Hypofractionated radiation therapy versus conventional radiation in the adjuvant setting of breast cancer; is there any difference in toxicity?

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Abstract
Recent studies of radiation toxicity in the treatment of breast cancer have shown that; the effects on normal tissues can constitute a significant health problem. One of these problems is skin toxicity. The aim of the current study is to compare the acute skin toxicity between two different fractionation schedules of adjuvant breast radiation: the conventional radiation (CFR) versus hypofractionated radiation (HFR).

This is a prospective randomized study done in breast cancer patients referred for adjuvant radiation therapy. Radiation therapy was given in either one of two ways: CFR (5000 cGy/ 25 fractions / 5 weeks; 200 cGy per fraction) or HFR (4005 cGy/15 fractions / 3 weeks; 267 cGy per fraction). Acute radiation reactions were graded according to the Radiation Therapy Oncology Group toxicity grading system (RTOG) (1).

A comparison was done between the incidence of these reactions and different variables as: total radiation dose, type of surgery, number of surgically dissected nodes, etc.

Seventy eight patients were accrued to the study, of whom 57.7% had breast conservative surgery (BCS), while 42.3% had modified radical mastectomy (MRM). Patients who had received HFR represented 53.8%, while those who received CFR represented 46.2% of all patients. The majority of patients (64.1%) had grade 0/II radiation reaction, and 35.9% had grade III/IV reaction.

On univariate analysis, there was a statistically significant difference between the two radiation arms regarding the incidence of radiation reaction, with higher incidence (52.8%) in CFR as compared to 21.4% in HFR (p 0.004), while the other variables (type
of surgery, number of surgically removed nodes, etc) were not statistically significant.

On multivariate analysis; the only factor of statistical significance regarding the incidence of radiation reaction was the radiation therapy schedule, with a higher incidence in CFR (p value 0.03).

There is a statistically less incidence of acute radiation reactions in hypofractionated arm as compared to conventional fractionated arm in the adjuvant radiation of breast cancer.

**Key words:**
Adjuvant radiation therapy - breast cancer - hypofractionation - acute skin toxicity.

**Introduction**
The standard five weeks adjuvant radiation therapy regimen to breast either following MRM, or BCS; has recently become an area of intense research; as in certain patient population; including the elderly, and those living at areas far from radiation therapy facility; the delivery of the standard 5 weeks radiation therapy regimen needs a lot of physical effort and in some patients financial and social burden (2, 3).

The biological basis of using a hypofractionated radiation regimen is the use of biological equivalent dose (BED) which had been used in many trials to initiate a different radiation therapy schedules (4, 5).

The BED is obtained by multiplying number of fractions by dose per fraction by the sum of 1 + dose per fraction divided by \(\alpha/\beta\) ratio (6).

A lot of hypofractionation schedules had been tried in the adjuvant setting in breast cancer. Although most of these studies reported an acceptable toxicity profile in both acute and late phases (7); the use of hypofractionated radiation therapy in those patients is not standardized in most of radiation therapy centers.

The aim of the current study is to compare between 2 adjuvant radiation therapy regimens of breast cancer, CFR versus HFR, in terms of acute toxicity profile in a prospective way.

