Postmastectomy hypofractionation comparison with conventional radiotherapy in breast cancer patients: A prospective study

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Abstract

Background: Postmastectomy radiotherapy reduces loco-regional recurrence among women with operable breast cancer and improves survival for up to 10 years.

Objectives: Conventional fractionated radiotherapy (CF) has been limited by patient's compliance, travelling, unplanned interruption and others. Hypofractionated (HF) schedule would be more appealing and convenient for both patients and radiotherapists. We prospectively tested for OS, DFS, locoregional control, and treatment related toxicities, in patients treated with CF and HF schedules.

Methods: 47 patients suffering from cancer breast stage T2-4, any N, underwent surgery and received adjuvant systemic and radiation therapies. These patients were scheduled for *adjuvant* radiotherapy and randomly divided into two groups; CF (n = 162), and HF (n = 181).The logrank test examined differences in OAS and DFS rates. Data of radiation toxicities, and disease relapse in both CF and HF groups were compared using Chi-square test.

Findings: The median follow up was 34 months (range: 13 – 53 months). Four-year OAS rates for the both groups were 98 % with 100% for CF and 96% for HF group, and with no significant difference (P value= 0.37). The 4 year disease free survival rate for both were 87% with 81% and 92% for CF and HF respectively (p-value= 0.47) and HR= 0.52 (0.09-2.13). As regard treatment related toxicity, 3 patients (12%) of HF group had toxicity compared with 1 patient (4.5%) in CF, yet, not statistically significant.

Interpretation: these data showed that HF 42 Gy radiotherapy in 16 fractions was not inferior, safe and comparable to CF in terms of OAS, loco-regional tumor control and toxicities. These results need to be tested in large scale multicenter randomized control trials.

Keywords: Breast cancer; Hypofractionation; Survival

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Introduction

Breast carcinoma is the leading cancer in women **[Kamangar F, et al. 2006]** and radiation therapy is an integral part of management in all breast conservation surgeries (BCSs) and for a large percentage of postmastectomy patients. Atypical course of radiation therapy lasts for 6 weeks in post-BCS patients and nearly 5 weeks for postmastectomy patients. A number of reports of cosmetic assessment with schedules using 1.8 to 2.0 Gy per fraction have been published with 60% to 90% of patients reporting well to excellent cosmetic outcome. **[Dinshaw KA, et al. 2006]** Therefore, a technique which reduces the treatment time by half (3 weeks instead of the present 6 weeks) while maintaining cosmetic

and control rates needs to be viewed with great interest. In this context, recent studies examining 13 to 16 fractions of hypofractionated radiation therapy (using larger dose per fraction) compared with the present 25 fractions are providing crucial supportive evidence. **[Whelan T, et al. 2002; Shelley W, et al. 2000; Yarnold J, et al. 2005]** Hypofractionation in breast cancer is an issue that can have widespread implications in breast cancer throughout the world. This is because conventional irradiation has major implications on both patient quality of life and RT departments **[Fisher B, et al. 2002; Veronesi U, et al. 2002]** and success of hypofractionated radiation therapy may sound like music to oncologists, planners of oncology resources, and patients with breast cancer. **[Munshi A. 2006]** As this would result in cost-effective benefit for radiotherapy departments. [**Whelan T, et al. 2002**] Due encouraging data, HF has been attracting increased interest of the world about using it in curative setting in BCSs and yet no enough data about its use in postmastectomy setting in Egyptian patients. To test comparability of hypofractionated (HF) and conventional fractionation (CF) in Egyptian breast cancer patients, we prospectively evaluated OAS, DFS, locoregional control, and treatment related toxicities, of these two schedules in early breast cancer patients treated at our center.

Patients and methods

After informed consent and approval of the Ethical Review Board, 47 patients with breast cancer proved pathologically underwent modified radical mastectomy (MRM) and received adjuvant systemic treatment. Patients with age >18 years, T1-4N03-M0, and the distance from midline to mid-axillary line <25cm were considered eligible for the study. Patients with history of serious nonmalignant disease (e.g., cardiovascular or pulmonary), severe mental or physical disorder were excluded from the study. The initial evaluation included chest radiograph, abdominal ultrasound, bone scan when indicated, full blood picture, kidney and liver function tests. Consecutive eligible patients who met the inclusion criteria were randomly allocated into the two groups: group A of Conventional Fractionation (CF) of 50 Gy/25f, 2Gy/f and 5f/wand group B: Hypofractionated (HF) of 42.72 Gy/16f, 2.67Gy/f and 5f/w.

