Hypofractionated radiotherapy and adjuvant chemotherapy do not increase radiation-induced dermatitis in breast cancer patients

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ABSTRACT

Purpose

Radiation-induced dermatitis is a common side effect of breast irradiation, with hypofractionation being a well-known risk factor. In the context of the widespread adoption of hypofractionated breast radiotherapy, we evaluated the effect of hypofractionated radiotherapy on the incidence of skin toxicity in patients receiving adjuvant chemotherapy.

Patients and Methods

We retrospectively reviewed the records of patients with breast cancer treated from 2004 to 2006 at a single institution. Patients undergoing lumpectomy with or without adjuvant chemotherapy followed by hypofractionated radiotherapy consisting of 42.4 Gy in 16 fractions were included in the study. Using cosmetic and skin toxicity scales, all patients were evaluated weekly during treatment and at scheduled follow-up visits with the radiation oncologist.

Results

During the study period, 162 patients underwent radiotherapy, and 30% of those (n = 48) received chemotherapy. Radiotherapy boost to the tumour bed was more common in the chemotherapy group [n = 20 (42%)] than in the radiotherapy-alone group [n = 30 (26%)]. We observed no statistically significant difference between the groups with regard to acute skin toxicity of grade 3 or higher (2.1% in the chemotherapy group vs. 4.4% in the radiation-alone group, p = 0.67) or of grades 1–2 toxicity (62.5% vs. 51.7% respectively, p = 0.23). There was also no significant difference in late grade 3 or higher skin toxicity between the groups (2.1% vs. 0% respectively, p = 0.30) or in grades 1–2 toxicity (20.8% vs. 25.5% respectively, p = 0.69). Similarly, excellent or good cosmetic result scores were similar in both groups (p = 0.80)

Conclusions

In our single-institution review, we observed no adverse effects of chemotherapy in combination with hypofractionated whole-breast irradiation. Further investigations are necessary to better elucidate the effects of chemotherapy on skin toxicity in the context of hypofractionated irradiation.

KEY WORDS

Breast cancer, hypofractionated radiotherapy, chemotherapy, skin toxicity

1. INTRODUCTION

Breast-conserving therapy, consisting of a breast-conserving surgery followed by whole-breast irradiation, has become the standard of care in the treatment of early-stage breast cancer [1,2]. The addition of a boost to the tumour bed has been shown in several randomized controlled trials to lower the rate of local recurrence and has now become part of breast irradiation [3,4]. Although this treatment scheme has been widely adopted, much debate remains about the ideal radiotherapy regimen to use. Several alternative fractionation regimens have recently been assessed [5] and compared with the standard fractionation schedule (25 fractions of 2 Gy each over 5 weeks) [6–9].

The alternative fractionation schedule that has received the most attention is hypofractionation, in which radiation is delivered using a lower number of fractions of more than 2 Gy each [6–9]. The theoretical advantages of hypofractionation include an improvement in cell killing from the increase in fraction size and a reduction in treatment duration [10]. Furthermore, shortening the treatment duration means that more patients can be treated with a limited number of machines, a concern that arises in many countries in which access to radiation therapy is limited. On the other hand, increases in the fraction size can potentially result in increased long-term side effects [11,12]. After the publication of several randomized

controlled trials in which hypofractionation was shown to achieve local control similar to that with standard fractionation [6–9], without an increase in long-term side effects, this approach was adopted in several parts of the world, including Canada and the United Kingdom.

In a randomized trial by Cancer Care Ontario (CCO), investigators compared the standard schedule with a hypofractionated regimen consisting of 42.5 Gy in 16 fractions of 2.66 Gy each over 22 days [6,7]. At 5 and 10 years, local control rates were similar for the two regimens. Furthermore, no differences were observed in either cosmetic outcome or late radiation morbidity to the skin or subcutaneous tissues. No patient enrolled in that trial received a boost to the tumour bed, and only 11% of patients received adjuvant chemotherapy. Furthermore, the effect of hypofractionation on cosmetic outcomes in patients receiving adjuvant chemotherapy was not separately assessed.

