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Original Research Article

Late cutaneous effects of a local potent steroid during adjuvant radiotherapy for breast cancer

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ABSTRACT

Purpose: The aim of this study was to evaluate whether treatment with a local potent corticosteroid during adjuvant external radiotherapy (ERT) of breast cancer is associated with late skin toxicity.
Material and methods: Sixty patients (32 treated with potent corticoid cream versus 28 controls treated with moisturizer) who had been included in a randomized study on prophylactic local corticosteroid treatment under adjuvant ERT in 2009 and 2010 were subjected to a follow-up study in 2016.
Assessments of skin texture were registered according to the Late Radiation Morbidity Scoring Scheme (RTOG). Dryness, skin colour and skin thickness were objectively measured using non-invasive instruments. The patients were assessed for differences between their treated and untreated breasts.
Results: Skin atrophy was not noticed in any of the 60 patients. Objective instrumental measurements did not reveal any significant differences in skin dryness, colour, pigmentation or skin thickness over the average follow-up time of six years. Clinical assessment based on the RTOG scoring system revealed that the odds ratio of having late skin problems in patients treated with moisturizer compared to patients treated with corticosteroid was 3.2 (95% CI: 1.0–10.1).
Patients reported minor cosmetic dermatological sequelae. Seven patients developed telangiectasia, which caused cosmetic inconvenience.
Conclusion: In this study, prophylactic corticosteroid treatment to ameliorate radiation dermatitis during adjuvant ERT of breast cancer was not associated with an increase in late skin toxicity nor did it result in skin atrophy. This study is limited by its small sample size, and the risk for false positive findings.
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Introduction

Adjuvant external radiotherapy (ERT) is an essential component of breast cancer treatment. However, ERT often causes acute, consequential late or chronic skin reactions [1–3]. Acute toxicity manifesting as redness, dryness, desquamation and moist desquamation within the treated skin area develops within the first weeks of ERT [4]. The onset of chronic skin reactions has a long latency from months to several years after ERT [1]. Skin atrophy, fibrosis, changes in pigmentation, telangiectasia and skin cancer can develop [5]. The incidence of long-term adverse effects on the skin varies from 5 to 30% for fibroses and telangiectasia [6].

There is no clear cut association between the degree of radio dermatitis and the development of late reactions [7]. However, moist desquamation has been shown to be correlated with the development of telangiectasia but did not influence the extent of fibrosis [8]. Many studies have shown that prophylactic treatment with a potent corticosteroid cream ameliorates acute radio dermatitis [9–12]. However, long-term local safety, especially the development of skin atrophy, is an issue of concern [13]. To our knowledge, no studies have assessed the long-term skin effects of corticosteroid treatment administered in parallel with ERT.

The aim of this study was to evaluate whether treatment with a local potent corticosteroid during adjuvant ERT of breast cancer is associated with late skin toxicity.

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Material and methods

The study was performed from September 2016 to December 2016. Patients treated with ERT for breast cancer in 2009 and 2010 were invited to participate. They had been included in a randomized study on prophylactic local treatment using either a potent corticosteroid (betamethasone 0.1%) or a moisturizer (brand name Essex) [14]. Patients underwent adjuvant ERT with 50 Gy/25 fractions after initial mastectomy or breast-preserving surgery. In some patients, the radiation field was extended to the armpit and the supraclavicular fossa. Patients who had undergone mastectomy received a 3 cm marginal bolus around the scar. When the bolus was used, patients received 105–110% of the scheduled dose corresponding to the volume beneath the bolus of 55 Gy/25 fractions. Patients younger than 40 years of age and patients who underwent a surgery that was not radically performed were given a boost of 16 Gy/8 fractions, according to national guidelines [15]. Acute radiodermatitis was assessed by using the Radiation Morbidity Scoring Scheme from the Radiation Toxicity Oncology Group (acute RTOG) at the end of ERT. This scoring system ranks dermatitis signs from minor signs (grade 1) to severe signs (grade 4). Acute RTOG was stratified into two groups: 0–1 (mild) and 2–3 (severe).

Out of 102 patients participating in the original study, 42 were not included in the present study due to the following reasons: 14 had died (10 due to metastatic disease of internal organs, one due to loco-regional recurrence and pulmonary metastases, and three due to other diseases), seven did not respond after contacting, five lived in other counties, 10 could not participate for practical reasons, and six refused to participate. Thus, 60 patients were included in the present study. All patients obtained a study information letter and thereafter were asked by phone to participate in the study. Written informed consent was signed on the patients' first visit. All patient data were recorded in case report forms. Baseline data were collected on the first visit to the clinic and saved in Excel files. Demographic data and treatment provided to the 60 patients are shown in Table 1.

Assessments

Skin texture was registered according to the Late Radiation Morbidity Scoring Scheme from the Radiation Toxicity Oncology Group (Late RTOG), which has two separate evaluation scales, one for registration of changes of the dermis and epidermis, and the other for registration of changes of subdermal structures. Dermal and epidermal changes were registered as follows: grade 0: none; grade 1: slight atrophy, pigmentation change, some hair loss; grade 2: patch atrophy, moderate telangiectasia, total hair loss; grade 3: marked atrophy, gross telangiectasia; and grade 4: ulceration.