**Patients and Methods**
This study is a prospective randomized trial done on female patients with breast cancer referred for adjuvant radiation therapy at King Abdel Aziz University Hospital,
Jeddah, Saudi Arabia during the period from January 2003 till March 2005 (inclusive). Inclusion criteria included: a pathological diagnosis of breast cancer and primary surgical intervention; which was either breast conservative surgery (BCS) done initially in early breast cancer (T1, or T2 lesions), or after neoadjuvant chemotherapy (Docetaxel 100mg/m2 IV day1, and Adriamycin 60 mg/m2 IV day1 to be repeated every 3 weeks for 4-6 cycles) in locally advanced lesions (T3, or T4), who were subjected to either MRM or BCS according to their response to chemotherapy. Patients who had BCS were given adjuvant chemotherapy, while those with locally advanced disease who had neoadjuvant chemotherapy; after surgical intervention, were given adjuvant chemotherapy if there is residual disease after surgery. Patients included in the study would be referred for adjuvant radiation therapy after they received their adjuvant chemotherapy (4 cycles of AC i.e. Adriamycin 60 mg/m2 IV day1, and Cyclophosphamide 600 mg /m2 IV day 1; and cycles were repeated every 21 days after checking the hematological profile). All patients who had BCS were referred for adjuvant radiation therapy, while patients who had MRM should have T3, or T4 lesions, and or N1, or N2 stage. Radiation was started 3 weeks after completion of last cycle of 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. Patients were simulated in supine position after centralization using laser lines and were positioned over a breast board with arms directed cranially. A midline was drawn after checking the mid plane with fluoroscopy (considered as the medial tangential border), then planning for lines of midaxillary area (with lead wire pasted over it), superior border of tangential field, inferior border of tangential field, and supraclavicular and anterior axillary field (if indicated to be included in radiation field) was done. Rotating the gantry and observing through fluorooscopy the coverage of an adequate area of the chest wall and coincidence of the medial tangential border with lateral tangential border (which was marked by lead strip) would be done and the gantry angle was
recorded. Then a contour of the chest wall (or breast) was done and the source axis distance technique (SAD) was implemented. A check films of the tangential and supraclavicular and anterior axillary fields (if done) were taken, reviewed by two radiation oncologists and signed and dated by them before patient went out off the simulation couch. After confirmation of all planning details by the radiation oncologist; all the information (field sizes, SAD, gantry angle, couch angle, and collimator angle if done) were registered electronically and saved and marks on the patient skin were tattooed. The radiation dosimetrist then scanned the contour drawn by the therapist, and sent the contour to a computerized planning system (CadPlan TM plus version 6.4.7) and an isodose curves were positioned over the tangential field to choose the best ones with the best isodose curve would be chosen to get the best distribution. Supraclavicular and anterior axillary field were treated as a given dose at D max. All the treatment planning parameters were reviewed by a radiation physicist and should be approved by 2 radiation oncologists and signed by them for approval.

All eligible patients were blindly randomized using a closed envelop between one of two regimens; either conventional fractionation radiation (CFR), or hypofractionated radiation (HFR).

Patients randomized to CFR 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; it was 6 MeV photons from linear accelerator. During the radiation therapy schedule; patients were closely observed by the radiation oncologist for the acute radiation reactions that may develop during treatment; and it was reported and graded using the Radiation Therapy Oncology Group (RTOG) toxicity criteria (table 1) (1).

<table>
<thead>
<tr>
<th>Grade of radiation skin</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Description of the toxicity criteria</td>
<td>No toxicity</td>
<td>Faint erythema or dry desquamation</td>
<td>Moderate to brisk erythema or a patchy moist desquamation mostly confined to skin folds and creases; moderate edema.</td>
<td>Confluent moist desquamation ≥ 1.5 cm diameter and not confined to skin folds; pitting edema.</td>
<td>Skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion.</td>
</tr>
</tbody>
</table>

Table (2) Patient and disease related characteristics in the study

<table>
<thead>
<tr>
<th>Criteria</th>
<th>CFR * arm</th>
<th>HFR ** arm</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients:</td>
<td>36 (46%)</td>
<td>42 (54%)</td>
<td></td>
</tr>
<tr>
<td>Type of surgery:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRM ***</td>
<td>14 (39%)</td>
<td>19 (45%)</td>
<td></td>
</tr>
<tr>
<td>BCS ****</td>
<td>22 (61%)</td>
<td>23 (55%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Primary tumor (T stage):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>7 (19%)</td>
<td>9 (22%)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>20 (56%)</td>
<td>18 (43%)</td>
<td>0.02</td>
</tr>
<tr>
<td>T3</td>
<td>2 (6%)</td>
<td>13 (31%)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>4 (11%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Tx</td>
<td>3 (8%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Lymph node (N stage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>11 (31%)</td>
<td>14 (33%)</td>
<td></td>
</tr>
</tbody>
</table>
Using SPSS software for statistical analysis, a simple descriptive analysis of all patient and disease related criteria and frequency of radiation reaction and its 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 patients (46%) were given CFR, while 42 (54%) were given HFR. Their mean age was 48.6 years ± 12.5 (standard deviation [SD]). Regarding surgical intervention; it was found that, 58% of patients had BCS, while 42% had MRM. The mean size of the primary tumor for the whole group was 3.9 cm ± 2.29 (SD) , and for CFR the mean was 3.7 cm ± 2.2 (SD) , and for HFR, it was 4 cm ± 2.3 (SD) , and the difference was not statistically significant (p 0.63) . There was an adequate number of lymph nodes dissected in the study group with a mean number of 14 nodes ± 7.9 (SD) for the whole group , and the mean was 14.9 ± 8.7(SD) in CFR , and it was 13.2 ± 7.2 (SD) in HFR , and the difference was 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; of the total number of patients; 11 patients (14 %) developed grades III/IV RTOG radiation reaction, while 67 patients (86%) had grades 0-II reaction. In CFR, 8 patients out of 36 (22%) had grade III/IV reaction, as compared to 3 patients only out of 42 (7%) in HFR. Twenty eight patients out of 36 in CFR (78%) had grade 0-II reaction as compared to 39 patients out of 42 (93%) in HFR group .

