Postmastectomy Hypofractionated Irradiation in Egyptian patients with Breast Cancer: Zagazig University Experience

Bader A. Abdelmaksoud*, Mostafa M. Toam, Alaa A. Fayed

Department of Clinical Oncology and Nuclear Medicine, faculty of Medicine, Zagazig University, Egypt

Abstract

Background: Hypofractionated regimen delivers greater than 2 Gy of radiation per fraction while reducing the total cumulative dose through reducing the number of treatment sessions. Radiobiologically, this approach appears to be as effective as the conventional schedule. Financially, this treatment method is useful in reducing breast cancer radiotherapy costs.

Purpose: To evaluate the efficacy and toxicities of postmastectomy hypofractionated schedule compared to conventional fractionated radiotherapy.

Methods: This study included one hundred and forty patients, they were randomly divided into two groups; Treatment group [hypofractionated radiotherapy group (N: 62)] received 40 Gy (2.67 Gy per fraction) over 3 weeks and Control group [conventional fractionated radiotherapy group (N: 78)] received 50 Gy (2 Gy per fraction) over 5 weeks, the radiation toxicities and local tumor control were compared in both groups.

Results: The local recurrence and distant metastasis in hypofractionated group was 3.2% and 1.6% respectively while in conventional group were 3.8% and 2.6% respectively, grade II acute radiation dermatitis was reported in 22.6% in hypofractionated group versus 7.7% for patients receiving conventional radiotherapy, also, there was increase in the incidence of subcutaneous fibrosis in hypofractionated group in which grade II was reported in 17.7% versus 3.8% in conventional group, otherwise, other toxicities were comparable in both groups.

Conclusion: Hypofractionated radiotherapy was tolerated and has comparable outcome compared to conventional fractionation regarding local tumor control and treatment toxicities.

Keywords: Breast cancer; Hypofractionation; Radiation toxicities

Introduction

Worldwide, breast cancer is increasingly recognized as the commonest cancer in females and a leading cause of cancer-related mortality in women in both developed and developing countries[1]. Radiotherapy is an important part of adjuvant management for large percentage of patients after mastectomy[2]. Conventional radiotherapy after breast surgery requires at least 5 weeks of daily treatment[3]. Treatment of patients with conventional fractionation resulted in 60 to 90% good cosmetic outcome[4]. Data from randomized trials showed that breast cancer tissue is probably similarly sensitive to fraction size as healthy tissue, this means that larger fractions could be safely delivered with better therapeutic outcome[5]. Therefore, this technique results in reduction of the treatment time from five weeks or more to three weeks or less with maintenance of both tumor control and cosmetic rates, also, it has advantage that it was more convenient to the patients and financially better, as it has lower costs due to fewer travels to radiotherapy centers compared with conventional radiotherapy[6]. Radiobiologically, the low α/β ratio which is close to that of late-responding normal tissues could be an indication towards hypofractionation[7-10]. Furthermore, LQ model suggests that, when the α/β ratio for the tumor is similar to that of the surrounding late-responding normal tissue, the hypofractionated regimen may be equally or potentially more effective than the conventional one, however, it was noted that the possibility of late normal tissue damage was increased with larger fractions of radiation[11,12].
Patients and Methods

Eligibility
Patients with confirmed breast cancer (stage T3-4, N0-N1), underwent modified radical mastectomy and received adjuvant chemotherapy treatment. Other inclusion criteria include: Age > 30 years; ECOG performance status 0 - 2, separation (midline - mid-axillary line) < 25 cm. Patients were excluded if had non-epithelial breast malignancies (e.g., sarcoma or lymphoma), history of other diseases comorbidities (e.g., pulmonary or cardiovascular), also, patients with severe physical or mental disorder were excluded. Informed consent was given by every patient who participated in this study.

Pretreatment evaluation
Before treatment, patients were subjected to thorough medical history and physical examination, assessment of ECOG performance status, echocardiography for cases with left breast cancer, routine laboratory investigations (full blood count, liver and kidney functions, serum calcium), abdominal ultrasound, chest radiographs or computed tomography (CT) and bone scan.

Treatment schedule
The patients met the inclusion criteria were randomly divided into two groups; hypofractionated radiotherapy group (N: 62) receive 40 Gy (2.67 Gy per fraction) over three weeks and conventional fractionated radiotherapy group (N: 78) receive 50 Gy (2 Gy per fraction) over five weeks.

Endpoints
The primary endpoint was toxicities of radiotherapy in both groups, secondary endpoints were disease relapse and overall survival (OS).

