Journal of the Egyptian Nat. Cancer Inst., Vol. 16, No. 3, September: 178-187, 2004

Hypofractionation versus Conventional Fractionation Radiotherapy after Conservative Treatment of Breast Cancer: Early Skin Reactions and Cosmetic Results

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ABSTRACT

Purpose: To compare in a prospective trial the acute skin reaction and late cosmetic effects of normal fractionation versus hypofractionation radiotherapy after breast conserving surgery.

Patients and Methods: Thirty patients with T1-2N0M0 breast cancer who underwent breast conserving surgery (BCS) were included in the study. Half of the patients received whole breast irradiation, consisting of 50 Gy/25f/5w+boost 10Gy/5f/1w to tumor bed (group A). The other half received 42.5Gy/16f/22 days (group B). The two groups were comparable otherwise. Early skin reaction and late cosmetic results were graded according to RTOG guidelines.

Results: The study showed no statistical significant difference between the two treatment groups as regards acute skin reactions and cosmetic appearance. However, the maximum skin reaction occurred 2 weeks earlier for patients within group B (3^{rd} week) compared to group A (5^{th} week). Apart from breast volume, there was no significant correlation between any of the patients or tumor factors and the incidence of acute skin reactions in either group of patients. Patients with large breast volume >1100cc had a higher rate and a longer duration of maximum skin reaction in group A (4 weeks versus 2 weeks in patients with small breast volume ≤1100cc), while in group B, all patients had a maximum duration of 4.5 weeks. This difference was not statistically significant. After median follow-up of 22 months, again there was no difference between the two groups as regard the cosmetic outcome. Lumpectomy volume and lumpectomy/breast volume ratio (regardless of the tumor volume) were the only factors that significantly affected the cosmetic appearance.

Conclusions: Preliminary results support the use of a shorter fractionation schedule of 42.5Gy/16f/22 days in patients with breast conserving surgery. The study is still going on to study the late effects on a larger number of patients for final evaluation of this regimen.

Key Words: *Hypofractionation - Breast cancer - Early skin reaction - Cosmetic results.*

INTRODUCTION

For early breast cancer, prospective randomized trials comparing breast conservative therapy (BCT) versus mastectomy have all shown equivalent local control and disease-free survival rates between the two treatment modalities **[1,2]**. Many factors had been postulated to contribute to the poor cosmetic results. Some of these factors are patients related which could be extrinsic or intrinsic **[2]**. Extrinsic factors include age, smoking, immunosuppression, cardiovascular disease, diabetes as well as breast size. Intrinsic factors include individual variation in radiosensitivity. From analysis of studies in which the dosimetry was well controlled, it is thought that 70-80% of normal tissue effects may be due to intrinsic factors **[3]**.

The high incidence of breast cancer that receive post-operative radiotherapy led many to think of a shorter course of irradiation, which would result in considerable decrease in machine-time, working hours, and less patients visits. However, since the conservative treatment of breast cancer patients aimed mainly (besides local control and survival) at cosmetic results, any treatment schedule that achieves these goals will be satisfactory. Radiotherapy centers in the United Kingdom and Canada have tested a shorter schedule for breast irradiation, based on a radiobiological model, for a larger dose per fraction to be just as effective as the conventional schedule of 50Gy in 25 fractions **[4,5]**.

In the NCI of Egypt, breast cancer constitutes 33% of all female cancers. The median age is 46 years and 60.5% of patients are pre-

menopausal **[6]**. With the increase of patients' awareness and improvements in the health care services, patients present in an earlier stage than before. Those patients constitute a big load to the radiotherapy department. Therefore, a shorter course of irradiation is strongly needed to perform our tasks more efficiently.

The aim of the present study is to compare the acute skin reaction and late cosmetic results of hypofractionated regimen with the 5-weeks conventional schedule in patients receiving irradiation after conservative breast surgery (CBS).