Radiation technique:

All patients were planned using 2D system; two tangential portals for the chest wall were planned through simulator-based planning. This technique was used for adjusting the medial and lateral tangential fields. Direct anterior filed to the supraclavicular and axillary areas was planned with < 0.5 cm gap junction from tangential fields, superior divergence of tangential portals was eliminated by 5° couch rotation and head of humerus was shielded. Patients were treated in the supine position with ipsilateral arm raised above the shoulder and properly positioned using breast wedge. The medial border of the target volume was located at the mid-sternal line, and the lateral border at the mid-axillary line (to include the chest wall and to limit the lung volume at the central plane to less than 2.5-3cm). The superior border was located at a horizontal line drawn through the suprasternal notch- if no supraclavicular lymph node treated, and the inferior border 2cm below the contralateral infra-mammary fold. For determination of the target volume and separation, CT cuts every 1cm were done and transferred to the planning system. Patients were treated using a 6-

MV linear accelerator.

Assessment of treatment outcomes and toxicities

The primary endpoints were overall survival, disease free survival, and disease relapse, in both groups. Secondary endpoint was radiation toxicities. Disease free survival (DFS) was defined as the interval from enrollment of patients to the date of first event (relapse, progression, or death from any cause) or to the date of last follow-up. Overall survival (OS) was defined as the interval from enrollment to the date of death from any cause or to last follow-up. Early and late toxicity were scored according to the Radiation Therapy Oncology Group criteria in both groups of patients.

Statistical analysis

The study cutoff point was December, 2013. Disease free survival and OS rates were estimated using Graphed prism program, and compared between the conventional and hypofractionated groups by the log-rank test. Data of radiation related toxicities and disease relapse in the two studied groups were compared using Chi-square test. The 3 p-value reports are two-tailed and an alpha level of 0.05 was used to assess statistical significance.

Results

This study included 47 cases; there were even distribution of patients in both CF and HF radiation groups. Through 5 years from 2009 to end of 2013, patients were treated initially by MRM followed by systemic treatment then allocated for randomization.

Patient Population and characteristics data Analysis

A total of 47 female patients were considered eligible with above criteria for randomization, patients were treated initially by MRM followed by systemic treatment then allocated for randomization. Analysis of patient data revealed HF patients with older average age for patients (55 years HF (range 33-69 years); 46.5 years CF (range 35-70 years); with no statistically significant difference p=0.16). Both groups were evenly distributed, majority of patients were with performance status 1 in either group (95% and 84% for CF and HF respectively). They also had a longer average travel distance from their home to the treating facility by more than 100 kilometers (28%compared to 22% in CF).). No significant differences were found between patients receiving CF compared to HF with regard to laterality (left or right-sided breast), comorbid conditions (lupus, diabetes, cardiac comorbidities) with 5% CF having ischemic cardiac disease. [Table 1]

Analysis of Disease Characteristics

Regarding disease characteristics, patients receiving HF had smaller tumor size, were less likely to have positive lymph nodes but more likely to have a right breast cancer, all these differences were not statistically significant. Invasive ductal carcinoma was the commonest pathological type in both arms (95% and 88% for CF and HF respectively) while invasive lobular carcinoma was found nly in 2 patients in HF group (8%). Stage II disease was the highest in both arms followed by stage III (53%, 56% and 30%, 36% for CF and HF respectively). Patients receiving HF were more likely to have positive hormonal receptors, 68% compared to 54.5% in CF but not statistically significant. [Table 2]

Analysis of Treatment Characteristics

Treatment analysis revealed only one patients in CF did not receive any chemotherapy and one received it as pre-operative treatment. The most frequent regimen used was FAC and FEC either alone or followed by taxanes with a course of 6 cycles. As regard radiotherapy, no significant differences were found between patients receiving