Similarly, the START (Standardisation of Breast Radiotherapy) A and B trials in the United Kingdom respectively compared the standard schedule with schedules of 41.6 Gy in 13 fractions (each 3.2 Gy) over 5 weeks and 40 Gy in 15 fractions (each 2.67 Gy) over 3 weeks [8,9]. Neither trial showed a difference in local control or late adverse effects between the hypofractionated regimen and standard fractionation. Patients receiving adjuvant chemotherapy were eligible to participate in both trials, and between 22% and 35% of enrolees received adjuvant chemotherapy. Again, cosmetic outcomes in the patients receiving adjuvant chemotherapy were not separately analyzed. Boost to the tumour bed was administered in some patients, but the effect of hypofractionation on the cosmetic outcome of patients receiving a tumour bed boost was not separately assessed.

In the context of the widespread adoption in Canada of hypofractionated radiotherapy since the completion of the aforementioned studies, we evaluated the effects of hypofractionated radiotherapy (42.4 Gy in 16 fractions) on cosmetic outcomes and skin toxicity in patients receiving either adjuvant chemotherapy or tumour bed boost.

2. PATIENTS AND METHODS

We retrospectively reviewed prospectively collected data on consecutive patients with breast cancer treated at the Jewish General Hospital (Montreal, Quebec).

2.1 Selection Criteria

Selected patients had to fulfil these criteria:

- Presence of pathologically proven early-stage invasive breast cancer or ductal carcinoma *in situ* (pT1, pT2, or pTis; cN0 or cN1)
- Treatment with breast-conserving surgery followed by adjuvant whole-breast hypofractionated radiotherapy consisting of 42.4 Gy in 16 fractions

Patients receiving adjuvant hormonal therapy or adjuvant chemotherapy (or both) were included in the review. No requirement was imposed regarding the type of chemotherapy used, although concomitant chemoradiation was not allowed.

Per departmental policy, patients with a breast separation larger than 25 cm were not eligible for the hypofractionated regimen.

2.2 Radiotherapy

All patients underwent computed tomography simulation for radiotherapy planning. Simulation and treatment were done in the supine position, with the ipsilateral arm raised above the shoulder. An inclined breast board was used for immobilization. Treatment volume consisted of the whole breast and the underlying chest wall. Treatment used a pair of opposed tangential fields. Field borders were determined at simulation and generally resulted in a 1-cm to 2-cm margin around the whole breast. Typically, the inferior border was located 1–2 cm below the infra-mammary fold, the superior border at the level of the suprasternal notch, the medial border at the mid-sternal line, and the lateral border at the mid-axillary line. All treatment plans were dosimetrically verified, and wedge compensation was used to ensure uniform dose distribution throughout the treatment volume. A uniform prescription point, located mid-way on the central plane, at two thirds of the distance from the skin to the deep field margin, was used. Heterogeneity of –5% to +7% was accepted. Treatment was delivered daily, Monday through Friday. Weekly portal films were obtained in the treatment position with a therapeutic beam to confirm adequate patient positioning. Patients were treated with a linear accelerator of 6 MV energy or more. No attempt was made to treat the axilla or the supraclavicular or internal mammary lymph nodes. Boost radiotherapy using electrons was given to selected patients in doses ranging from 9 Gy to 15 Gy in 3–6 fractions.

2.3 Patient Evaluation

All patients were evaluated weekly during treatment, at 1 month after radiotherapy, every 6 months for 5 years, and annually thereafter. Bilateral mammograms were obtained annually. Acute toxicity was evaluated using the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events,* version 3.0, during treatment and at the 1-month follow-up visit [13]. On further follow-up visits scheduled by the radiation oncologist, cosmetic outcome and radiation

toxicity were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) cosmetic rating system [14] and the Radiation Therapy Oncology Group (RTOG)/EORTC late skin radiation toxicity scale, version 2 [15]. Radiation oncologists involved in the study and trained to use the toxicity scales conducted the evaluations. The single worst score for every patient was used in the dataset. The validated tools measured skin and subcutaneous toxicity on a 5-point scale from grade 0 (no toxicity) to grade 4 (severe toxicity). The overall cosmetic outcome was measured as excellent, good, fair, or poor.

2.4 Statistical Analysis

Outcomes data were analyzed using the Prism software application (version 4.0: GraphPad Software, La Jolla, CA, U.S.A.). The two-tailed Fisher exact test was used to compare outcomes between the study groups. A p value less than 0.05 was considered statistically significant.

3. RESULTS

Between 2004 and 2006, 162 patients undergoing radiotherapy at our institution fulfilled the inclusion criteria. Of those patients, 114 did not receive chemotherapy; 48 did. Median follow-up was 28 months.