PATIENTS AND METHODS

From August 2002 to May 2003, a controlled randomized, open (with allocation cocealment using closed envelope method), parallel-group study was held in the radiotherapy depatment, National Cancer Institute, Cairo University. Patients with age >65 years, T1-2N0-M0 ≥1cm negative surgical margin, with at least 10 dissected nodes, and the distance from midline to mid-axillary line <25cm were considered eligible for the study. Patients with history of contralateral breast cancer, presence of multicentric disease, serious nonmalignant disease (e.g, cardiovascular or pulmonary), severe mental or physical disorder or delay of radiotherapy treatment more than 4 months after surgery were excluded from the study. The initial evaluation included chest radiograph, abdominal-ultrasound, postoperative bilateral mammography, bone scan, full blood picture, kidney and liver function tests. Consecutive eligible patients who met the inclusion criteria were registered. Written informed consent was obtained from the patients before assignment to either treatment arm. Thereafter, patients were randomely allocated into the two groups using sealed-envelope method.

Surgery:

Lumpectomy with a safety margin of at least 1cm, and axillary dissection with clearance is the standard surgical procedure adopted in the NCI. For positive or close surgical margins, wider excision is considered. For cosmetic consideration, a radial incision was used for all lower half tumors and curvilinear incision for upper half. The incision was made directly over the primary tumor to minimize the area of possible contamination with tumor cells. The axilla was dissected through a separate incision for better cosmetic results.

Radiotherapy:

Patients were randomly allocated to one of the following groups:

Group A: Whole breast irradiation using conventional fractionation (50Gy/25f, 2Gy/f and 5f/w), followed by boost to tumor bed (10Gy/5f/5 days).

Group B: Whole breast irradiation using hypo-fractionation schedule (42.5Gy/16f, 2.66Gy/f and 5f/w). The Biological Effective Dose (BED) was calculated and compared using Linear Quadratic formula:

$$BED = n\,[1+d/(\alpha/ß)]\ Gy\ x$$

Where n=number of fractions, d=dose per fraction, and the subscript x denotes the $(\alpha/ß)$ ratio used in calculation. For late reactions $(\alpha/ß)$=3Gy so, x=3 and for early reactions $(\alpha/ß)$=10Gy so, x=10

All patients were planned through simulator-based planning with isocentric technique. This technique was used for adjusting the medial and lateral tangential fields so that their posterior (deep) borders lie on one straight line with no divergence into the lung. Only the breast, with the underlying chest wall, is considered the target volume. No attempt was made to treat peripheral lymphatics. 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 breast with 2cm margin and to limit the lung volume at the central plane to less than 3cm). The superior border was located at a horizontal line drawn through the supra-sternal notch, and the inferior border 2cm below the infra-mammary fold. For determination of the breast volume and separation, CT cuts every 1cm were done and transferred to the three-dimensional planning system (Helax). Patients were treated using a 6-MV linear accelerator. Electron beam was used for boosting the tumor bed, for group A patients only. Its energy was chosen according to the depth of tumor bed as determined by breast ultrasonography.

Systemic Treatment:

Patients received systemic treatment in the form of CMF, FAC, FEC (I.V. every 21 days for 6 cycles), and hormonal treatment (Tamoxifen), according to Saint Gallen recommendations **[7]**. Patients indicated for chemotherapy received 3-4 courses of their systemic treatment before the start of radiotherapy.

Evaluation:

As regards acute reactions, patients were evaluated at 1,8, and 16th week from start of RTh. The RTOG scoring system for radiation reactions were used to score radiation toxicity **[8,9]**. The cosmetic outcome was scored at 6,12 and 24 months. The second author was the one to score cosmeses blinded of the treatment arm. The items to be scored were: The appearance of the surgical scar, breast size, breast shape, nipple position, and shape of areola. In scoring these items the treated breast was compared with the untreated breast, using a 4-point scale: Excellent (0) if there was no difference between both breasts; good (1) if there was only a slight difference; fair (2) when a more marked difference was present; and poor (3) in case of a disturbing difference **[10]**. Nipple retraction assessment (NRA) is measured as in fig. (1). The vertical distance between the nipple and the level of the supra-sternal notch is assigned as L_1 and L_2 for the normal and treated breasts, respectively. Similarly, the horizontal distances are assigned as H_1 and H_2. The NRA is calculated as:

$$NRA = \sqrt{(H_2-H_1)^2 + (L_1-L_2)^2}$$

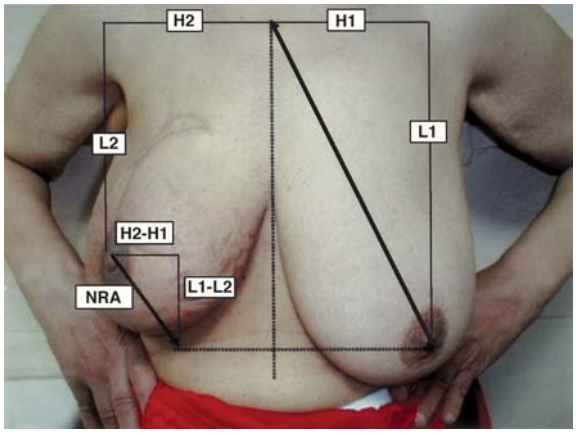


Fig. (1): Illustration for nipple retraction assessment (NRA).

For all the patients, the treated breast volume was measured from the Dose Volume Histogram. Both tumor and lumpectomy volume were recorded in the pathology specimen. Patients had a mean follow-up period of 23±3 months (ranging from 18-27 months).

Statistical Analysis:

Analysis was done using Stat View version 4.5 package (Abacus Concepts. Inc. Berkeley, CA.19.) Quantitative data were summarized as means and standard deviations, qualitative data as percentage. Data of the two studied groups and their relation with early radiation reactions and cosmetic results were compared using Chi-square test. Fisher exact test was used whenever appropriates **[11]**. All reported *p* values are two sided; *p* value of ≤0.05 was considered significant.

RESULTS

From August 2002 to May 2003, 30 patients were recruited in the study, 15 in each arm. Apart from T-stage, both treatment groups were comparable in terms of baseline characteristics including age, menstrual status, site, pathology, grade, the use of adjuvant chemotherapy, breast volume, tumor volume, lumpectomy volume, lumpectomy/breast volume ratio, and gap between surgery and radiotherapy (Table 1).

The mean age of patients was 47.5±10 years (range 25-65 years). Premenopausal patients constituted more than half of our patients (17/30, 56.7%). The most common site was upper outer quadrant (11/30, 36.7%) followed by central (9/30, 30%) and upper inner quadrant (7/30, 23.3%). Twenty-two patients (73.3%) had T2 tumors [14 and 8 patients in group A and group B, respectively], while eight patients (26.7%) only had T1 tumors [1 and 7 patients in group A and group B, respectively], and this difference was statistically significant (*p*=0.04). Invasive duct carcinoma was the commonest pathological type (28/30, 93.3%), while invasive lobular carcinoma was found in only two patients (6.7%). As regards the grade of the tumor, the majority of the patients had grade II tumors (23/30, 76.7%), while 6 patients had grade III tumors (20%) and only 1 patient in group A had grade I tumor. As regards the adjuvant chemotherapy, 10 patients did not receive any chemotherapy (33.3%). Adjuvant CMF was given to

two patients (6.7%), while adjuvant FAC was given to 14 patients (46.7%). Two patients received CEF (6.7%) and another two received FEC (6.7%). The mean breast volume was 1030±404cc (range 106cc-1912cc). The tumor volume ranged from 1.5-80cc with a mean value of 16.3±20.1cc. The lumpectomy-specimen volume ranged from 30-1260cc with a mean value of 478.3±304.1cc. Lumpectomy/breast volume ratio ranged from 0.1-0.9 with a mean value of 0.4±0.2. Surgery-radiotherapy period ranged from 16-120 days with a mean value of 61.4±31.7 days.

Acute Skin Reactions:

For simplicity, patients were considered to have mild skin reaction for those with G0 and G1, and sever skin reaction for those with G2-G4 reaction. Severe reaction (all G2) occurred in 9 patients (60%) in the conventional fractionation treatment group compared to 6 patients (40%) (5 G2 and 1 G3) in the hypo-fractionation schedule (p=0.47) (Table 2). In fig. (2) the peak incidence of severe skin reaction occurred during the 5th week of the radiation therapy for the conventional fractionation group and lasted for 3 weeks, while in hypo-fractionation group, it occurred during the 3rd week of the radiation therapy and lasted for 5 weeks.