CF compared to HF with tissue separation as calculated at the beam entrance through the deep chest wall (CF and HF average 20 cm, and range was 17-25 cm for CF and 16-24 cm for HF). The worthy notice were that there a statistically significant difference in the time period from MRM till start of radiotherapy as the median time was 147 and 170 days (p value= 0.03). [Table 3]

Survival and toxicity data analysis

After a median follow up of 34 months (range: 13 – 53 months). Four-year OS rates for the both groups were 98 % with 100% for CF and 96% for HF group, and with no significant difference (P value= 0.37). [Figure 1, 2] [Table 5] The 4 year disease free survival rate for both were 87% with 81% and 92% for CF and HF respectively (p-value= 0.47) and HR= 0.52 (0.09-2.13). [Figure 3, 4] As regard treatment related toxicity, 3 patients (12%) of HF group had toxicity compared with 1 patient (4.5%) in CF, yet, not statistically significant.

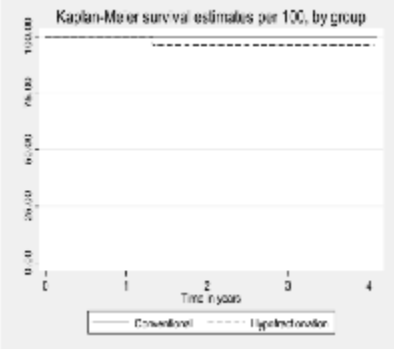

Fig.1: Kaplan-Meier plot of OS.

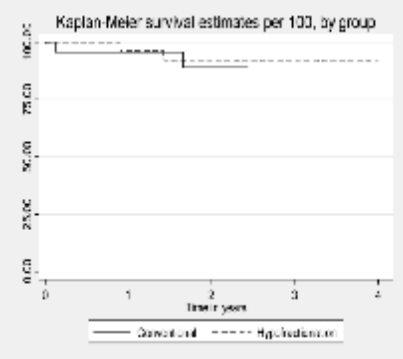

Fig.2: Kaplan-Meier plot of Proportion of patients with disease free survival during period of follow up

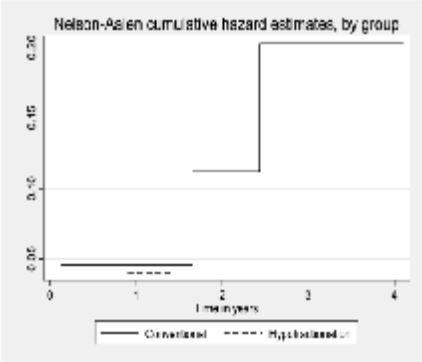

Fig3: Nelson-Aalen cumulative hazard plot of tumour recurrence in the patients

Table 1: Patients' characteristics in hypofractionated and conventional radiotherapy groups.

Conventional N=22	*Hypofractionation N=25*	*P value*	
Age *Mean (SD)* *Median (range)*	*49.41 (11.26)* *46.50 (35-70)*	*53.44 (8.05)* *55 (33-69)*	*0.16*
Performance status *0 1*	*1 (4 %)* *21 (95 %)*	*4 (16. %)* *21 (84. 0%)*	*0 . 2 0*
Residence *Sohag* *Qena* *Luxury* *Assuit*	*17 (77 %)* *5 (22 %)* *0 (0 %)* *0 (0 %)*	*18 (72%)* *5 (20 %)* *1 (4 %)* *1 (4 %)*	*0.61*
Performance status *0 1*	*1 (4 %)* *21 (95 %)*	*4 (16 %)* *21 (84 %)*	*0.20*
Menopausal status *Pre* *Peri* *Post*	*10 (45 %)* *2 (9 %)* *10 (45 %)*	*5 (20 %)* *1 (4 %)* *19 (76 %)*	*0.10*
Contraception use *No* *Yes*	*19 (86 %)* *3 (13 %)*	*20 (80 %)* *5 (20 %)*	*0.56*
Heart disease *No* *IHD*	*21 (95 %)* *1 (4 %)*	*25 (100 %)* *0 (0 %)*	*0.28*
Liver disease *No* *Yes*	*17 (77 %)* *5 (22 %)*	*17 (68 %)* *8 (32 %)*	*0.48*

t test was used for quantitative data and chi square was used for categorical data.