Treatment evaluation and patients’ follow-up
Re-evaluation during radiotherapy every week for early toxicities then patients were re-evaluated every month, for late toxicities for at least one year. Skin, subcutaneous, and pulmonary complications were evaluated according to RTOG/EORTC Radiation Morbidity Scoring System[13]. Echocardiography for patients with left-sided breast cancer was done two months after radiotherapy. Disease free survival (DFS) was defined as the interval from enrollment of patients to the date of first event (local recurrence, metastasis) or to the date of the last follow-up. OS was defined as the interval from enrollment to the date of death or to the last follow-up.

Statistical analysis
Data were analyzed by SPSS for windows version 18.0 (SPSS Inc., Chicago, IL, USA) and Med Calc for windows version 13 (Med Calc Software bvba, Ostend, Belgium). Shapiro-Wilk test was used for continuous variables to check the normality while Mann-Whitney U was used to compare two groups of non-normally distributed data. Percent of categorical variables were compared using Chi-square test or Fischer’s exact test when appropriate. All tests were two sided.

Results
This study included one hundred and forty patients with breast cancer (stage T3-4, N0-N1) referred to department of clinical oncology and nuclear medicine, faculty of medicine, Zagazig university Egypt, after surgery to receive adjuvant treatment.

Clinicopathological data
The mean age for hypofractionated group was 45.58 years (range 31 -72 years) and 48 years (range 31 -71 years) for conventional group, patients more than 50 years represented 22.6% of patients that received hypofractionated radiotherapy while in conventional group was 33.3% (p = 0.162). Premenopausal women represented 54.8% of hypofractionated group versus 38.5% for conventional group. The right breast was affected in 38.7% of patients in hypofractionated group and 30.8% in conventional group. The most prevalent histopathological grade in hypofractionated group was grade II (45.2%) and (56.4%) in conventional group. Fifty-six patients (90.3%) in hypofractionated group had T3 tumor and in conventional group was 97.4%. N1 (1 to 3 positive axillary lymph nodes) was reported in 38.7% for hypofractionated group and 30.8% in conventional group. The right breast was affected in 22.6% of patients that received hypofractionated radiotherapy and 28.2% in conventional group, patients more than 50 years represented 22.6% for hypofractionated group versus 15.4% for conventional group. Menopausal status for hypofractionated group was grade I (22.6%) and (28.2%) for conventional group, patients with left-sided breast cancer were 34.8% in hypofractionated group and 38.5% in conventional group.

Fifteen patients in hypofractionated group had negative hormonal receptor versus twenty-two in conventional group (Table 1).

| Clinicopathological data | Group I HF (N = 62) | Group II CF (N = 78) | p-value |
|-------------------------|---------------------|----------------------|---------|
| **Age**                 |                     |                      |         |
| Mean ± SD               | 45.48 ± 10.83       | 48 ± 10.16           | 0.060*  |
| Median (Range)          | 45 (31 – 72)        | 48 (31 – 71)         | 0.162‡  |
| < 50 years              | 48                  | 77.4%                |         |
| ≥ 50 years              | 14                  | 22.6%                |         |
| **Menopausal status**   |                     |                      |         |
| Premenopausal           | 34                  | 54.8%                |         |
| Perimenopausal          | 14                  | 22.6%                | 0.146§  |
| Postmenopausal          | 14                  | 22.6%                |         |
| **Side of breast cancer** |                   |                      |         |
| Right breast            | 24                  | 38.7%                | 0.326§  |
| Left breast             | 38                  | 61.3%                |         |
| **Histopathological grade** |                 |                      |         |
| Grade I                 | 12                  | 19.4%                | 0.417§  |
| Grade II                | 28                  | 45.2%                |         |
| Grade III               | 22                  | 35.5%                |         |
| **Tumor size (T)**      |                     |                      |         |
| T3                      | 56                  | 90.3%                | 0.139‡  |
| T4                      | 6                   | 9.7%                 |         |
| **Lymph node (N)**      |                     |                      |         |
| N0                      | 38                  | 61.3%                | 0.377§  |
| N1                      | 24                  | 38.7%                |         |
| **TNM stage grouping**  |                     |                      |         |

Abdelmaksoud, B.A., et al.