We could not find any correlation between the maximum skin reaction and any of the patients' characteristics in either treatment group (Table 3). In Table (4), 12 patients had their breast volume >1100cc, 10 of them (83.3%) developed severe acute skin reactions compared to 7/18 patients (38.8%) with breast volume ≤1100c (p=0.016). For the patients with either large or small breasts, the treatment modality had no affect on the incidence of sever skin reactions. For the conventional group of patients, those with a large breast had longer duration of skin reaction (4±2.4 weeks) compared to 2±1.4 weeks duration in patients with small breast volume. The corresponding figures in the hypofractionation group were 4.5±3 and 4.5±2 weeks, respectively. However, this difference was not statistically significant (Table 4).

For simplicity, cosmetic outcome was classified as satisfactory (excellent and good) and unsatisfactory (fair and poor). Out of the 30 patients, one (in the hypofractionation group) was lost for follow-up. Seventeen patients (59%) got unsatisfactory results, (11, and 6 in conventional and hypofractionation group, respectively). For the 12 patients with satisfactory cosmetic outcome, four patients were in the conventional group and eight patients were in the hypofractionation group (p=0.14). Although there was, a higher incidence (73%) of unsatisfactory cosmeses in the patients who developed early sever-skin reaction (11/15 patients), it did not reach a significant level (p=0.13). Table (5) shows the prognostic effect of the patients and tumor factors on cosmetic results. Apart from lumpectomy volume and lumpectomy/breast volume ratio, no studied factors showed any correlation with the breast cosmeses. Patients with a satisfactory cosmeses had a mean lumpectomy specimen volume of 329.6±184.3 compared to 548.2± 341.1cc for patients with unsatisfactory outcome (p=0.05). The ratio between lumpectomy volume to the remaining irradiated breast-volume was a more sensitive predictor to the cosmetic outcome. Those with satisfactory results had a lower ratio of 0.3±0.2 compared to their counterpart who had a ratio of 0.5±0.2 (p=0.02). On the other hand tumor volume itself didn't have any correlation with cosmeses (p=0.29). Fig. (3) shows a picture of a patient with a good cosmeses (A) and another one with a poor cosmeses (B).

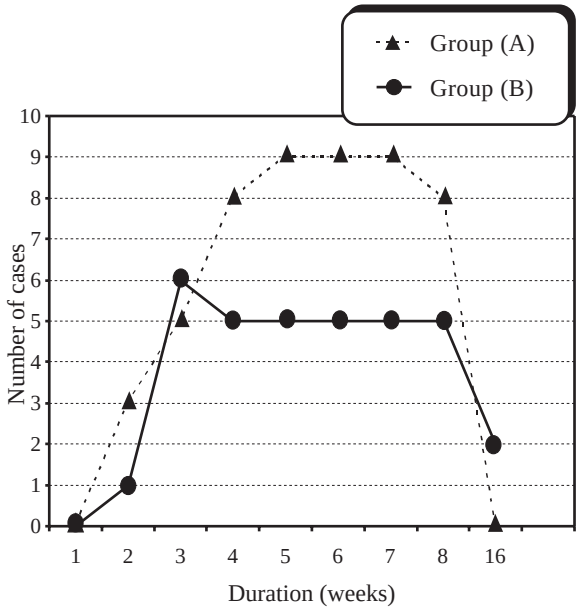
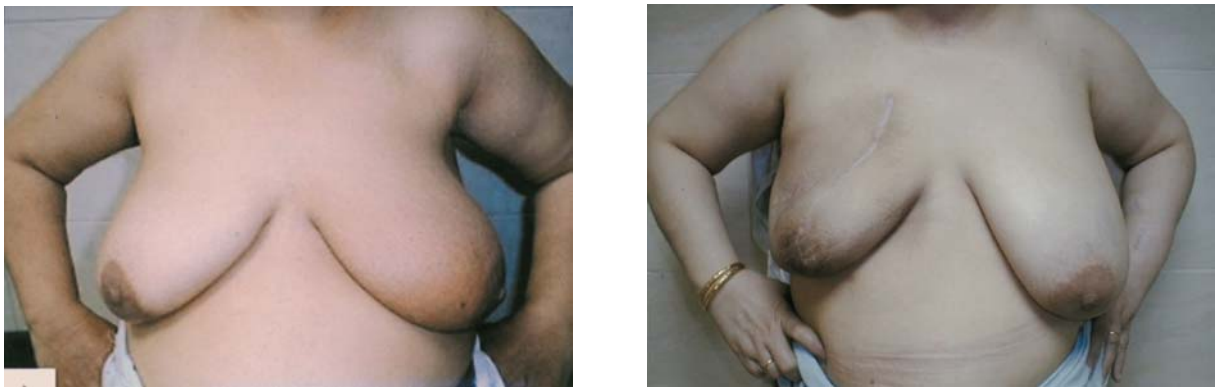


Fig. (2): Time-related incidence of sever skin reaction (G2-3) in both treatment group.