3.1 Patient Characteristics

Baseline characteristics of the two groups were slightly different (Table I). Patients in the chemotherapy group were younger, with a median age of 55 years as compared with 59 years in the no-chemotherapy group. Patients in the chemotherapy group were also more likely to have T2 and node-positive disease. Median follow-up and breast separation were similar in both groups.

3.2 Treatment Characteristics

Because chemotherapy was prescribed at the discretion of the treating medical oncologist, several different regimens were used in the chemotherapy group (Table II). The regimen most commonly prescribed (in 63% of patients receiving chemotherapy) was 4 cycles of doxorubicin and cyclophosphamide. Other regimens included doxorubicin, cyclophosphamide, and trastuzumab, or doxorubicin, cyclophosphamide, and a taxane.

Radiotherapy boost to the tumour bed was given to 50 patients; the median dose was 10 Gy (range: 9–15 Gy) and the median number of fractions, 4 (range: 3–6 fractions). Boost was performed with electrons in 91% of patients and with photons in 9%. Tissue-equivalent bolus was used in 12 patients. Tumour bed boost was more likely to be given to patients in the chemotherapy group, with 42% of those

TABLE I Patient characteristics

Characteristic	*Chemotherapy*	
	No	*Yes*
Patients (*n*)	114	48
Age at diagnosis (years)		
Median	59	55
Range	42–88	29–75
T stage [*n* (%)]		
Tis	43 (38)	0 (0)
T1	57 (50)	32 (67)
T2	14 (12)	15 (31)
Tx	0 (0)	1 (2)
N stage [*n* (%)]		
N0	95 (83)	33 (69)
N1	3 (3)	13 (27)
Nx	16 (14)	2 (4)
Breast separation (cm)		
Median	19	19
Range	15–24	15–23.5

TABLE II Treatment characteristics

Characteristic	*Chemotherapy*	
	No	*Yes*
Patients [*n* (%)]	114 (70)	48 (30)
Follow-up (months)		
Median	27	32
Range	16–46	21–40
Tumour bed boost [*n* (%)]	30 (26)	20 (42)
Chemotherapy type [*n* (%)]		
Adjuvant		48 (100)
AC ×4		30 (63)
AC ×4 + H		5 (10)
AC-T ×4		5 (10)
AC ×4 + T ×4		4 (9)
AC ×3		1 (2)
Navelbine + H		1 (2)
FEC ×3 + T ×3		1 (2)
FEC ×6		1 (2)

AC = doxorubicin–cyclophosphamide; H = trastuzumab; T = taxane; FEC = 5-fluorouracil–epirubicin–cyclophosphamide.

patients receiving it compared with 30% of those in the no-chemotherapy group.

3.3 Acute Skin Toxicity

Data on acute skin toxicity were collected for 156 of 162 patients (96%). In both groups, most patients developed grade 1 acute skin toxicity, with grade 0 reactions coming second (Table III). Only 5 patients developed grade 3 acute skin toxicity, and no patients in the study developed grade 4 toxicity. We observed no significant difference in acute skin toxicity between the two study groups ($p = 0.67$).

3.4 Late Skin Toxicity

Late skin toxicity was evaluated in 131 patients (81%) with a minimum follow-up of 16 months. As with acute skin toxicity, we observed no significant difference between the two study groups for late skin toxicity (Table IV). No late skin toxicity (grade 0) developed in 56.3% of patients receiving chemotherapy and in 56.1% of the no-chemotherapy patients; no patient developed grade 4 late skin toxicity.

3.5 Cosmetic Result

Cosmetic outcome was evaluated for 112 patients. Results were similar between the groups (Table V), with most patients having at least a good cosmetic outcome (52.1% in the chemotherapy group and 49.1% in the no-chemotherapy group). Although a similar proportion of patients had a fair or poor outcome in both study groups, the proportion of patients having an excellent outcome was higher in the no-chemotherapy group, although the difference was nonsignificant ($p = 0.49$).

4. DISCUSSION

The current study, a single-centre retrospective analysis, confirms the feasibility of hypofractionated radiotherapy in patients receiving postoperative chemotherapy. Rates of acute and late skin toxicity were not significantly different with or without the use of chemotherapy. Similarly, cosmetic outcomes were at least good in 71.8% of evaluable patients without chemotherapy and in 73.6% with chemotherapy.