Table 2: Comparison between Conventional and Hypofractionation group as regard tumor characteristics

Conventional N=22	*Hypofractionation N=25*	*P value*	
Pathology			
IDC	*21 (95.45%)*	*22 (88 %)*	
ILC	*0 (0 %)*	*2 (8 %)*	*0.40*
Mixed	*1 (4.55%)*	*1 (4 %)*	
Tumor grade			
2	*18 (81.82%)*	*18 (72 %)*	*0.43*
3	*4 (18.18%)*	*7 (28 %)*	
Anatomical side			
Left	*13 (59.09%)*	*11 (44 %)*	*0.30*
Right	*9 (40.91%)*	*14 (56 %)*	
Stage			
IIA	*3 (13.64%)*	*7 (28 %)*	
IIB	*9 (40.91%)*	*7 (28 %)*	
IIIA	*5 (22.64%)*	*8 (32 %)*	
IIIB	*1 (4.55%)*	*0 (0 %)*	
IIIC	*1 (4.55%)*	*1 (4 %)*	*0.41*
TxN0M0	*0 (0 %)*	*1 (4 %)*	
TxN1M0	*0 (0 %)*	*1 (4 %)*	
TxN2M0	*2 (9.09%)*	*1 (4 %)*	
T3NxM0	*1 (4.55%)*	*0 (0%)*	
Tumor size			
Mean (SD)	*5.20 (1.21)*	*4.65 (1.36)*	*0.18*
Median (range)	*5 (3-7)*	*4.5 (3-8)*	
Number of positive node			
Mean (SD)	*2.90 (2.89)*	*2.12 (2.99)*	*0.20**
Median (range)	*2 (0-10)*	*1 (0-11)*	
Number of node removed			
Median (range)	*12 (1-29)*	*14 (6-33)*	*0.46*
Metastases			
No	*22 (100 %)*	*25 (100 %)*	
Estrogen receptor			
Negative	*7 (31.82%)*	*6 (24 %)*	*0.55*
Positive	*15 (68.18%)*	*19 (76 %)*	
HER2			
Negative	*8 (36.36%)*	*12 (48 %)*	
Positive	*3 (13.64%)*	*2 (8 %)*	
Unknown	*11 (50 %)*	*9 (36 %)*	*0.39*
Not assessed	*0 (0 %)*	*2 (8 %)*	
Progesterone receptor			
Negative	*6 (27.27%)*	*7 (28 %)*	
Positive	*13 (59.09%)*	*16 (64 %)*	*0.82*
Unknown	*3 (13.64%)*	*2 (8 %)*	

t test was used for quantitative data and chi square was used for categorical data * Mann-Whitney test was used

Table 3: Comparison between Conventional and Hypofractionation group as treatment characteristics

Conventional N=22	*Hypofractionation N=25*	**P value**	
Chemotherapy			
No	*1 (4.55%)*	*0 (0 %)*	
Pre operative	*1 (4.55%)*	*0 (0 %)*	*0.31*
Yes	*20 (90.91%)*	*25 (100 %)*	
Type of chemotherapy			
CMF	*2 (9.52%)*	*1 (4 %)*	
CMF/Txl	*1 (4.76%)*	*0 (0 %)*	
FAC	*12 (57.14%)*	*8 (32 %)*	
FAC/Txl	*0 (0 %)*	*1 (4 %)*	
FEC	*5 (23.81%)*	*13 (52 %)*	*0.22*
FEC/Txl	*0 (0 %)*	*1 (4 %)*	
FEC/Txt	*1 (4.76%)*	*0 (0 %)*	
FEC/Txt-cisp	*0 (0 %)*	*1 (4 %)*	
Number of cycles			
4	*0 (0.00%)*	*1 (4 %)*	
5	*1 (4.76%)*	*0 (0 %)*	*0.36*
6	*20 (95.24%)*	*24 (96 %)*	
Regularity			
Yes	*22 (100 %)*	*25 (100 %)*	
Hematological toxicity			
Non	*22 (100 %)*	*25 (100 %)*	
Time from MRM in days			
Mean (SD)	*29.87 (28.72)*	*20.76 (23.78)*	*0.33 **
Median (range)	*15 (7-100)*	*28 (9-120)*	

chi square was used * Mann-Whitney test was used

Table 4: Comparison between Conventional and Hypofractionation group as regard Radiotherapy(continued)