(A) **(B)**

Fig. (3): Cosmetic results: (A) good cosmeses (B) poor cosmeses.

Table (1): Patients and Tumor characteristics.

Variables	Conventional (gp.A) N =15	Hypo-fractionation (gp.B) N =15	*p*-value
Age (years):			
Range	25-65	25-65	0.24
Mean (SD)	49.7±10.4	45.2±10.3	
Menstrual status:			
Premenopausal	7 (46.7%)	10 (66.7%)	0.46
Postmenopausal	8 (53.3%)	5 (33.3%)	
Site:			
UOQ	7 (46.7%)	4 (26.7%)	0.59
LOQ	0	2 (13.3%)	
UIQ	3 (20%)	4 (26.7%)	
LIQ	0	1 (6.7%)	
CENT	5 (15.3%)	4 (26.7%)	
T stage:			
T1	1 (6.7%)	7 (46.7%)	0.04
T2	14 (93.3%)	8 (53.3%)	
Pathological types:			
Invasive duct carcinoma	13 (86.7%)	15 (100%)	0.48
Invasive lobular carcinoma	2 (13.3%)	0	
Grade:			
I	1 (6.7%)	0	0.43
II	12 (80%)	11 (73.3%)	
III	2 (13.3%)	4 (26.7%)	
Chemotherapy:			
Yes	9 (60%)	8 (53.3%)	0.98
No	6 (40%)	7 (46.7%)	
Breast volume (cc):			
Range	106-1912	570-1544	0.64
Mean (SD)	1066±495	994±301	
Tumor volume (cc):			
Range	1.9-80	1.5-70	0.45
Mean (SD)	19.2±20.8	13.3±19.8	
lumpectomy volume (cc):			
Range	74-1260	30-780	0.21
Mean (SD)	550±358	401±222	
Lumpectomy/breast volume ratio:			
Range	0.1-0.9	0.1-0.8	0.3
Mean (SD)	0.5±0.2	0.4 ±0.2	
Surgery-RTH gap (days):			
Range	16-120	19-120	0.69
Mean (SD)	61.5±28.4	61.3±35.8	

Table (2): Incidence of acute skin reaction and cosmetic outcome.

Grade	Conventional fractionation		Hypofractionation		*p*-value
	N	%	N	%	
0	0	0	2	13.3	
1	6	40	7	46.7	
2	9	60	5	33.3	0.47
3	0	0	1	6.7	
4	0	0	0	0	

Table (3): Prognostic factors affecting skin reaction by treatment groups.

Factor	Conventional (group A) N =15			Hypo-fractionation (group B) N =15		
	Mild	Sever	*p*-value	Mild	Sever	*p*-value
Age (years):	44.7±6.8	46±14.9	0.84	48.2±12.3	50.8±9.5	0.65
Menstrual status:						
Premenopausal	2 (33.3%)	5 (55.6%)	0.61	7 (77.8%)	3 (50%)	0.33
Postmenopausal	4 (66.7%)	4 (44.4%)		2 (22.2%)	3 (50%)	
Stage:						
T1	1 (16.7%)	0	0.4	4 (44.4%)	3 (50%)	>0.99
T2	5 (83.3%)	9 (100%)		5 (55.60	3 (50%)	
Pathology:						
IDC	4 (66.7%)	9 (100%)	0.14	9 (100%)	6 (100%)	0.14
ILC	2 (33.3%)	0		0	0	
Chemotherapy:						
Yes	3 (50%)	6 (66.7%)	0.62	6 (66.7%)	2 (33.3%)	0.32
No	3 (50%)	3 (33.3%)		3 (33.3%)	4 (66.6%)	
Breast volume (cc):	904±282	1131±297	0.16	807±547	1238±399	0.09
Tumor volume (cc):	26.4±20.5	16.9±11.3	0.41	15.8±10.2	15.4±12.7	0.97
Surgery-RTH gap (days):	64.6±38.5	56.5±34.1	0.69	57.5±41.1	64.2±18.4	0.72

Table (4): Grade II and III acute skin reactions by breast volume and treatment group.