The difference, between the two groups regarding 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 arm revealed that; Grade III reaction was seen in 7 patients out of 36 (19.4%) in CFR group, and only 3 patients out of 42 (7%) in HFR group. Grade IV reaction was seen in 1 patient only (2.7%) in CFR group, and not seen in HFR group. Grade 0 reaction was seen in 14 patients (39%) in CFR group , and 32 patients (76%) in HFR group , grade I reaction was seen in 3 patients (8.3%) of CFR group, and 5 patients (12%) of HFR group , grade II reaction was seen in 11 patients (31%) in CFR group, and 2 patients only (5%) in HFR group .

Univaried 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). The incidence of radiation reaction among the study groups is shown in figure (1).

Figure (1)
Incidence of acute radiation reactions among the study groups

<table>
<thead>
<tr>
<th>Grade of radiation reaction (RTOG)</th>
<th>CFR</th>
<th>HFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0: Grade 0 radiation reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI: Grade I radiation reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GII: Grade II radiation reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIII: Grade III radiation reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIV: Grade IV radiation reaction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of patients

- **CFR**: Conventional fractionated radiation
- **HFR**: Hypofractionated radiation
- **G0**: Grade 0 radiation reaction
- **GI**: Grade I radiation reaction
- **GII**: Grade II radiation reaction
- **GIII**: Grade III radiation reaction
- **GIV**: Grade IV radiation reaction
- **RTOG**: Radiation Therapy Oncology Group

Multivariate analysis using logistic regression model (enter method) revealed 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; like 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), percentage of positive lymph nodes (p = 0.25).

**Discussion**

Many literature reviews in oncology revealed that there are some subcategories of 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 (8, 9, 10). Knowing that worldwide; almost two thirds of all newly diagnosed female breast cancer patients are in postmenopausal age group (11), with their anticipated comorbidities; the magnitude of the problem of undertreatment of this group of patients will be very clear. Long time ago; a clinical trials were done to evaluate the feasibility of hypofractionation in the adjuvant setting of breast cancer; however; due to the relatively poor techniques at these times; the incidence of both acute and late radiation effects was relatively high (12, 13, 14). More recently clinical trials of hypofractionation were implemented using a better radiation technique than the past; so minimizing the radiation reactions to those patients. The aim of the current study was to compare between two methods of radiation therapy to the breast; the conventional arm (5000 cGy/25 fractions/5 weeks; 200 cGy per fraction) [CFR], and the hypofractionated arm (4005 cGy/15 fractions/3 weeks; 267 cGy per fraction) [HFR] in a prospective randomized 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 value; 0.004. Even in multivariate analysis between different variables and the incidence of acute radiation reaction, the treatment arm showed a statistically significant impact with HFR showing a less incidence of acute radiation reactions (p value; 0.03). A recent study was done by Whelan et al (2002) (7) who compared standard fractionation radiation versus hypofractionated radiation using 42.5 Gy in 16 fractions within 22 days (which is close to the regimen of the current study). They found 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 (LFSR) between the two arms to evaluate the efficacy of
Hypofractionated radiation