Clinicopathological data of studied groups.
Stage II 38 61.3% 42 53.8% 0.377§
Stage III 24 38.7% 36 46.2%

Hormone receptor status
Negative 15 24.2% 22 28.2% 0.593§
Positive 47 75.8% 56 71.8%

• Mann Whitney U test, § Chi-square test, ‡ Fischer’s exact test, p < 0.05 is significant

Systemic treatment
All studied patients received systemic treatment in the form of adjuvant chemotherapy. Most of the studied patients received FAC (5-fluorouracil, doxorubicin, cyclophosphamide) regimen, 71% in hypofractionated group and 66.7% in conventional group. After radiotherapy, most of the studied patients received tamoxifen, 64.5% in hypofractionated group and 60.3% in conventional group

Table 2: Systemic treatment.

| Systemic treatment | Group I HF (N = 62) | Group II CF (N = 78) | p-value |
|--------------------|-------------------|---------------------|--------|
| Chemotherapy regimen |                   |                     |        |
| FAC                | 44 71%            | 52 66.7%            | 0.857§ |
| FEC                | 8 12.9%           | 12 15.4%            |        |
| AC-Taxol           | 10 16.1%          | 14 17.9%            |        |
| Hormonal treatment |                   |                     |        |
| Not received       | 15 24.2%          | 22 28.2%            | 0.593§ |
| Received           | 47 75.8%          | 56 71.8%            |        |
| Tamoxifen          | 40 64.5%          | 47 60.3%            |        |
| AI                 | 7 11.3%           | 9 11.5%             |        |

Acute radiation dermatitis was noted in hypofractionated group, where, grade II was reported in 22.6% versus 7.7% for patients receiving conventional radiotherapy (p < 0.001). Only one patient in hypofractionated group had grade II acute pneumonitis while three patients in conventional group with statistically insignificant difference (p = 0.088)

Table 3: Acute radiation complications.

| Acute radiation complications | Group I HF (N = 62) | Group II CF (N = 78) | p-value |
|-------------------------------|-------------------|---------------------|--------|
| Acute dermatitis             |                   |                     |        |
| G0                            | 10 16.1%          | 58 74.4%            | < 0.001§ |
| GI                            | 38 61.3%          | 14 17.9%            |        |
| GII                           | 14 22.6%          | 6 7.7%              |        |
| Acute pneumonitis            |                   |                     |        |
| G0                            | 54 87.1%          | 73 93.6%            | 0.088§ |
| GI                            | 7 11.3%           | 2 2.6%              |        |
| GII                           | 1 1.6%            | 3 3.8%              |        |

Table 4: Chronic radiation complications.

| Chronic radiation complications | Group I HF (N = 62) | Group II CF (N = 78) | p-value |
|---------------------------------|-------------------|---------------------|--------|
| Chronic dermatitis             |                   |                     |        |
| G0                              | 59 95.2%          | 72 92.3%            | 0.792§ |
| GI                              | 2 3.2%            | 4 5.1%              |        |
| GII                             | 1 1.6%            | 2 2.6%              |        |
| Chronic pneumonitis            |                   |                     |        |
| G0                              | 58 93.5%          | 75 96.2%            | 0.361§ |
| GI                              | 4 6.5%            | 2 2.6%              |        |
| GII                             | 0 0%              | 1 1.3%              |        |
| Subcutaneous fibrosis           |                   |                     |        |
| G0                              | 43 69.4%          | 70 89.7%            | 0.007§ |
| GI                              | 8 12.9%           | 5 6.4%              |        |
| GII                             | 11 17.7%          | 3 3.8%              |        |
| Cardiac toxicities              |                   |                     |        |
| No                              | 34 89.5%          | 49 90.7%            | 0.840§ |
| Yes                             | 4 10.5%           | 5 9.3%              |        |

Table 5: Local recurrence and distant metastasis.

| Local recurrence and distant metastasis | Group I HF (N = 62) | Group II CF (N = 78) | p-value |
|----------------------------------------|-------------------|---------------------|--------|
| Local recurrence                       | 2 3.2%            | 3 3.8%              | 0.908§ |
| Distant metastasis                     | 1 1.6%            | 2 2.6%              |        |
| Disease free                           | 59 95.2%          | 73 93.6%            |        |

Survival
After a median follow-up of 30 months (range: 12 – 45 months), three-years (OS) rates were 95.1% for hypofractionated radiotherapy group and 98.7% for conventional radiotherapy group, with no significant difference (p-value = 0.759). The 3 years disease free survival (DFS) rate was 95.2% for treatment group and 93.6% for control group (p-value = 0.908)[14].