Breast volume	Incidence of sever skin reactions				
	Total	*p*-value	Group A	Group B	*p*-value
≤1100cc.	7/18 (38.8%)	0.016	5/9 (55.6%)	2/9 (22.2%)	0.14
>1100cc.	10/12 (83.3%)		5/6 (83.3%)	5/6 (83.3%)	1.00
	Duration (weeks)				
	Total	*p*-value	Group A	Group B	*p*-value
≤1100cc.	2±2.9	0.013	2±1.4	4.5±2	0.11
>1100cc.	4.8±2.6		4±2.4	4.5±3	0.76

Table (5): Prognostic factors affecting cosmetic outcome.

Variables	Satisfactory N=12	Unsatisfactory N=17	*p*-value
Fractionation group:			
Conventional	4 (33.3%)	11 (65%)	0.14
Hypofractionation	8 (66.7%)	6 (35%)	
Acute skin reaction:			
Mild	8 (66.7%)	6 (35%)	0.13
Sever	4 (33.3%)	11 (65%)	
Age (years):			
mean (SD)	44.5±10.7	49.4±10.3	0.23
Menstrual status:			
Premenopausal	8 (66.7%)	8 (47%)	0.45
Postmenopausal	4 (33.3%)	9 (53%)	
Stage:			
T1	3 (25%)	5 (29%)	>0.99
T2	9 (75%)	12 (71%)	
Pathology:			
IDC	12 (100%)	15 (88%)	0.49
ILC	0	2 (12%)	
Breast volume:			
Small	9 (75%)	9 (53%)	0.27
Large	3 (25)	8 (47%)	
Tumor volume (cc):			
Mean (SD)	13.7±9.4	22.3±13.9	0.29
lumpectomy volume (cc):			
Mean (SD)	329.6±184.3	548.2±341.1	0.05
Lumpectomy/breast volume ratio:			
Mean (SD)	0.3±0.2	0.5±0.2	0.02
Chemotherapy:			
Yes	9 (75%)	10 (59%)	0.45
No	3 (25)	7 (41%)	
Surgery-RTH gap (days):			
Mean (SD)	62.3±36.8	58.4±27.9	0.75

DISCUSSION

The principal long-term effects that impair cosmeses are fibrosis and atrophy of the breast. Fibrosis and atrophy are the result of specific responses of fibrocytes to irradiation. Fibrosis represents a proliferative response of the surviving fibrocytes to growth factors released by injury, and atrophy reflects both loss of fibrocytes and collagen reabsorption **[12]**. Manipulation of the dose-time relationship aims at optimization of treatment results i.e. achieving a maximum tumor response with minimal normal tissue reactions **[13]**. Shorter treatment schedule 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. However, it is known that hypo-fractionation reduces the therapeutic ratio by reducing the tumor response and increasing the late normal tissue damage **[12,13]**. To help alleviate the strain on patient and institutional resources that a 5 to 6-week radiotherapy treatment course causes, many authors have explored the delivery of shorter radiotherapy regimens. Most of these regimens demonstrated acceptable cosmeses and local control of breast cancer in nonrandomized, and randomized prospective studies as well as retrospective matched-control series **[1,5,15-17]**.

The present study showed no significant difference between the two treatment groups regarding the incidence and the grade of the acute skin reactions as well as the cosmetic results. This is similar to what was reported by Whelan et al. in a randomized trial for 1234 women with early stage negative nodes breast cancer, status post lumpectomy and axillary dissection **[5]**. They compared conventional fractionation (50Gy/25f/35 days) versus hypofractionation (42.5Gy/16f/22 days) and they concluded that there was no difference regarding the early, late toxicity and cosmetic outcome between the two regimens. Almost similar results were reported by Olivotto et al. in a non randomized study of 186 patients treated with 44Gy/16f/22 days **[16]**. The authors reported results to be comparable to their historical patients. Other series also matched these results **[1,17]**.

