

A Comparison Study of Radiotherapy Toxicity between Conventional and Hypofractionated Whole Breast Radiotherapy

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Abstract. The aim is to compare the acute skin toxicity between two different fractionation schedules of adjuvant whole breast radiotherapy, conventional fractionation radiotherapy and hypofractionated radiotherapy. This is a prospective study of breast cancer patients referred for adjuvant radiation therapy. Radiation therapy was given either as conventional fractionation radiotherapy (5000 cGy/ 25 fractions / 5 weeks) or hypofractionated radiotherapy (4005 cGy/15 fractions / 3 weeks). Acute RT toxicity was evaluated using the Radiation Therapy Oncology Group toxicity grading system; the incidence of radiation therapy toxicity was compared. Seventy-eight patients were accrued in the study, 58% had breast conservative surgery and 42% had modified radical mastectomy. 54% were treated with hypofractionated radiotherapy and 46% with conventional fractionation radiotherapy, while 64% had Grade 0-II radiation therapy toxicity and 36% had Grade III-IV toxicity. On univariate analysis, the incidence of radiation therapy toxicity was (52.8%) in conventional fractionation radiotherapy group as compared to 21.4% in hypofractionated radiotherapy group ($p = 0.004$); other variables were not statistically significant. On multivariate analysis radiotherapy fractionation was the only factor of statistical significance regarding the incidence of radiation reaction ($p = 0.03$). This study showed fewer incidences of acute radiation reactions in hypofractionated arm as compared to conventional fractionated arm in the adjuvant whole breast radiotherapy.

Keywords: Breast radiotherapy, Hypofractionation, Skin toxicity.

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Introduction

The standard prolonged course of five weeks schedule of adjuvant whole breast radiotherapy has been challenged, especially with certain patient population including the elderly, and those living at areas far from radiation therapy facility. The delivery of 5 weeks radiation therapy regimen needs a physical effort, and in some patients it is a financial and social burden^[1,2].

The biological basis of a hypofractionated radiation schedule is using a biological equivalent dose (BED) that has been used in many trials to initiate different radiation therapy schedules^[3,4]. The BED can be calculated using a formula that includes the number of fractions, dose per fraction and α/β ratio^[5].

Different hypofractionated schedules had been used in the adjuvant setting in breast cancer. And most of these studies reported an acceptable acute and late toxicity profile^[6].

Several factors influence the ultimate appearance of the treated breast. The technique of surgery, the presence of postoperative complications, the radiation technique such as volume and dose used, the presence of systemic therapy, also tumor and host factors, have all been associated with cosmetic outcome^[7,8].

The aim of this study is to compare two adjuvant radiation therapy schedules of whole breast radiotherapy, conventional fractionation radiotherapy (CFR) (5000 cGy / 25 fractions / 5 weeks) and hypofractionated radiotherapy (HFR) (4005 cGy / 15 fractions / 3 weeks) in terms of acute toxicity profile in a prospective study.

Patients and Methods

This study is a prospective trial done on female patients with breast cancer referred for adjuvant radiation therapy at King Abdulaziz University Hospital, Jeddah, Saudi Arabia during the period from January, 2005 till March, 2007.

Inclusion criteria includes: a pathological diagnosis of breast cancer and primary surgical intervention breast conservative surgery (BCS) or modified radical mastectomy (MRM). Radiation started 3 weeks after completion of the last cycle of adjuvant chemotherapy. Exclusion criteria included those who cannot sign a written informed consent, and those

who have a skin disease that may interfere with the true representation of the radiation toxicity.

Radiation Therapy Techniques

Patients were simulated in a supine position over a breast board with arms directed cranially using computerized tomography (CT) simulation, with CT slices of 3 mm thick. Standard two tangential fields were used to treat the breast; an additional supraclavicular field was added; lymph nodes treatment was indicated. 3D planning system was used (Eclipse). The patients were given the choice between the short or long fractionation courses. CFR group were given 5000 cGy/ 25 fractions / 5 weeks at 200 cGy per fraction, 5 days per week; while those randomized to HFR were given 4005 cGy/ 15 fractions / 3 weeks at 267 cGy per fraction, 5 day per week.

