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EPIDEMIOLOGY

No effect of scalp cooling on survival among women with breast cancer

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Abstract Scalp cooling can prevent chemotherapy-induced alopecia in some cancer patients. It is not used in all countries. No data are available regarding its impact, if any, on survival. The aim of this study was to compare overall survival according to whether or not scalp cooling was used during neoadjuvant or adjuvant chemotherapy for non-metastatic breast cancer. We conducted a retrospective cohort study of 1,370 women with non-metastatic invasive breast carcinoma who received chemotherapy in the neoadjuvant or adjuvant setting. A total of 553 women who used scalp cooling came from a tertiary breast cancer clinic in Quebec City (diagnosed between 1998 and 2002) and 817 were treated in other hospitals in the province of Quebec (between 1998 and 2003) where scalp cooling was not routinely available. Overall survival of women who used scalp cooling and those who did not was compared using Cox proportional hazards models. Median follow-up for the scalp-cooled and the non-scalp-cooled groups was 6.3 years and 8.0 years, respectively. Overall mortality was no different (adjusted hazard ratio 0.89, 95 % confidence interval: 0.68–1.17, $p = 0.40$) among scalp-cooled women, compared to those not getting scalp cooling. Among women getting neoadjuvant or adjuvant chemotherapy for non-metastatic breast cancer, scalp cooling used to prevent chemotherapy-induced alopecia had no negative effect on survival. To our knowledge, this is the first study to compare survival of women who used scalp cooling to that of women who did not.

Keywords Breast cancer · Scalp cooling · Survival · Alopecia

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Introduction

Chemotherapy-induced alopecia is a common side effect of chemotherapy given in the neoadjuvant or adjuvant setting to women with breast cancer. Even though hair usually grows back after chemotherapy, hair loss is a side effect that is distressing for women and its impact on various aspects of women's lives is underestimated by doctors and nurses [1, 2]. Alopecia can be permanent in a minority of patients [3].

Scalp cooling can be used to decrease the likelihood of total or partial alopecia [4, 5]. The cooling device is installed a few minutes before chemotherapy starts and left in place for an additional 60–90 min after chemotherapy completion. From the Dutch scalp-cooling registry, the proportion of women who did not need to wear a wig or head cover after scalp cooling varies between 33 and 94 % except in the case of taxane/anthracycline combination regimens, after which only 8–29 % of women did not need to wear a wig or head cover [6]. Without scalp cooling, the vast majority of women getting chemotherapy for breast cancer will experience complete alopecia as a result. Scalp cooling use is quite variable from one country to another: it is routinely offered in many European countries, but rarely is in North America given that scalp cooling systems are not approved by the U.S. Food and Drug Administration (FDA).

With respect to safety, there might theoretically be an increased risk of scalp metastasis because of the postulated decreased chemotherapy activity in the cooled scalp [7, 8]. In a group where scalp cooling was not used, the incidence of scalp metastasis was reported to be 0.5 % in a cohort of 885 breast cancer patients after a median follow-up of over 9 years [9]. Our group published a retrospective cohort study of 644 non-metastatic breast cancer patients where 553 patients used scalp cooling and 87 did not [10]. We found a risk of scalp metastases of 1.1 % among the patients who got scalp cooling (median follow-up 5.8 years) and 1.2 % (1/87) among those who did not (median follow-up 5.4 years), although this single patient in the latter group had used scalp cooling in the metastatic setting but never in the adjuvant or neoadjuvant setting.

Even though these studies are reassuring, a negative impact of scalp cooling on survival could still be hypothesized. This could occur if scalp cooling, in which less chemotherapy reaches the scalp, resulted in secondary seeding to other organs from dormant cells in the scalp not killed by chemotherapy. To our knowledge, there are no data in the literature comparing the survival of patients who used scalp cooling to that of patients who did not. The objective of the present study was to compare survival in relation to scalp cooling use. We studied overall mortality after scalp cooling among women treated in the adjuvant/neoadjuvant setting in our centre [10] and, adjusting for possible confounding factors, compared it to mortality among a cohort of women treated in other centres of the province of Quebec where scalp cooling was not routinely used.