Subdermal structures were registered as follows: grade 0: none; grade 1: slight induration and loss of subcutaneous fat; grade 2: moderate fibrosis but asymptomatic, slight field contracture, <10% linear reduction; grade 3: severe induration and loss of subcutaneous fat, slight field contracture, >10% linear reduction; and grade 4: necrosis [16].

The late RTOG values noticed for skin and subcutaneous tissue were merged into two groups, RTOG = 0 and RTOG > 0, and patients treated with corticosteroid versus moisturizer were compared.

A dermatologist who had no information regarding the result of the acute RTOG during ERT assessed late RTOG. Clinical examinations included registration of any tumour in the skin of the treated area.

The differences in cosmetic features (skin texture and colour) between the treated and untreated breasts of patients were assessed by the patients as follows: grade 1: almost identical; grade 2: minimal difference; grade 3: fair; and grade 4: substantial difference.

The group of patients who underwent mastectomy were not asked about cosmetic outcomes.

Skin thickness was measured using 20 MHz Ultrasound (Dermascan C®, Cortex Technology, Hadsund, Denmark) [17,18]. Scans were obtained in four different sites in the ERT-treated field, and three measurements were made for each scan. Thus, skin thickness was considered the mean of 12 recordings. Scans were taken at least 2 cm from the surgical scar [19]. Dryness of the epidermis was measured as electrical capacitance using a Corneometer CM 820®, (Courage-Khazaka, Cologne, Germany) [20]. Five measurements were recorded at prefixed locations and averaged.

Redness (a*) and skin pigmentation (L) were measured with a narrow band Colormeter (DSM II ColorMeter®, Cortex Technology, Hadsund, Denmark) [21]. Four recordings were made at prefixed locations and averaged.

All recordings by non-invasive instrumental methods were made in the ERT-treated field and symmetrically on the healthy breast. In the final evaluation, measurements obtained on the ERT-treated side were considered with historical information, i.e., treatment with corticosteroids or moisturizer.

Adjuvant chemotherapy and/or anti-hormonal treatments after ERT were recorded.

Table 1
Distribution of surgical procedures, ERT, chemotherapy and endocrine treatment in the two treatment groups for the 60 patients.

Treatment groups	Corticosteroid	Moisturizer	Total number of patients
Study population	28	32	60
Median age, years (range)	67 (42–75)	65 (33–80)	
Surgical procedures			
Mastectomy, modified	9	10	19
Breast preserving surgery	19	22	41
ERT			
Chest wall with bolus	9	10	19
Whole breast	19	22	41
Supplementary armpit and supraclavicular fossa	9	8	17
Chemotherapy before ERT			
Without chemotherapy	15	22	37
FEC every third week x 3, and paclitaxel weekly x 12	13	10	23
Endocrine therapy after ERT			
Tamoxifen or/and aromatase inhibitors	23	21	44

Statistics

Descriptive statistics were used to describe the patient population. Paired *t*-tests were used to evaluate differences in skin characteristics between treated and untreated breast, for which each treated patient also served as her own control. For differences in treatment with steroid or moisturizer, *t*-tests were performed on the group level. A p-value ≤ 0.05 was considered statistically significant.

Ethic

The study protocol, patient information and consent forms were reviewed and approved by the Regional Ethics Committee no. 2014/449-32 at the Linköping University and by the Swedish Medical Products Agency (EudraCT 2009-018059-18) prior to the inclusion of patients. The study was conducted in accordance with the protocol, regulatory requirements, and ethical principles of the

Table 2
Dryness, redness, pigmentation and skin thickness characteristics and differences in dryness, redness, pigmentation and skin thickness after ERT in combination with treatment with a potent steroid compared to a moisturizer.

Measurement	Corticosteroid treated breast (mean)	Ci	Moisturizer treated breast (mean)	Ci	Difference moisturizer – corticosteroid	Ci	*p*-Value	Healthy breast (mean)	CI
Dryness, (Capacitance)	69.6	65.2–74.0	70.1	66.9–73.2	0.44	−4.8 to 5.7	0.86	69.9	67.5–72.3
Redness colorimeter (a*)	10.6	9.4–11.8	9.9	9.0–10.8	−0.19	−1.6 to 1.6	0.98	10.2	9.1–11.4
Pigmentation colorimeter (L)	29.5	28.4–30.6	29.8	28.4–31.0	0.3	−1.3 to 1.9	0.71	29.0	28.2–29.9
Skin thickness (mm) ultrasound	1.28	1.17–1.39	1.20	1.12–1.29	−80.1	−214.2 to 54.1	0.23	1.17	1.08–1.27

Declaration of Helsinki. Informed consent was obtained from each patient.