Radiation energy was the same in the two groups; 6 MV photons from linear accelerator.

Radiation Toxicity and its Grading

During the radiation therapy schedule; patients were weekly observed by the radiation oncologist for the acute radiation reactions that may develop during treatment. Furthermore, it was reported and graded using the Radiation Therapy Oncology Group (RTOG) toxicity criteria (Table 1)^[9].

Table 1. Radiation Therapy Oncology Group (RTOG) skin toxicity criteria^[9].

Grade	Description
0	No toxicity
I	Faint erythema or dry desquamation
II	Moderate to brisk erythema or a patchy moist desquamation mostly confined to skin folds and creases; moderate edema
III	Confluent moist desquamation \geq 1.5 cm diameter and not confined to skin folds; pitting edema
IV	Skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion

Statistical Analysis of Data

Using SPSS software for statistical analysis, a simple descriptive analysis of all patients, disease related criteria, frequency of radiation reaction and grades among the study groups were analyzed. A

correlation between the incidence of radiation reaction and different variables in the study was done in a univariate analysis. A multivariate analysis was done between the incidence of radiation reaction and the different variables in the study.

Results

The study included 78 female patients; thirty-six (46%) patients were given CFR and 42 (54%) were given HFR. The mean age was 48.6 years \pm 12.5 (standard deviation (SD)). Forty-five (58%) patients had BCS and 33 (42%) patients had MRM.

The mean size of the primary tumor for the whole group was 3.9 cm \pm 2.29 (SD), for CFR it was 3.7 cm \pm 2.2 (SD) and for HFR it was 4 cm \pm 2.3 (SD), these differences were not statistically significant ($p = 0.63$).

The mean number of lymph nodes dissected in the study group was 14 nodes \pm 7.9 SD for the whole group and the mean was 14.9 \pm 8.7 SD in CFR and 13.2 \pm 7.2 SD in HFR. The differences were not statistically significant ($p = 0.35$).

The patients in both groups were not statistically different regarding their clinical and pathological features as shown in Table 2.

During radiation therapy course for all patients, only 11 patients (14%) developed grades III-IV RTOG radiation reaction and 67 patients (86%) had grades 0-II reaction. In CFR group 8 (22%) patients had grade III-IV reaction as compared to 3 (7%) patients in HFR group. Twenty-eight (78%) patients in CFR group had grade 0-II reaction as compared to 39 (93%) patients in HFR group. These differences between the two groups in the incidence of acute radiation reaction was statistically significant with a higher incidence in CFR group ($p = 0.004$).

Sub-analysis of the different grades of radiation reaction and treatment groups showed that Grade III reaction was seen in 7 (19.4%) patients in CFR group and only in 3 (7%) patients in HFR group. Grade IV reaction was seen in 1(2.7%) patients in CFR group and was not seen in HFR group.

Grade 0 reaction was seen in 14 (39%) patients in CFR group and 32 (76%) patients in HFR group. Grade I reaction was seen in 3 (8.3%) patients of CFR group and 5 (12%) patients of HFR group. Grade II

reaction was seen in 11 (31%) patients in CFR group and 2 (5%) patients in HFR group.

Table 2. Patient and disease related characteristics in the study.

Criteria	CFR* Arm	HFR [‡] Arm	p Value
Number of Patients:	36 (46%)	42 (54%)	
Type of Surgery:			
MRM [§]	14 (39%)	19 (45%)	0.72
BCS	22(61%)	23 (55%)	
Primary Tumor (T) Stage:			
T1	7 (19%)	9 (22%)	0.02
T2	20 (56%)	18 (43%)	
T3	2 (6%)	13 (31%)	
T4	4 (11%)	1 (2%)	
Tx	3 (8%)	1 (2%)	
Lymph node (N stage)			
N0	11 (31%)	14 (33%)	0.67
N1	23 (64%)	23 (55%)	
N2	2 (5%)	4 (10%)	
Nx	0	1 (2%)	
Hormone receptor status :			
Hormone receptor positive	12 (33)	10 (24%)	0.27
Hormone receptor negative	17 (47%)	17 (40%)	
Hormone receptor unknown	7 (20%)	15 (36%)	