Methods

Patients

Study population

This was a retrospective cohort study based on two cohorts. The first cohort, about which detailed information was previously published [10] included patients treated at the Centre des Maladies du Sein Deschênes-Fabia (CMSDF). The CMSDF is a specialized breast cancer centre in Quebec City, Quebec, Canada, where scalp cooling is offered routinely. At the CMSDF, there were 2,328 women diagnosed from June 1st 1998–June 30th 2002, among whom 644 were treated with chemotherapy for a non-metastatic breast cancer. In this cohort, 553 used scalp cooling (86.4 %) and are identified here as "scalp-cooled". Scalp cooling methods varied during this time period. Methods used were either a cold cap changed at regular intervals (ice packs or Penguin® caps) or a helmet with circulating cold fluids applied on the head before chemotherapy and until 45–90 min after its completion. Information on staging, pathology and treatment received was obtained from our breast cancer database, while information concerning use of scalp cooling was obtained by chart review. Survival information up to October 31st 2008 was obtained through linkage to the relevant Quebec provincial administrative databases.

The non-scalp-cooled comparison cohort came from a population-based random sample of 2,301 breast cancer patients diagnosed in 1998 and 2003 in the province of Quebec. These women represented approximately 20 % of all new cases of breast cancer diagnosed in Quebec during those years [11]. These women were part of a study conducted through the *Institut National de Santé Publique du Quebec* (INSPQ) to examine trends over time in diagnosis and treatment of women with breast cancer in the province [11]. Stratified random sampling was used to identify this group. First, hospitals were stratified according to the volume of breast cancer cases and then in each such stratum, hospitals were randomly selected. Then, patients were randomly selected from each selected hospital in each stratum. Among the 2,301 women selected, 817 received adjuvant or neoadjuvant chemotherapy for a non-metastatic breast cancer in centres other than the CMSDF, and were included in this study as the "non scalp-cooled"

comparison group. A survey on scalp cooling use in these other centres found that scalp cooling was only exceptionally or very rarely used. Information on staging, pathology and treatment was obtained through chart review. Survival among these non-scalp-cooled women was available up to May 1st 2009 and was obtained in the same way as for the scalp-cooled group.

The *Hôpital du Saint-Sacrement* ethics review board approved this study.

Analysis

Characteristics of scalp-cooled and non-scalp-cooled groups were compared using Chi-square for categorical data and the *t* test for continuous data. The Cox proportional hazards model was used to calculate unadjusted and adjusted hazard ratios (HRs), and their 95 % confidence intervals (CIs) for overall mortality according to use of scalp cooling [12]. Cox models were adjusted for the following variables: age at diagnosis, stage using the AJCC version 5, grade, presence of lymphovascular invasion, type of chemotherapy, oestrogen receptor status, participation in a clinical trial and timing of chemotherapy given (adjuvant, neoadjuvant). In exploratory analyses, we assessed whether the effect of scalp cooling differed when used in the neoadjuvant or adjuvant setting. Thus, an interaction term between scalp-cooling and neoadjuvant group (that is, the timing of chemotherapy) was included in the models to test whether chemotherapy timing was a modifying factor. Follow-up of women in the scalp-cooled cohort was censored on October 31st 2008, and on May 1st 2009 for those in the non-scalp-cooled cohort.

A hazard ratio (HR) 1 indicates that mortality rates in the two groups compared were the same, whereas a HR $>$ 1 or HR $<$ 1 means, respectively, a higher or lower death rate in the scalp-cooled group compared to women in the non-scalp-cooled group. The proportional hazards assumption, where HRs are constant over time, was verified for the exposure variable, scalp cooling versus not, in unadjusted and adjusted models. A p value <0.15 for the interaction term was considered significant. Finally, sensitivity analyses were conducted comparing the patients treated with scalp cooling [all from a single centre with a high volume of breast cancer (defined as $\geq$90 cases per year)], to women in the non-scalp-cooled cohort also treated in high-volume centres. This analysis was conducted to avoid confounding by organisational or quality-of-care factors correlated with the centres' breast cancer case load [13]. Finally, in an analysis restricted to women not treated with neoadjuvant or adjuvant chemotherapy, we also compared overall mortality of women at the CMSDF to that among women treated in centres other than the CMSDF. This was done to assess whether observed differences might be attributable to unmeasured centre characteristics rather than to the use of scalp cooling. In these analyses, the reference group was "Centres other than the CMSDF". These analyses were conducted for both all women meeting these criteria and in the subset of those treated in large-volume centres.