Conventional N=22	*Hypofractionation N=25*	*P value*	
Radiotherapy Yes	*22 (100 %)*	*25 (100 %)*	
Total dose in cGy 4272 5000	*0 (0 %) 22 (100%)*	*25 (100) 0 (0 %)*	*<0.0001*
RT interruption by days Mean (SD) Median (range)	*6.2 (13.82) 0 (0-45)*	*1.2 (3.04) 0 (0-12)*	*0.21*
Distance between RT field borders Mean (SD) Median (range)	*19.59 (1.87) 20 (17-25)*	*20.02 (1.83) 20 (16-24)*	*0.43*
RT time from MRM in days Mean (SD) Median (range)	*140.86 (54.40) 147 (25-240)*	*166.84 (28.58) 170 (92-240)*	*0.03**
RT time from chemotherapy Mean (SD) Median (range)	*32.76 (27.39) 20 (9-100)*	*28.5 (23.97) 24.5 (6-127)*	*0.77**
Acute toxicity No Skin	*20 (90.91%) 2 (9.09%)*	*19 (76 %) 6 (24 %)*	*0.18*
Chronic toxicity No Yes	*21 (95.45%) 1 (4.55%)*	*22 (88 %) 3 (12 %)*	*0.36*
Hormonal treatment No Yes Unknown	*6 (27.27%) 15 (68.18%) 1 (4.55%)*	*6 (24 %) 18 (72 %) 1 (4 %)*	*0.96*
Type of hormonal treatment AI TAM TAM/AI	*7 (46.67%) 7 (46.67%) 1 (6.67%)*	*8 (44.44%) 10 (55.56%) 0 (0 %)*	*0.51*
Regularity No Yes	*7 (31.82%) 15 (68.18%)*	*7 (28 %) 18 (72 %)*	*0.78*

t test was used for quantitative data and chi square was used for categorical data *Mann-Whitney test was used

Table 5: Comparison between Conventional and Hypofractionation group as regard time of follow up and fate

Conventional N=22	*Hypofractionation N=25*	*P value*	
Time to death/ study end Mean (SD) Median (range)	*2.65 (1.09) 2.8 (1.37-4.10)*	*2.65 (0.78) 2.59 (1.32-4.06)*	*0.94**
Death (OS) No Yes	*22 (100 %) 0 (0 %)*	*24 (96 %) 1 (4 %)*	*0.34*
Time to recurrence/ study end Mean (SD) Median (range)	*2.48 (1.22) 2.40 (0.12-4.10)*	*2.60 (0.81) 2.59 (0.90-3.99)*	*0.88**
Recurrence (DFS) No Yes	*19 (86 %) 3 (13 %)*	*23 (92 %) 2 (8 %)*	*0.53*

chi square test was used * Mann-Whitney test was used , Log-rank test for equality of survivor functions was used (N.B. time by years)

Discussion

Hypofractionated regimens have been used at some institutions for many decades. **[Shelley W, et al. 2000; Olivotto IA,. Et al 1996; Owen JR,. et al.2006; Fujii O,. et al. 2008; Froud PJ,. Et al. 2000; Kuusk U, et al. 1992]**