*Conventional fractionation radiation arm

‡Hypofractionated radiation arm

§Modified radical mastectomy

||Breast conservative surgery

Unvaried analysis between the two treatment arms regarding the difference between them, in every grade of radiation reaction, revealed a statistically significant difference in favor of CFR which was associated with more radiation reactions than HFR (p = 0.003). Figure 1 showed the incidence of radiation reaction among the study groups.

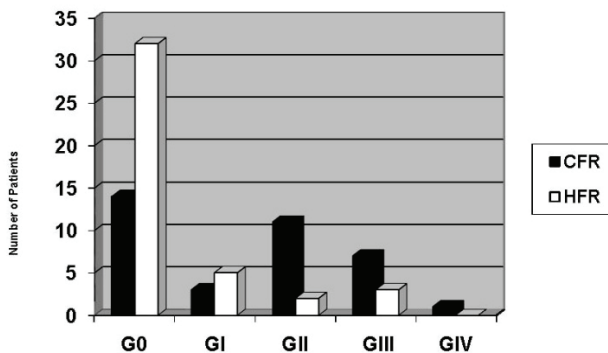


Fig. 1. Incidence of acute radiation reactions.

Multivariate analysis using logistic regression model (enter method), showed that the only factor that influenced the incidence of acute radiation reaction was the technique of radiation therapy with a statistically higher incidence of acute reactions in the CFR as compared to HFR ($p = 0.03$).

Other factors were not of statistical significance; age of the patient ($p = 0.64$), type of surgery ($p = 0.56$), primary tumor stage ($p = 0.56$), lymph node stage ($p = 0.59$), number of surgically resected lymph nodes ($p = 0.99$), and percentage of positive lymph nodes ($p = 0.25$).

Discussion

Many literature reviews in oncology, showed that there are some breast cancer patients who are undertreated mainly because of their inability to sustain the relatively long treatment duration (almost 5 weeks in conventional radiation schedule), especially the elderly patients and those who have a poor performance status from other disease comorbidities^[10-12]. Two-thirds of all newly diagnosed female breast cancer patients are in postmenopausal age group^[13], with anticipated comorbidities.

In the past, clinical trials were done to evaluate the feasibility of hypofractionation in the adjuvant setting of breast cancer. However, due to the relatively poor radiotherapy techniques at that time, the incidence of both acute and late radiation effects was relatively high. More recent clinical trials of hypofractionation were implemented using a better radiation technique than those in the past, and resulted in less radiation reactions to those patients^[14-16].

The aim of the current study was to compare between two fractionation schedules of radiation therapy to the breast; the CFR (5000 cGy/ 25 fractions / 5 weeks; 200 cGy per fraction), and the HFR (4005 cGy/ 15 fractions / 3 weeks; 267 cGy per fraction) in a prospective way. During the radiation therapy course out of 78 patients with breast cancer, 36 were treated with CFR and 42 patients were treated with HFR.

A statistically significant lower incidence of RTOG grade III-IV, acute radiation reaction was observed in HFR (7%) as compared to that in CFR (22%), $p = 0.004$. Even in multivariate analysis between different variables and the incidence of acute radiation reaction, the

treatment group showed a statistically significant less incidence of acute radiation reactions with HFR ($p = 0.03$).

A study by Whelan *et al.*^[17] who compared standard fractionation radiation versus hypofractionated radiation using 42.5 Gy in 16 fractions within 22 days. It showed that the rates of acute radiation reaction between the two arms were not statistically different. More important, this study looked at the 5 years local free survival rate between the two arms to evaluate the efficacy of the hypofractionation arm, and was found to be 97.2% in hypofractionation arm compared to 96.8% in the standard arm.