Discussion
For patients with breast cancer underwent total mastectomy, there are several studies demonstrated that postmastecto-
my radiotherapy reduced locoregional recurrence (LR) as well as improved disease-free survival (DFS) and overall survival (OS)\cite{15,16}. Hypofractionation was considered in several randomized trials to be as safe and effective as conventional fractionation with therapeutic and financial advantages\cite{17}. In the current study, the median age was 45 years in treatment arm and 48 years in control arm (p = 0.060). This results are in agreement with Kumbhaj et al study in which the median age was 47 years, Ali and Abd AlMageed study in which the median age was 46.6 years in Almaged treatment arm and 55 years in hypofractionation arm\cite{18,24}. Regarding menopausal status, premenopausal women represented 54.8% of hypofractionated group versus 38.5% for conventional group, these results were slightly different from Ali and Abd AlMageed study where premenopausal patients represented 20% of hypofractionation arm and 45% of conventional arm while postmenopausal patients were 76% and 45% in both groups respectively, these results were different from that in Kumbhaj et al study, in which postmenopausal women represented 60% and 56% in hypofractionation and conventional arms respectively, also, 75.8% of hypofractionated group had positive hormonal receptor versus 71.8% in conventional group, this is in agreement with Ali and Abd AlMageed study where hormone positive patients represented 76% in hypofractionation arm and 68% in conventional arm. Fifty-six patients (90.3%) in hypofractionated group had T3 tumor and in conventional group was 97.4%. From 1 to 3 positive axillary lymph nodes was reported in 38.7% of hypofractionated group and 46.2% in conventional group. The three-years OS rates was 95.1% in hypofractionated radiotherapy group and 98.7% in conventional radiotherapy group, with insignificant difference (p-value = 0.759). Also, three-years DFS rate was 95.2% and 93.6% for conventional radiotherapy group and hypofractionation radiotherapy group, respectively with insignificant difference (p-value = 0.908). Treatment toxicities were comparable between both groups, these results are the same as that of Whelan et al who reported that was no statistically significant difference in OS between hypofractionated and conventional group and that of Canadian trial update\cite{19}. The same results were achieved in START A, B trials\cite{7,8} and Spooner study\cite{20} in which there was no evidence that hypofractionated regimens were associated with a worse overall survival rate. The incidence of recurrence was 3.2% in hypofractionated group and 3.8% in conventional one, (p = 0.908), but, three-years DFS rate were 95.2% and 93.6% for treatment group and control group respectively (p-value= 0.908), these results are the same as that obtained by Eldeep et al and Shaltout and Abd El Razek, who reported in their studies that there was statistically insignificant difference between the two groups regarding DFS and local control\cite{21,22}. In our study, acute radiation dermatitis was higher in hypofractionated group, as grade II was reported in 22.6% versus 7.7% for patient receiving conventional radiotherapy (p < 0.001), this results was in accordance with Kumbhaj et al study, who reported that grade I, II and III reactions were 20%, 50% and 20% respectively in hypofractionation arm versus 30%, 45% and 5% in conventional fractionation arm respectively with no significant difference between both arms, however, Ali and Abd AlMageed in their study showed significant difference between both arms regarding skin toxicity in favor of hypofractionated arm. Only one patients in hypofractionated group had grade 2 acute pneumonitis while three patients in conventional group with non-significant difference (p = 0.088). In Ali and Abd AlMageed study, grade 0 radiation induced pneumonitis was 87.8% in treatment arm vs 81.5% in control arm while grade 1 was 9.4% vs 11.1% respectively with no significant difference between both arms. Grade II chronic radiation dermatitis in hypofractionated group was 1.6% versus 2.6% in conventional group respectively (p = 0.792). Grade II chronic pneumonitis had not occurred in any patients received hypofractionated radiotherapy versus one patient in conventional group, there was a significant difference between hypofractionated group and conventional group regarding subcutaneous fibrosis where grade II was reported in 17.7% versus 3.8% respectively (p = 0.007), these finding are reported also in Pinipatcharalert et al and Shaltout and Abd El Razek studies\cite{21,23}.

### Conclusion and Recommendation

Post mastectomy hypofractionated radiotherapy is well tolerated and has local tumor control, DFS and OS rates comparable to conventional fractionation without evidence of higher adverse effects. So, hypofractionated radiotherapy can be considered as safe and effective alternative to conventional fractionation for patients with breast cancer and this should confirmed in meta analysis and phase III future studies.