Results

The average observation period of patients treated in 2009–2010 with ERT, corticosteroids or moisturizer and included in the present study was six years (mean of 76 months, median of 77 months, range 71–83). No skin cancers or loco-regional recurrence of breast cancer were observed.

Instrumental measurements and assessment by RTOG

No major differences were found between the ERT-treated and untreated breasts (paired *t*-test, not reported here) in skin capacitance indicating dryness, colorimetric recordings indicating redness, or pigmentation and skin thickness measured by ultrasound (Table 2).

Late RTOG, skin

Clinical signs of skin atrophy were not observed in any of the 60 patients. Ten out of sixty patients (17%) had other noticeable skin changes. Three patients (5%) had altered pigmentation (grade 1) and seven (12%) patients had telangiectasia (grade 3). All seven patients with telangiectasia had undergone mastectomy and ERT to the chest wall and to the axilla and fossa. Telangiectasia was distributed in the bolus area, in the fossa and in the suprascapular area [15]. All seven patients had acute RTOG 2–3.

Late RTOG, subcutaneous tissue

Slight fibrosis of grade 1 was observed in 13 (21%) patients.

Six out of 28 patients treated with a corticosteroid had late RTOG grade > 0 compared to 15 out of 32 treated with moisturizer, odds ratio of 3.2 (95% CI: 1.0–10.1). Nine-teen out of 43 patients with acute RTOG 2–3 (severe) had late RTOG grade > 0 compared to 2 out of 17 with acute skin reactions RTOG grade 0–1 (mild), odds ratio of 5.9 (95% CI 1.2–29.2) (Table 3). The wide CI is an effect of few patients in the subgroups.

Patient-reported outcomes

Out of the 39 patients who underwent breast conserving surgery, 20 patients noticed cosmetic differences between the treated and untreated breast: 12 reported a minimal difference (score 2), 6 a fair difference (score 3) and 2 a substantial difference (score 4). Eleven patients noticed differences in skin texture, and five patients noticed differences in skin colour. There was no significant difference between the two treatment arms. We did not ask the patients who underwent a mastectomy if they experienced a cosmetic difference between the treated and untreated breast, as such a difference is obvious following mastectomy and may be a sensitive and emotional topic to patients.

All seven patients with telangiectasia underwent a mastectomy and ERT with bolus.

Table 3
Comparison of acute and late RTOG assessments.

	Late RTOG grade 0	Late RTOG grade > 0
Acute RTOG grade 0	1	0
Acute RTOG grade 1	14	2
Acute RTOG grade 2	17	11
Acute RTOG grade 3	7	8

Discussion

The present study identified no long-term sequelae following six weeks of local corticosteroids used prophylactically to ameliorate radio dermatitis during adjuvant ERT in breast cancer patients.

The development of skin atrophy is of particular concern as corticosteroids used for months or years, locally or systemically, are known to result in atrophy of the skin [22]. General fear of skin atrophy may explain the unwillingness of physicians and patients to use corticosteroid cream to prevent ERT dermatitis [23]. Studies of normal skin of healthy volunteers exposed to a potent local corticosteroid for six weeks have shown that the skin becomes thinner but the reduction of skin thickness, amounting to approximately 15%, returns to normal a few weeks after discontinuation of the corticosteroids [22]. In our previous report, corticosteroids were used for six weeks to prevent radio dermatitis.

In this study, clinical assessments via RTOG showed that one-third of patients had minor late sequelae, such as slight fibrosis, changes in pigmentation and telangiectasia, which mainly occurred in the group treated with the moisturizer compared to the group treated with corticosteroid with an odds ratio 3.2 (95% CI: 1.0–10.1). Patients treated with moisturizer during ERT who developed severe acute skin reactions experienced more late skin sequelae compared to those treated with corticosteroid. Thus, short course corticosteroid treatment during adjuvant ERT might also have a protective effect against late sequelae. Future studies should confirm this finding.

The cosmetic outcome of patients treated with breast-conserving surgery and ERT appeared to be favourable, as half of the patients did not report any differences between the treated and untreated breast. On the other hand, in the group that underwent mastectomy, seven patients out of 21 developed of telangiectasia, which was visible and disturbing to them. Earlier publications have shown that the development of telangiectasia due to radiation is more common in patients with acute radiodermatitis with moist desquamation (acute RTOG grade 3) and radiation dose [6,8]. All patients with telangiectasia had an acute RTOG score of 2–3 and had received a bolus.

A follow-up time of six years seems to be an adequate observation period [24]. In a study by Bentzen, [25] the length of time to the expression of 90% of the final frequency of moderate to severe complications was 3.2 years for fibrosis and 4.7 years for telangiectasia.

The sample we studied is of limited size, and thus, we cannot exclude an effect of local corticosteroid on the direction of cutaneous sequelae. The use of quantitative measurements to depict subtle effects did not detect any tendency towards atrophy. In conclusion, it remains unlikely that prophylactic corticosteroid treatment to ameliorate acute radio dermatitis during adjuvant ERT of breast cancer has any clinically relevant adverse effects on late skin reactions.

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