Application of Linear Quadratic formula on both treatment limbs showed that group (A) has slightly higher values for both acute and late effects than group (B). Biological Effective Dose was calculated assuming $\alpha/ß$ ratio equals 10Gy for early reactions and 3Gy for late reactions. In group A: BED was 60Gy for early effects and 83.5Gy for late effects versus 53.9Gy and 80Gy in group B respectively. In the study design, we were expecting higher rate of acute and chronic reaction in hypo-fractionation group. Therefore, we did not add boost to the tumor bed in arm B. Almost no studies concerned with hypo-fractionation in BCT used boost to the tumor bed **[5,16-17]**. On the other hand, the EORTC study showed a negative effect on cosmetic outcome for those patients with boost to the tumor bed compared to those with no boost **[10]**. Since our early results did not show difference in the skin reaction, now we are using boost in both groups of patients.

It was found that the severe skin reactions occurred 2 weeks earlier in group (A) compared with group (B), 5th and 3rd week, respectively. The explanation for this may be due to dependence of timing and magnitude of the inflammatory response to radiotherapy on the rate of dose accumulation (RDA), since inflammatory response does not fade within hours of each radiation exposure as sublethal damage generally does. Therefore, the inflammatory response accumulates quickly with the maximum skin reaction occurred earlier within hypofractionation schedules **[19]**.

The present study also showed significant correlation between breast volume and the severity of the acute skin reactions. Ten out of twelve patients with breast volume >1100cc. (83.3%) in both groups had severe acute skin reactions in comparison with seven out of eighteen patients (38.8%) with breast volume ≤1100cc. On the other hand, there was no statistically significant difference between the two treatment groups regarding the relation between the severity of acute skin reactions and the breast volume. In the conventional fractionation group, patients with large breast volume >1100cc had longer duration of skin reaction (4 weeks versus 2 weeks in patients with breast volume ≤1100cc). For patients treated with the shorter radiation course, those with either large or small breasts had a maximum duration of skin reactions of 4.5 weeks. This difference between the treatment groups was not of statistical significance. In a prospective assessment of late changes in breast appearance in 559 patients (all treated with conventional fractionation), Moody et al. noted a strong association with breast size **[20]**. Only 6% of patients with small breasts developed moderate or severe late changes compared with 22% with medium sized breasts and 39% of patients with large breasts (p<0.001). To explore the reason, radiation dose distributions were assessed in three-level transverse CT images of the breast. There was a significant correlation between breast size and dose inhomogeneity, which may account for the marked changes in breast appearance reported in women with large breasts **[20]**. Confirmatory similar results were reported by Vrieling et al. who demonstrated that as the breast size increases, the acute skin reactions become more pronounced **[10]**.

The present study also did not show significant correlation between systemic treatment given to the patients and the acute skin reactions. Similar results were reported by Turesson et al. who showed no correlation between the systemic treatment and the acute skin reactions, but he reported that the effect of chemotherapy is more pronounced on late skin reactions **[3]**.

It was found also that there is no correlation between the age or menopausal status and acute skin reactions. This is contrary to what was

reported by Turesson et al. who showed increased skin reactions in old age post menopausal women than the young premenopausal ones **[3]**.

In the EORTC trial 22881/10882, 5569 patients treated with BCT using conventional fractionation (50Gy/25f/35 days) ± boost to the tumor bed (16 Gy/8f/1.5w) were analyzed to identify the parameters that have the largest impact on the cosmetic outcome based on a quantitative and qualitative assessment of the cosmetic results **[10]**. The authors concluded that the factors associated with a worsened cosmeses were a large excision volume, an increased pathological tumor size, an increased radiation dose inhomogeneity, the presence of postoperative breast complications, and the radiotherapy boost. In this study, there was no difference between the two treatment schedules as regards cosmetic results (p=0.14). The only two factors associated with unsatisfactory cosmetic results (regardless of tumor size) were lumpectomy size and, to a further extent, the ratio of lumpectomy size to the remaining breast volume (p=0.05 and 0.02 respectively). In fact, there is no standard recommendation as regards the optimum lumpectomy size. Surgeons are always concerned with lumpectomy with adequate safety margin. Lumpectomy specimen ranges from resection of the tumor with 1cm margin up to unnecessary quadrantectomy. Frozen section during surgery is the only way that assures the minimum lumpectomy size with adequate safety margin.