Another study of hypofractionation in breast cancer by Gittleman *et al.*^[18], in 20 patients with duct carcinoma in situ, radiation therapy was given as hypofractionation regimen. A total of 42 Gy was given over 3 weeks period at 2.8 Gy per day, acute radiation effects were seen only in 6 (30%) patients and were only grade I reaction.

Ortholan *et al.*^[19] reported 150 patients with breast cancer treated with surgery (BCS in 71.5% and MRM in 28.5%), then adjuvant chemotherapy followed by radiation. Radiation therapy was given as hypofractionation, only as once/weekly radiation at a dose of 6.5 Gy per fraction to a total dose of 32.5 Gy over 5 weeks. The acute radiation reactions (Grade III-IV) were 26.5% as compared to 14% in the current study. After a median follow up of 65 months, the late radiation skin reactions were found in almost 45.4% of patients, and the 5 and 10 years disease free survival rate were 80% and 71.5%, respectively. The 5- and 10-years overall survival rates were 71.6% and 46.5%, respectively. This relatively higher incidence of acute radiation reactions is most probably due to the use of a very high dose radiation per fraction (6.5 Gy).

Four high quality trials^[20-24], randomizing 7095 women, convincingly demonstrated that hypofraction can be performed with low morbidity rates and low local recurrence rates when used as adjuvant therapy following surgical treatment of breast cancer. The five-year local recurrence rates reported in these studies (2.0% to 9.1% in the new series) are much lower than those reported by randomized clinical trials for patients treated with BCS without radiation (24% to 37%). These large differences are unlikely to be due to the selection bias, given that the results appear comparable to the standard fractionation schedule in all of the randomized comparisons. In general, the cosmetic outcomes were

similar with standard fraction sizes and the larger fraction sizes used in the trials. Fraction sizes above 3.0 Gy appeared to give the worse cosmetic outcomes, although, they also tended to result in lower local recurrence rates. Late radiation damage to other normal structures (heart, lung, ribs) was rare and did not occur most frequently in women treated with the hypofractionation schedules studied in these trials. However, longer follow-up is needed to adequately rule out the increase of these uncommon late adverse events.

In conclusion the hypofractionated radiation therapy is an acceptable modality in the adjuvant setting of breast cancer with relatively low acute reactions. Moreover, this may be suitable for elderly patients and those who had poor performance status or living away from the radiation therapy facility.

To evaluate late radiation effects, and the impact of hypofractionated radiation on disease free and overall survival, a longer follow-up with larger number of patients is required.

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دراسة مقارنة بين العلاج بالأشعة للثدي بطريقة التجزئة التقليدية وطريقة التجزئة المكثفة

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المستخلص. تهدف هذه الدراسة إلى المقارنة بين التأثير الحاد على الجلد بين طريقتين لتجزئة برنامج العلاج بالأشعة المساعد للثدي، وهي الطريقة التقليدية (ط ت)، والطريقة المكثفة (ط ك). هذه الدراسة مستقبلية لمرضى سرطان الثدي الموصلة للعلاج بالأشعة المساعد. أعطى العلاج بالأشعة بإحدى الطريقتين التجزئية التالية (ط ت) لمدة خمس أسابيع، أو (ط ك) لمدة ثلاثة أسابيع، التأثيرات الجانبية الحادة على الجلد، تم تقييمها ومقارنتها حسب تصنيف مجموعة العلاج بالأشعة للأورام. النتائج لـ ٧٨ مريضاً شملتهم الدراسة، منهم ٥٨٪ تم علاجهم بطريقة (ط ك)، و ٤٢٪ بطريقة (ط ت). ٥٤٪ شدة تأثير الجلد حتى الدرجة الثانية، و ٤٦٪ أكثر من الدرجة الثانية. نسبة تأثير الجلد كانت ٥٢,٨٪ في مجموعة (ط ت) مقارنة بـ ٢١,٤٪ في مجموعة (ط ك). طريقة تجزئة الأشعة كانت هي العامل الوحيد ذو العلاقة بدرجة تأثير الجلد. أوضحت الدراسة أن تأثير الجلد الحاد أقل في المجموعة التي تم علاجها بطريقة التجزئة المكثفة.