### References

1. Siegel, R.L., Miller, K.D., Jemal, A. Cancer statistics, 2016. (2016) CA Cancer J Clin 66(1): 7-30.
2. Dinshaw, K.A., Sarin, R., Budrukkar, A.N., et al. Safety and feasibility of breast conserving therapy in Indian women: Two decades of experience at Tata Memorial Hospital. (2006) J Surg Oncol 94(2): 105-113.
3. Veroncsi, U., Cascinelli, N., Mariani, L., et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. (2002) N Engl J Med 347(16): 1227-1232.
4. Fisher, B., Anderson, S., Bryant, J. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. (2002) N Engl J Med 347(16): 1233-1241.
5. Marcus, L.G. Altered fractionation in radiotherapy: From radiobiological rationale to therapeutic gain. (2010) Can Treat Rev 36(8): 606–614.
6. Taher, A.N., El-Baradie, M.M., Essa, H., et al. Hypofractionation versus conventional fractionation radiotherapy after conservative treatment of breast cancer: early skin reactions and cosmetic results. (2004) J Egypt Natl Canc Inst 16(3): 178-187.
7. START Trialists’ Group, Bentzen, S.M., Agrawal, R.K., et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. (2008) Lancet Oncol 9(4): 331-41.
8. START Trialists’ Group, Bentzen SM, Agrawal R, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. (2008) Lancet 371(9618):1098-107.
9. Owen, J.R., Ashton, A., Bliss, J.M., et al. Effect of radiotherapy frac-
Citation: Abdelmaksoud, B.A., et al. Postmastectomy Hypofractionated Irradiation in Egyptian patients with Breast Cancer: Zagazig University Experience. (2018) Int J Cancer Oncol 5(1): 8-12.

10. Yarnold, J., Ashton, A., Bliss, J., et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomized trial. (2005) Radiother Oncol 75(1): 9-17.

11. Brenner, D.J. Hypofractionation for prostate cancer radiotherapy: what are the issues? (2003) Int J Radiat Oncol Biol Phys 57(4): 912-914.

12. Archambeau, J.O., Pezner, R., Wasserman, T. Pathophysiology of irradiated skin and breast. (1995) Int J Radiat Oncol Biol Phys 31(5): 1171-1185.

13. Cox, J.D., Stetz, J., Pajak, T.F. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). (1995) Int J Radiat Oncol Biol Phys 31(5): 1341-1346.

14. Tunio, M.A., Rafi, M. Post mastectomy adjuvant radiotherapy in breast cancer: a comparison of three hypofractionated protocols. (2009) J Pak Med Assoc 59(9): 656-657.

15. Gebski, V., Lagleva, M., Keech, A. Survival effects of post-mastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective. (2006) J Natl Cancer Inst 98(1): 26-38.

16. Ragaz, J., Olivotto, I.A., Spinelli, J.J., et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. (2005) J Natl Cancer Inst 97(2): 116–126.

17. Yarnold, J., Bentzen, S.M., Coles, C., et al. Hypofractionated whole-breast radiotherapy for women with early breast cancer: myths and realities. (2011) Int J Radiat Oncol Biol Phys 79(1): 1-9.

18. Kumbhaj, P.R., Sharma, R., Saini, P.K., et al. A Study of Two Different Dose Fractionation Schedules of Post Mastectomy Chest Wall Irradiation in Carcinoma Breast Patients. (2013) Int J Med Sci Pub Health 2(4): 1001-1005.

19. Whelan, T., Pingol, J., Levine, M.N., et al. Long term results of hypofractionated radiation therapy for breast cancer. (2010) Engl J Med 362: 513-520.

20. Spooner, D., Stocken, D.D., Jordan, S., et al. A randomised controlled trial to evaluate both the role and optimal fractionation of radiotherapy in the conservative management of early breast cancer. (2012) Clin Oncol (R Coll Radiol) 24(10): 697-706.

21. Shaltout, E.A., Abd El Razek, Adjuvant postmastectomy hypofractionated radiotherapy in Egyptian cancer patients: A 2 years’ follow-up. (2012) Annal Oncol 23(2): 34-36.

22. Eldeep, H., Awad, I., Elhanafy, O. Hypofractionation in post-mastectomy breast cancer patients: Seven-year follow-up. (2012) Med Oncol 29(4): 2570-2576.

23. Pinitpatcharalert, A., Chitapanarux, I., Euathrongchit, J. A retrospective study comparing hypofractionated radiotherapy and conventional radiotherapy in postmastectomy breast cancer. (2011) J Med Assoc Thai 94(Suppl 2): 94-102.

24. Ali, E.M., Abd AlMageed, M.K. Post-mastectomy Hypofractionation Radiotherapy in Breast Cancer Patients. (2014) Can Oncol Res 2(7): 87-93.

Submit your manuscript to Ommega Publishers and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in all major indexing services
- Maximum visibility for your research

Submit your manuscript at
https://www.ommegaonline.org/submit-manuscript