Results

A total of 1,370 women were included in the primary analysis (Table 1). All scalp-cooled women ($n = 553$) were from the CMSDF. The 817 non-scalp-cooled women were distributed as follows in terms of the volume of breast cancer cases per year in the centre where they were treated: 43.1 % from high-volume centres ($\geq$90 cases/year), 43.6 % from medium volume (30–89 cases/year) and 13.3 % from low-volume centres ($<$30 cases/year). The CMSDF, where all the scalp-cooled patients were treated, was a high-volume centre. There were 107 deaths in the scalp-cooled group and 199 in the non-scalp-cooled group. The median follow-up for survival was 6.3 years (range 3.2–10.3) and 8.0 years (range 6.4–10.3) in the scalp-cooled and non-scalp-cooled groups, respectively. Women in the scalp-cooled group were more likely to have higher stage tumours, to have oestrogen receptor-positive cancer, to have received first generation types of chemotherapy (AC or CMF) and to have participated in a clinical trial.

All-cause mortality was not significantly different when the scalp-cooled group was compared to the non-scalp-cooled group: the crude and adjusted HRs were 0.80 (CI 0.63–1.01) and 0.89 (CI 0.68–1.17), respectively (Table 2). When the analysis was limited to high-volume centres, the crude and adjusted HRs were 0.99 (CI 0.73–1.34) and 1.11 (CI 0.77–1.59), respectively.

When we explored the HRs according to timing of chemotherapy, in the adjuvant setting adjusted HRs comparing scalp-cooled women to those who were not were below 1, indicating lower mortality (0.81, CI 0.59–1.12) and above 1 (higher mortality) in the neoadjuvant setting (1.93, CI 0.95–3.93). However, the interaction term testing the effect of scalp cooling for chemotherapy in the adjuvant versus the neoadjuvant setting was not significant (adjusted p-interaction $= 0.19$).

Among women who did not receive chemotherapy, the crude and adjusted HRs were 0.71 (0.58–0.86) and 0.99 (0.78–1.25), respectively, when comparing such women from the CMSDF to similar women from other centres in Quebec. In comparisons limited to patients treated in high-volume centres who did not get chemotherapy, the crude HR was 0.80 (0.63–1.03) and the adjusted HR was 1.07 (0.79–1.44) (Table 3).

Table 1 Patient breast cancer and treatment characteristics

Characteristics	No scalp cooling (*N*=817)	Scalp cooling (*N*=553)	*p* value
Age at diagnosis (mean in years +/−SD)	52.5 ± 10.9	51.8 ± 9.6	0.24
Stage*			0.009
I	206 (26.1%)	115 (20.8%)	
II	516 (65.4%)	367 (66.5%)	
III	67 (8.5%)	70 (12.7%)	
Unknown	28	1	
Grade			0.11
I	143 (18.4%)	85 (17.6%)	
II	325 (41.8%)	177 (36.7%)	
III	309 (39.8%)	220 (45.7%)	
Unknown	40	71	
Lymphovascular invasion			0.0002
Yes	295 (49.6%)	212 (38.5%)	
No	300 (50.4)	338 (61.5%)	
Unknown	222	3	
Hormone receptors (oestrogens)			0.0096
Positive	525 (66.4%)	403 (73.0%)	
Negative	266 (33.6%)	149 (27.9%)	
Not done	26	1	
Type of chemotherapy			<0.0001
AC or CMF	339 (46.7%)	338 (61.1%)	
Anthracyclines**	300 (41.4%)	163 (29.5%)	
Taxane-based	86 (11.9%)	52 (9.4%)	
Unknown	92	0	
Had neoadjuvant chemotherapy			0.12
Yes	75 (9.2%)	65 (11.8%)	
No	742 (90.8%)	488 (88.2%)	
Adjuvant hormone therapy			<0.0001
Yes	493 (60.3%)	392 (70.9%)	
No	324 (39.7%)	161 (29.1%)	
Participated in a clinical trial			<0.0001
Yes	85 (10.4%)	104 (18.8%)	
No	732 (89.6%)	449 (81.2%)	

SD standard deviation; *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

* When neoadjuvant chemotherapy was given, the stage was clinical. Staging was based on the AJCC 5th edition

** Anthracyclines chemotherapy corresponds here to the following regimens: CEF, CE, FEC or FAC

Discussion

To our knowledge, this is the first study comparing mortality among women with non-metastatic breast cancer treated with chemotherapy who used scalp cooling to that of similar women who did not. We found no negative impact on survival for women who used scalp cooling with their chemotherapy.