Conclusion:

Our results (skin reactions & cosmetic appearance) matched with the published data, that support the use of a shorter fractionation schedule of 42.5Gy in 16 fractions over 22 days, in early breast cancer patients after breast conserving surgery. We are continuing the study for accrual of a large number of patients and to follow them for a longer time for final evaluation of this regimen.

REFERENCES

1- Veronesi U, Salvadori B, Luini A, Greco M, Saccozzi R, del Vecchio M, et al. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomized trials on 1,973 patients. Eur J Cancer. 1995; 31A (10): 1574-1579.

2- Coles CE, Moody AM, Wilson CB, Burnet NG. Reduction of Radiotherapy-induced Late Complications in Early Breast Cancer: The Role of Intensity-modulated Radiation Therapy and Partial Breast Irradiation. Part I - Normal Tissue Complications. Clin Oncol. 2005, 17: 16-24.

3- Turesson I, Nyman J, Holmberg E, Oden A. Prognostic factors for acute and late skin reactions in radiotherapy patients Int J Radiat Oncol Biol Phys. 1996, 36 (5): 1065-75.

4- Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989, 62 (740): 679-94.

5- Whelan TJ, MacKenzie R, Julian J, Levine M, Shelley W, Grimard L, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst. 2002, 94 (15): 1143-50.

6- EL-Bolkainy N. Topographic pathology of cancer. Cairo, National Cancer Institute. 1998, 81-87.

7- Kerbrat P, Namer M. Adjuvant treatments for operable cancer of the breast: What conclusions? [Congress in Saint-Gallen, 25-28 February 1998] Bull Cancer. 1998, 85: (5) 89-90.

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

9- Rubin P, constine LS. (RTOG Late Effects Working Group). Overview: Late effects of normal tissues (LENT) scoring system. Int J Radiat Oncol Biol Phys. 1995, 31: 1041-1042.

10- Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JC, Jager JJ, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. Radio Oncol. 2000, 55: 219-232.

11- Saunders DB, Trapp GR. Basic and clinical biostatistics 2001, 3rd edition, Connecticut, Appleton and LanSchultz Hector S, Heart A. Radiopathology of organs and tissues. In: E Scherrer. KL. Trott. Ch. III, (Editors) Springer Verlag, Heidelberg. 1991, 347-368.

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

13- Awwad HK. Dose-Time-Volume relationships in normal tissue to radiation. In Radiation Oncology: Radiobiological and Physiological Prespective. Kluwer Academic, Dordecht/ Boston/ London. 1990, 129-187.

14- Fletcher GH. Hypofractionation: Lessons from complications. Radiother. Oncol. 1991, 20 (1): 10-15.

15- Carolyn I. Sartor, Joel E. Tepper. Is Less More? Lessons in Radiation Schedules in Breast Cancer. J Natl Cancer Inst. 2002, 94: 1114-1115.

16- Olivotto IA, Weir LM, Kim-Sing C, Bajdik CD, Trevisan CH, Doll CM. Late cosmetic results of short fractionation for breast conservation. Radiother Oncol. 1996, 41:7-13.

17- Shelley W, Brundage M, Hayter C, Paszat L, Zhou S, Mackillop W. A shorter fractionation schedule for postlumpectomy breast cancer patients. Int J Radiat Oncol Biol Phys. 2000, 47: 1219-28.

18- Whelan TJ, Levine M, Julian J, Kirkbride P, Skingley P. The effects of radiation therapy on quality of life of women with breast carcinoma: Results of a randomized trial. Ontario Clinical Oncology Group. Cancer. 2000, 88 (10): 2260-2266.

19- Denham JW, Hauer-Jensen M. The radiotherapeutic injury-a complex 'wound'. Radiother Oncol. 2002, 63: 129-145.

20- Moody AM, Mayles WP, Bliss JM, Owen JR, Regan J, Broad B, et al. The influence of breast size on late radiation effects and association with radiotherapy dose inhomogeneity. Radiother Oncol. 1994, 33: 106-112.