In contrast other institutions have adopted an 'extended' fractionation **MA, et al. 1989; Boyages J, et al. 1992;Solin LJ, Et al. 1995]** Advantages of hypofractionation for whole breast RT include patient convenience and lower out-ofpocket costs due to less travel for an extended course of RT, improved throughput for radiation therapy departments and ultimately lower health system costs per course of RT following BCS. Recent studies have demonstrated that the alpha/beta ratio for breast carcinoma is close to 4 and that the alpha/beta ratio for normal breast tissue is approximately 3.4. **[Whelan TJ, et al. 2008; Whelan T, et al. 2002; START Trialists' Group, Trail A. 2008; START Trialists' Group, Trial B. 2008]** Therefore, there is both theoretical and clinical evidence to support the hypothesis that a modest increase in the dose per fraction coupled with a modest decrease in the total dose may be a safe and effective way to improve care as compared to the traditional 2 Gy per fraction schedule. **[Yarnold J, et al. 2005; Douglas BG, et al. 1984; Cohen L. 1952]** Hypofractionation to the breast has been evaluated in RCTs, [**Owen JR,. et al.2006; Whelan T, et al. 2002; START Trialists' Group, Trail A. 2008; START Trialists' Group, Trial B. 2008; Hopwood P, et al. 2010; Whelan TJ, et al. 2010]** but has not been widely accepted in North America. Criticism has focused on concerns about efficacy approach using 1.8 Gy per day fractions to the whole breast and with all patients receiving a boost to the primary site to compensate for the relatively low radiobiologically equivalent dose(BED)of 5 weeks of RT using 1.8 Gy daily fractionation . **[Harris JR. 2000; Rose**

equivalence, insufficient follow-up to adequately assess late normal tissue effects and the lack of data regarding how to implement the RCT data in broader circumstances such as among patients with ductal carcinoma insitu (DCIS),those requiring supraclavicular and axillary treatment, RT combined with chemotherapy or with patient characteristics that were not well represented in the trials such as women age <35 years or with very large breast size. Data from randomized trials regarding hypofractionation for treatment of women with breast cancer, confirm the safety and efficacy of schedules using fraction sizes of around 3 Gy, provided the correct downward adjustments to total dose are made **[Yarnold J, et al. 2011]** Hypofractionated radiation therapy offers the advantage of a more efficient and productive use of radiotherapy departments resources; whether machine time, staffing of treatment units, lower expenses in addition to far better patients convenience **[Taher AN, et al. 2004].** On the other hand, hypofractionation, with larger radiation dose per fraction increases the possibility of late normal tissue damage **[Archambeau JO, et al. 1995; Awwad HK. 1990].** However, the linear-quadratic model predicts that the normal tissue toxicity is not increased when the fraction dose is modestly increased and the total dose is reduced **[Yarnold J, et al. 2011]**.

This is confirmed by results of many trials where hypofractionated radiotherapy protocols are as effective as the conventional radiation of 50 Gy in 25 fractions **[Deantonio L, et al. 2010; Owen JR, et al. 2006]** regardless of disease stage or type of breast surgery. **[Pinitpatcharalert A, et al. 2011]** The use of hypofractionated schedules for post mastectomy or regional nodal irradiation is even more controversial. Again, this is done more commonly in the UK where there are constraints on budget. Given that this is the standard of care in the UK it is hard to be overly critical; the randomized studies which established the use of hypofractionated radiotherapy were however following breast conserving therapy and the results may not be applicable to post-mastectomy patients. There have been four large RCTs assessing the outcome of hypofractionated versus standard fractionation RT following BCS, Canadian, START A, START B, Royal Marsden Hospital (RMH) and the Gloucestershire Oncology Centre (GOC) .**[Owen JR,et al. 2006; Whelan T, et al. 2002; START Trialists' Group, Trial A. 2008; START Trialists' Group, Trial B. 2008; Yarnold J, et al. 2005]**

The endpoints of these studies appropriately included both the rate of local recurrence, RT side-effects and breast cosmoses, all four trials show that the rates of local relapse were equivalent or better among patients treated with hypofractionated whole breast RT compared to 50 Gy in 25 fractions. A similar conclusion was drawn by a Cochranereview. **[James ML, et al. 2008]** These have been reviewed in a meta-analysis which concluded that at 5 years, equivalent rates of local control, overall survival and cosmoses are seen for both treatments. American guidelines state that patients should only be considered for hypofractionation if they are older than 50, do not receive chemotherapy, have small tumors (T1 - T2), and have good dose homogeneity in the breast. This excludes a number of patients with lymph node metastases or who receive systemic therapy. In contrast, nearly all patients in the United Kingdom would receive hypofractionated radiotherapy (40 Gy in 15#) as per START-B. Arguments supporting this approach are that in other studies (eg. the EORTC boost trial), the rates of side effects at 5 years in each arm were similar to the rates of side effects at 10 years and therefore 5 year data should be a reasonable surrogate for late effects. Despite these RCTs were evaluating HF following breast conserving therapy and the results may not be applicable to post-mastectomy patients but there are some studies concerning postmastectomy HF in comparison with CF have showed that hypofractionated radiation as effective as conventional in postmastectomy breast cancer and short protocols were equally effective in locoregional disease control and toxicity was also comparable. They were helpful in reducing the work load and can be safely recommended for routine clinical use. **[Wu JX, et al. 2003; Bates TD, et al. 1975; Bates TD. 1988; Pinitpatcharalert A, et al. 2011; Shahid A, et al. 2009; Nicholas P. Rowell. 2009]**