This study has limitations. Although the total number of patients was large ($n = 1{,}370$) and we had 80 % power to detect a HR of 1.39, our study would have been somewhat underpowered to detect a smaller difference in survival associated with scalp cooling. The study was definitely underpowered for assessing the interaction we explored between scalp cooling and the timing of chemotherapy (neoadjuvant or adjuvant) although we did so because of its

Table 2 Hazard ratio comparing overall mortality in scalp-cooled and non-scalp-cooled group

Population	HR unadjusted	95% CI	*p* value	HR $^{*}_{adjusted}$	95% CI	*p* value
All centres						
All women ($N = 1{,}370$)	0.80	0.63–1.01	0.06	0.89	0.68–1.17	0.40
Adjuvant ($N = 1230$)	0.67	0.51–0.88	0.004	0.81	0.59–1.12	0.20
Neoadjuvant ($N = 140$)	1.37	0.82–2.29	0.24	1.93	0.95–3.93	0.07
Interaction scalp cooling*neoadjuvant treatment			0.02			0.19
High breast cancer case load centres						
All women ($N = 905$)	0.99	0.73–1.34	0.95	1.11	0.77–1.59	0.58
Interaction scalp cooling*neoadjuvant treatment			0.04			0.30

* Adjusted for age (<39, 40–49, 50–59, 60–69 and > 70 y.o.), stage (I, II, III, unknown), grade (I, II, III and unknown), lymphovascular invasion (yes, no, unknown), chemotherapy (CMF or AC, anthracyclines, taxanes-based, unknown), hormones receptors status (positive, negative, not done) and participation in a clinical trial (yes, no). The global model "all women" is also adjusted for neoadjuvant treatment

HR_a: hazard ratio; CI: confident interval

Table 3 Hazard ratio for overall survival in patients who did not receive chemotherapy, comparing women treated at the Centre des maladies du Sein Deschênes-Fabia with those treated in other centres in the province of Quebec

Population	$HR_{unadjusted}$	95% CI	*p* value	$HR^{*}_{adjusted}$	95%CI	*p* value
All women, no chemotherapy *N*=1,684	0.71	0.58–0.86	0.0006	0.99	0.78–1.25	0.93
All women treated in High-volume centres, no chemotherapy *N*=1,144	0.80	0.63–1.03	0.08	1.07	0.79–1.44	0.68

* Adjusted for age (<39, 40–49, 50–59, 60–69 and > 70 years), stage (I, II, III, unknown), grade (I, II, III and unknown), lymphovascular invasion (yes, no, unknown), hormone receptor status (positive, negative, not done) and participation in a clinical trial (yes, no)

clinical relevance. Second, the groups differed in terms of important prognostic factors and treatment characteristics. However, our conclusions did not materially change after adjusting for prognostic and treatment-related factors. Thirdly, we were unable to conduct analyses using disease-free survival or breast cancer-specific survival as the outcome because we did not have information on recurrences, site of relapse if present or on women's cause of death. We also had no information on scalp metastasis in the non-scalp-cooled group. Lastly, there might be differences between the CMSDF, which was the source of the scalp-cooled cohort, and other centres in the province of Quebec. This is why we compared overall survival in analyses restricted to women without chemotherapy. Hazard ratios were in the same directions as those in the comparison of scalp-cooled versus non-scalp-cooled groups. Strengths of this study are the large sample size, the population-based comparison group, and that all patients come from the same province, treated within a public health care system.

This study contributes important new information about the safety of scalp cooling. This is the first study to evaluate survival associated with the use of scalp cooling. Although chemotherapy-induced alopecia is very common and affects the majority of women receiving chemotherapy for non-metastatic breast cancer, scalp cooling is used unevenly around the world, in part because of lack of data on safety. This study contributes information in the North American context. Still, important questions about the effects of scalp cooling remain, particularly in the area of quality of life. Even if scalp cooling can decrease hair loss [4], the net benefit is unknown because 1) protection against hair loss might be partial instead of complete, and 2) scalp cooling will not prevent hair loss in all women. Data have shown that women who experience hair loss in spite of using scalp cooling might have worse quality of life than women who did not have scalp cooling [14, 15]. Therefore, further studies are required mainly on quality of life and on the impact on resource utilization of the health care system.

In conclusion, we found no impact of scalp cooling on survival when used with chemotherapy in the non-metastatic setting. The data presented here add important information for clinicians, patients and health care system decision makers.

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Conflict of interest The authors declare that they have no conflicts of interest.

Ethical standards The study is a chart review and scalp cooling use was routine at the CMSDF.

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