.

Scalp metastases occur rarely in breast cancer and, as reviewed above, scalp metastases seem to accompany and usually occur following the diagnosis of widespread metastatic disease regardless of the use of scalp cooling. This site of metastases is likely to represent the biology of the cancer, rather than a protected site such as the brain in HER2 positive disease. In the collected studies, follow-up and quality of data is insufficient to draw final conclusions. In this review we have nevertheless strived to find the available pertinent information, and have summarized our findings below.

4.1. Does adjuvant chemotherapy reduce the risk for scalp metastases in breast cancer patients?

The ability of adjuvant chemotherapy to specifically reduce scalp metastases presumes that there are dormant micrometastatic cells already seeded in the scalp from the primary tumor at the time of diagnosis of early stage disease. However, it is much more likely that adjuvant chemotherapy effects occult metastatic cells in other sites that might eventually metastasize to the scalp, although this site of disease is uncommon. Comparing the incidence of scalp metastases in patients who were treated before and after 1980 does not reveal a marked difference. The combined data in patients not treated with adjuvant chemotherapy (2.1.1.) found 5 scalp metastases that occurred at some stage of the disease among 167 patients with skin metastases. Assuming that the frequency of skin metastases was of similar magnitude across the studies in 2.1.2., 2.2.1., 2.2.2., and 2.2.3., the incidence of scalp metastases can be estimated at 0.7% (5 reported in 750 patients).

Looking at the incidence of scalp metastases in a setting where many breast cancer patients are likely to have been given adjuvant treatment, study 2.2.1. to 2.2.4., it does not appear that the reported incidence is lower than in patients not treated with adjuvant therapy. One limitation is that the reporting of scalp metastases varied between trials. Nevertheless these data do not suggest a marked reduction in the incidence of clinically manifest scalp metastases after the introduction of adjuvant chemotherapy in the treatment of early stage breast cancer.

The reported incidence of scalp metastases in studies where adjuvant chemotherapy was given together with scalp cooling, studies 3.2.1. to 3.2.5., is similar to the incidence reported in studies where patients were treated without scalp cooling. The combined results support the

assumption that adjuvant chemotherapy minimally reduces the incidence of scalp metastases, whether or not scalp cooling is used to prevent alopecia.

4.2. Does scalp cooling increase the incidence of scalp metastases as first sign of recurrence after adjuvant chemotherapy in breast cancer patients?

Scalp metastases are very rarely reported as the first metastatic site of recurrence in breast cancer patients treated with curative intent. Fisher from the NSABP reported in a communication to Judith Dean (6) that two patients in a sample of 7,800 women had scalp metastases as first site of recurrence. One of those patients had received adjuvant chemotherapy. The incidence of scalp metastases as the first site of recurrence can therefore be estimated to be around 0.025%, or lower (Fisher personal communication Oct 2008). The results of Pivot (6) are difficult to assess as only the number of distant skin metastases were reported. Specifics regarding the number of metastases in the scalp were not presented but could be expected to represent a small minority of the total events.

Would it be possible for scalp cooling in conjunction with adjuvant chemotherapy to increase the risk for scalp recurrence as the site for first recurrence? Based on available data this appears to be highly unlikely. Of all breast cancer patients treated with adjuvant chemotherapy together with scalp cooling there has not been a single case of scalp metastasis as site of first recurrence (10, 13-16). Considering the exceedingly low incidence of scalp metastasis as first site of recurrence, the risk appears vanishingly small for scalp cooling to increase the incidence of scalp metastases. In addition, the concept that scalp cooling could increase the incidence of metastases to the scalp suggests dormant cells in the scalp that later are responsible for recurrence. Based on what is now understood about the biology of breast cancer, and the exceeding small incidence of scalp metastases as the site of first recurrence, this seems highly unlikely to be an important mechanism for chemotherapy resistance.

4.3. Does scalp cooling have any negative effects on in metastatic breast cancer patients given palliative chemotherapy?

The concern for increased risk of scalp metastasis after adjuvant chemotherapy is of much less concern in the setting of palliative chemotherapy for breast cancer patients with established metastases. If a patient with metastases to the liver and lungs was interested in avoiding chemotherapy-induced alopecia, scalp cooling would be a reasonable option. A scalp metastasis is unlikely to be a source of risk in this setting.

5. Conclusion – Expert opinion

The use of scalp cooling over the past 30 years to prevent chemotherapy induced alopecia is well summarized by Breed (23). Additional data regarding safety and efficacy in the adjuvant setting from over 225 patients in a registry study of the Dignitana scalp cooling system in Japan will be presented at ASCO in June 2010. Scalp cooling has not been shown to increase the incidence of scalp metastases in patients with both early and late stage breast cancer. This is also the opinion of the TOPIC Trial Group in the UK who included scalp cooling in neoadjuvant breast cancer treatment in a multicenter trial involving close to 500 patients (24).
It is our expert opinion that scalp cooling can and should be offered to breast cancer patients who will be treated with adjuvant chemotherapy, and also those who are offered palliative chemotherapy associated with a significant risk of alopecia. The risks involved appear to be extremely small and the potential gain for the large number of women receiving adjuvant chemotherapy for breast cancer in the United States is substantial.

6. References

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Enclosures

1. CV of the expert