The current study being prospective in nature, and the two groups (CF and HF) had almost even in distribution of their tumor and clinical characteristics [Table 1, 2], it confirms the feasibility of hypofractionated radiotherapy in breast cancer patients and comparability in terms of local control, toxicities and OS. Most of

breast cancer patients in the CF group were ≥ 35 years of age, while of HF all except one above 45 years of age which obviates the former criticism mentioned above. This study included positive nodal disease even more it includes up to T4 with CF had 53% stage
II and 30% stage III disease, while HF group had 56% stage II and 36% stage III
disease. Regarding patient and tumor characteristics, the two groups were evenly distributed as regard all clinical, tumor and treatment characteristics. [Table 1, 2, 3, 4] Moreover, follow up schedule from time of diagnosis, MRM till end of study or recurrence showed no statistical difference. [Table 5] With a median follow up of 34 months (range: 13 – 53 months). Fouryear OS rates for the both groups were 98 % with 100% for CF and 96% for HF group, and with no significant difference (P value= 0.37). The 4 year disease free survival rate for both were 87% with 81%
and 92% for CF and HF respectively (p-value= 0.47) and HR= 0.52 (0.09-2.13). As regard treatment related toxicity, 3 patients (12%) of HF group had toxicity compared with 1 patient (4.5%) in CF, yet, not statistically significant. In our study we also reported a similar outcome to these trials as patients in the HF radiotherapy group,
showed comparable 4-year OS rate with those in CF schedule (96% versus 100%, p = 0.37). The previously mentioned studies confirmed our results, and reported that there was no evidence that hypofractionated radiotherapy was associated with a statistically
significantly difference in overall survival. An update of the Canadian trial, Whelan et al. **[Whelan T, et al. 2002]** results have not changed after a 10-year followup **[Whelan TJ, et al. 2010],** where the probability of survival over time was similar in the hypofractionatedradiation and conventional radiation groups (p = 0.79). The START A trial **[START Trialists' Group, Trial A. 2008]**, START B trial **[START Trialists' Group, Trial B. 2008]**, and Spooner [Spooner D, et al. 2009], reported also that, there was no evidence that any hypofractionated radiotherapy regimen was associated with a worse overall survival rate. No randomized trials have specifically compared fractionation alternatives during regional RT but indirect evidence suggests that hypofractionation and standard fractionated post-mastectomy RT (PMRT) have comparable outcomes. The British Columbia randomized trial of PMRT has reported 20-year followup among 318 pre- menopausal women with nodepositive breast cancer treated with modified radical mastectomy and adjuvant CMF chemotherapy who were randomized to receive loco-regional RT or no further treatment. Patients randomized to PMRT received 37.5 Gy in 16 fractions to the chest wall and 35 Gy in 16 fractions to the regional nodes including a direct field to treat both internal mammary node chains. Initial **[Ragaz J, et al. 1997]** and updated analyses **[Ragaz J, et al. 2005]** have confirmed a significant 10% overall survival advantage for subjects who received PMRT. At a median follow-up of 20.8 years, subjects treated with hypofractionated RT had 16% fewer isolated loco-regional recurrences (74% vs 90%, p= 0.002).The outcomes and survival advantage conferred by radiotherapy in the BC experience using short fractionation were comparable to the outcomes of the Danish trials that utilized conventional fractionation**.**

[Clarke M, et al. 2005; Overgaard M, et al. 1999; Overgaard M, et al. 1997]