the hypofractionation arm. They found that; the LFSR was 97.2% in hypofractionation arm compared to 96.8% in the standard arm. Another study done for the hypofractionation in breast cancer is that done by Gittleman et al (2004) (15). In this study, 20 patients with duct carcinoma in situ were accrued; in whom, radiation therapy was given as hypofractionation regimen was used whereby; a total radiation dose of 42Gy was given over 3 weeks period (no week ends) and at 2.8 Gy per day. Acute radiation effects were seen only in 6 patients only out of 20 (30%) and were only grade I reaction. The most recent study investigating the issue of hypofractionated radiation in the adjuvant setting of breast cancer is that done by Ortholan et al (2005) (16); whereby 150 patients with breast cancer were 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 (GIII/IV) reported in this study was 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 their 5 and 10 years disease free survival rate were 80%, and 71.5% respectively, and the 5 and 10 years overall survival rates were 71.6%, and 46.5% respectively. So as compared to the current study; Ortholan et al study (16) showed a relatively higher incidence of acute radiation reactions, most probably because of using a very high dose radiation per fraction (6.5Gy). So, from the previous studies, it is concluded that; hypofractionated radiation therapy is an acceptable modality in the adjuvant setting of breast cancer with a relatively low reactions; and this may encourage the radiation oncologists to use it in elderly patients and those who had poor performance status or living away from the radiation therapy facility. For late radiation effects and impact of hypofractionated radiation on disease free and overall survival; a longer follow up is needed to assess those issues.

References
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Gittleman A, Lymberis C, MacDonald S et al 2004: Phase I-II trial of hypofractionated...
دراسة مقارنة مضاعفات العلاج الإشعاعي المكمل بالعلاج الإشعاعي التقليدي لمرضى سرطان الثدي أثناء العلاج الإشعاعي المكمل لهم.

ديان عبد العزيز يهاد: البحوث الأمريكية للأشعة, الهرود, الكردي للأشعة.
دايهاب عصمت فوزى: دكتوراه العلاج الإشعاعي, كلية الطب جامعة القاهرة.
د. عزة محمد نصر: دكتوراه العلاج الإشعاعي معهد الأورام جامعة القاهرة.

تم إجراء هذا البحث كدراسة مستقبليّة لمرضى أورام الثدي واللائي تم البدء في علاجهن بالأشعة المكمل للثدي حيث تم تقسيم المرضى إلى مجموعتين: مجموعة العلاج الإشعاعي التقليدي (5000 سنتي جرام تقسم على 25 جلسة إشعاع على مدى خمسة أسابيع) ومجموعة أخرى تعطي العلاج الإشعاعي المكمل (4000 سنتي جرام تقسم على 15 جلسة إشعاع على مدى ثلاثة أسابيع). وقد تم تسجيل ملاحظة حدوث مضاعفات الجلدية المتتالية على العلاج بالإشعاع وتم قياسها حسب نظام التقييم الدولي لسمية العلاج بالإشعاع (أري اوجي) ومقارنة معدلات ونسب هذه المضاعفات بين المجموعتين.

تأتي نوعية الجراحة وعدد الغدد الليفاوية التي تم استئصالها على معدل حدوث هذه المضاعفات.

وقد تم دراسة 78 مريضة سرطان الثدي منهم 57.7% تم استئصال جزئي للثدي لهن و34.2% تم استئصال كلي للثدي. وقد تم علاج 46% من المرضى بالطريقة الإشعاعي التقليدية، و53.8% بالعلاج الإشعاعي المكمل.

وقد لوحظ أن الأغلبية من المرضى (64.1%) قد حدث لهم مضاعفات محدودة من الإشعاع (درجة 1 بمقاسات أري اوجي) بينما لوحظ أن الندوات الأعلى من المضاعفات للعلاج الإشعاعي قد تم حدوثها في 35.9% من المرضى. وعند إجراء التحليل الإحصائي للنتائج النهائية لبحث تم اكتشاف أن مضاعفات العلاج بالإشعاع توجد بثقل لدى المرضى الذين عولجوا بالعلاج الإشعاعي التقليدي (52.8%) منهم أصيبوا بمضاعفات العلاج بالإشعاع مقارنة بالمرضى الذين عولجوا بالإشعاع المكمل (21.4%) منهم أصيبوا بمضاعفات العلاج بالإشعاع) وقد لوحظ أن الفارق بين حدوث المضاعفات بين المجموعتين ذو دلالات إحصائية قوية.