To better understand these results, a comparison with the only randomized controlled trial using the same radiotherapy regimen is warranted. In the CCO study [6], late skin toxicity and cosmetic outcomes were both analyzed (acute skin toxicity was not). A good or excellent cosmetic outcome was found in 76.8% of patients, a result similar to that reported in the present study. Other series and trials using different hypofractionation regimens report good or excellent outcomes in 64%–89% of patients [16–19]. Of the evaluable patients in the present study, 70% did not develop late skin toxicity, a figure markedly lower than the 87% of patients with no late skin toxicity in the CCO study [6]. Patient and treatment characteristics cannot account for this difference between the two studies, but differences in the application and interpretation of the toxicity scoring scales might explain the discrepancy. Other studies did not assess and report late skin toxicity [8,9,20] and thus cannot be compared with the present analysis.

TABLE III Acute skin toxicity

Grade	*Chemotherapy [n (%)]*		p
	No	*Yes*	*Value*
0	45 (39.5)	16 (33.3)	0.67
1	50 (43.8)	26 (54.2)	
2	9 (7.9)	4 (8.3)	
3	5 (4.4)	1 (2.1)	
4	0 (0)	0 (0)	
NA	5 (4.4)	1 (2.1)	

NA = not available.

TABLE IV Late skin toxicity

Grade	*Chemotherapy [n (%)]*		p
	No	*Yes*	*Value*
0	64 (56.1)	27 (56.3)	0.43
1	25 (21.9)	9 (18.7)	
2	4 (3.6)	1 (2.1)	
3	0 (0)	1 (2.1)	
4	0 (0)	0 (0)	
NA	21 (18.4)	10 (20.8)	

NA = not available.

TABLE V Cosmetic outcome

Cosmetic score	*Chemotherapy [n (%)]*		p
	No	*Yes*	*Value*
Excellent	20 (17.5)	6 (12.5)	0.76
Good	36 (31.6)	19 (39.6)	
Fair	19 (16.7)	8 (16.7)	
Poor	3 (2.6)	1 (2.1)	
NA	36 (31.6)	14 (29.1)	

NA = not available.

As for early skin toxicity, approximately 12% of evaluable patients in the present study developed grade 2 or 3 toxicity, and no patient developed grade 4 toxicity. Data on acute skin toxicity in hypofractionated whole-breast radiotherapy are highly variable: combined grades 2 and 3 toxicity ranges from 9% in a Japanese trial (40 Gy in 16 fractions with a 10-Gy to 16-Gy tumour bed boost) [20] to 40% in a small Egyptian trial (42.5 Gy in 16 fractions to the whole breast) [21].

Although our study thoroughly addresses the issue of radiotherapy toxicity, it nonetheless has several limitations. It is retrospective, and patients that receive chemotherapy are chosen according to specific characteristics such as tumour pathology, staging, and age. A bias is thus introduced, because older patients are less likely to receive chemotherapy or boost radiation: 42% of patients receiving chemotherapy also received boost radiation, as compared with 26% in the group not receiving chemotherapy. It is nonetheless unclear whether this bias affects the overall results of the study.

A second important limitation of our study is the small sample size. For a difference of 3% in severe late toxicity between two treatments, as observed in the EORTC boost trial [3], a sample size exceeding 580 patients in each group is necessary to obtain a statistically significant result. Our results can thus be reassuring in that no important severe toxicity was seen when chemotherapy and hypofractionated radiotherapy were given, but no firm conclusions can be drawn because the study is underpowered to detect small differences in late toxicity.

A third limitation that should be acknowledged is the loss of patients to follow-up. Of the 164 patients initially included, only 156, 131, and 112 patients were included in the acute toxicity, late toxicity, and cosmetic assessments. For acute toxicity, missing data were not reported by the treating physician; for late outcome assessments, most missing data resulted from missed follow-up appointments. A bias might have been introduced if outcomes in patients lost to follow-up were different from those in the population studied.

Finally, examiners were not blinded to the patient's treatment. Although they used validated scales, their assessments of toxicity and cosmetic outcome may have been affected by their prior knowledge of the patient's treatments.

5. CONCLUSIONS

In patients undergoing hypofractionated whole-breast radiotherapy at a dose of 42.4 Gy in 16 fractions, the addition of adjuvant chemotherapy does not seem to significantly affect acute or late skin toxicity, or cosmetic outcome. Additional better-powered studies are necessary to assess the effects of chemotherapy on hypofractionated whole-breast radiotherapy.

6. ACKNOWLEDGMENTS

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7. CONFLICT OF INTEREST DISCLOSURES

The authors all declare that no financial conflicts of interest exist.

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