Other evidence in support of the comparability of hypofractionated and 'standard' fractionated PMRT comes from a meta-analysis of loco- regional RT trials that included the use of systemic therapy. **[Whelan TJ, et al. 2000]** That meta-analysis identified 18trials, 7 of which delivered daily fractions greater than 2 Gy per day.The efficacy of PMRT was similar across trials with an average mortality reduction odds ratio of 0.83. **[Whelan TJ, et al. 2000]** The survival advantage associated with adjuvant PMRT may be dose dependent. In a review of 36 PMRT trials subdivided according to biologically equivalent dose and target volumes, only trials that had administered a prescription biologically equivalent to 40-60 Gy in 2 Gy fractions were associated with a significant survival advantage of 2.9 % at 5 years and a 6.4 % at 10-years. **[GebskiV, et al. 2006]**

In the current study we used HF dose 42.72 Gy with 2.67 Gy per fraction which is matched with the recommended biologically equivalent dose to 40-60 Gy in 2 Gy fraction per dose and the locoregional outcome and survival were comparable to that of CF, the overall incidence of death/100patients =2.13 and incidence of death/100patients in CF= 0 and HF= 4 with P value=0.34. Also, as regard the locoregional control, overall incidence of recurrence/100 patients=10.64, with an incidence of recurrence /100 patients in CF=13.64 and HF=8, P value=0.53 and HR = 0.52 (0.09-2.13). None of both groups relapsed locally and the 3 cases relapsed remotely in either group; lung, liver and bone for HF while lung and bone for CF.

A summary of the accumulated evidence from large RCTs mentioned above is that approximately 25-40% of patients have mild adverse effects and up to 10% of 9 patient shave grade 2 or 3 adverse effects with intermediate to long-term follow-up. Effects were relatively independent of the RT prescription and there was no evidence that patients treated with hypofractionated RT had any worse outcomes compared to those treated with 50 Gy in 25 fractions. In contrast, for several end points, the hypofractionated RT resulted in lower rates of adverse effects compared to 50 Gy in 25 fractions. For example in the START Trials A and B, there was a lower rate of change in skin appearance after 39 Gy in 13 fractions over 5 weeks or 40 Gy in 15 fractions over 3 weeks when compared with 50 Gy in 25 fractions over 5 weeks (HR 0.63, 95% CI 0.47-0.84 and HR 0.76, 95% CI 0.60-0.97 respectively. **[Hopwood P, et al. 2010]** This observation is consistent with both 39 Gy in 13 fractions and 40 Gy in 15 fractions having a lower BED compared to 50 Gy in 25 fractions. Concern regarding late RT effects of hypofractionation is not limited to the breast tissue but also the ribs, lungs, heart and brachial plexus. However, in the RCTs adverse events in these organs were extremely rare with any of the treatment regimens. In our work, patients with hypofractionated radiation was safe and showed acceptable toxicity rate with 24% incidence of grade II dermatitis and resulted in only 1 week treatment interruption compared with 9% in CF with 10 days interrupted treatment. Right apical lung fibrosis was seen in only 1 patient (4%) in HF and 2 patients (8%) with late skin toxicity while 1 patient in CF (4.5%).

These finding are consistent with data published
from RCTs above. Finally, this short (hypofractionated) RT schedule would be more convenient for patients (especially those coming from remote areas to RT facilities) and for health care providers, as it would increase the turnover in RT departments. The use of a 16-fractions, instead of a 25-fractions regime, would save 900 treatment sessions per 100 patients (2500 - 1600 = 900). This corresponds to an additional 56 (900:16) patients who could be treated with the same number of fractions. This would result in substantial economic benefit as breast cancer patients represent the majority of patients treated in RT departments **[Plataniotis G. 2010].**

Conclusions and Recommendation

Recent randomized trials justify the routine use of HF for adjuvant radiotherapy in women with breast cancer. Postmastectomy still an open area for extensive research, our study showed that hypofractionated radiation therapy is comparable to that of CF without evidence of inferior local tumor control or higher adverse effects. Hypofractionated radiation therapy can be recommended as safe and effective alternatives to CF for postmastectomy chest wall radiotherapy. These results need to be evaluated with multicenter larger sample size.

Conflict of Interests

The authors declare that they have no conflict of interests.

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