



Retrospective Analysis of the Effect of Radiation Boost versus No Boost Using Hypofractionation Schedule on Breast Cancer Loco-Regional Recurrence

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Abstract. Background: Radiation treatment to the preserved breast following breast-conserving surgery lowers the mortality risk from breast cancer and cuts the disease's recurrence rate in half. The aim of this work was to define the effectiveness and feasibility of two different hypo fractionation schedules in the adjuvant settings of non-metastatic breast cancer.

Methods: This retrospective study included 50 patients, aged ≥ 50 years old, who had breast conservative surgery or mastectomy, invasive breast cancer with p T1-3, p N0-2 and non-metastatic breast cancer verified by clinical evaluations and imaging (X-ray chest and ultrasound or CT scan chest and abdomen). Patients were divided into two equal groups: Control arm: received standard 40.05 gray (2.67 Gy/ fx) over 15 fractions over 3 weeks with or without boost and experimental arm: received 26 Gray (5.2) over 5 fractions over 1.5 weeks using one of the offered regimens.

Results: Lymph vascular invasion (LVI), Adjuvant treatment, clinical target volume (CTV, level1, level 2 and level 3 were significantly lower in boost group than non-boost group ($P < 0.05$). Supraclavicular nodes (SCV), ipsilateral lung v5, mean lung, mean heart, pigmentation and erythema were significantly lower in boost group than non-boost group ($P < 0.05$). Skin toxicity, recurrence and distant recurrence were not significantly different between both groups. Overall survival (OS) in months was statistically lower in boost group than non-boost group ($P < 0.05$).

Conclusions: Boost group have statically significant lower LVI, Adjuvant treatment, CTV, level1, level2 and level3, SCV nodes, ipsilateral lung V5, mean lung, and mean heart than non-boost group and complication of radiation after mastectomy of breast cancer are less pigmentation, erythema and OS in months while, recurrence and distant recurrence are indifferent to conventional surgery without post radiation.

Keywords: Radiation Boost, Hypofractionation Schedule, Breast Cancer, Recurrence

Introduction

Breast cancer represents more than 30% of female cancer cases in Egypt. It is considered the first common malignancy in females (1).



Non metastatic breast cancer constitutes the majority of cases worldwide while metastatic disease constitutes around 6% only of new cases due to incorporation of screening mammogram (2). The ten-year overall survival (OS) in months rates for stage I and II-III are around 93% and 62% respectively (3).

Local irradiation is indicated in almost all patients with breast conservative surgery with few exceptions to old female with hormonal positive invasive breast cancer providing that it's small tumour size (4). In post mastectomy, the value of radiotherapy is limited to size of tumour more than 5 cm or positive LNs (5). However, in tumour more than T1 and negative node with extensive Lymph vascular invasion (LVI) or young age or triple negative; radiotherapy led to decrease local recurrence significantly compared to observation (6, 7).

The standard fractionation for adjuvant breast irradiation had changed over the past years. Whelan reported that 42 Gray over 16 fractions was non inferior to conventional fractionation after 10 years in early breast cancer (8). The same concept was confirmed in further studies in which hypo fractionation showed no difference in OS and local recurrence with no difference in toxicity profiles (9). In patients with high risk disease post mastectomy, hypo fractionation was shown to be non-inferior to conventional fractionation (10).

The rationale behind hypo fractionation is primarily based on the alpha-beta ratio (α/β) and the overall treatment time. The ratio for breast cancer is about 4, which is marginally lesser than that of additional tumours like head and neck cancers. A smaller ratio requires a larger dose per fraction to compensate for the slower proliferation of tumours (11). Furthermore, the length of treatment can affect the breast cancer local recurrence; longer treatment periods are linked to a greater chance of recurrence (12). Late toxicity is the main concern in using higher dose per fraction. Lymphedema, lung fibrosis and cardiac toxicity are considered the challenging issue in this approach. However, limitation of hot spot and use of modern techniques lead to acceptable and comparable long term toxicities (13).

One fraction per week over five weeks of radiotherapy had been proved to be effective with acceptable toxicity profiles in the British Fast trial (14). The update of this study after 10 years reported that there was no change in local recurrence using 5 fractions either 30 Gray or 28 Gray or 25 fractions of total 50 Gray (14). Five fractions over one week approach was used in British Fast forward trial which included high risk patients with node positive disease showed no concern regarding acute toxicity (15).

This work aimed to define the efficiency and feasibility of two different hypo fractionation schedules in the adjuvant settings of non-metastatic breast cancer.

Patients and Methods

This retrospective study included 50 patients with age of ≥ 50 years old, who done any of breast conservative surgery or mastectomy, invasive breast cancer with p T1-3, p N0-



2 and non-metastatic breast cancer verified by clinical investigations and imaging (X-ray chest and ultrasound or CT scan chest and abdomen). The study was performed with approval from the Ethical Committee of Kafr El Sheikh University, Kafr El Sheikh, Egypt (approval code: KFSIRB200-43) at the date 28/8/2023. Informed written consent was obtained from all patients.

Exclusion criteria were proof of distant metastases, prior irradiation, inflammatory breast cancer, T4 tumor (nodules in skin or fixed to chest wall or ulceration), involvement of 10 nodal metastasis or more and tumor with positive margins.

Patients were divided into two equal groups: Control group: received standard 40.05 gray (2.67 Gy/ fx) over 15 fractions over 3 weeks with or without boost and experimental group: received 26 Gray (5.2) over 5 fractions over 1.5 weeks through one of suggested schedules.

All patients were exposed to complete history taking, clinical examination, pathology documentations and radiological examination.

Each patient was evaluated weekly for the duration of radiotherapy and monthly for three months after radiotherapy to monitor acute toxicity, with findings recorded in line with the Common Terminology Criteria for Adverse Events (CTCAE) v4 (16), patients were assessed clinically every 3 months for 2 years to assess ipsilateral recurrence by clinical examination and ultrasound and late toxicity, any symptomatic late toxicity was assessed and documented according (CTCAE) v4 (16).

Radiotherapy technique

A CT based planning with the patient in supine position was done. CT slice 5mm was taken. CT images were transferred to the planning system. Supine using breast board with angle adjusted to allow chest wall to be parallel to the floor. Two tangents: fields in case of local breast or chest wall irradiations. Three fields' techniques for regional irradiations as indicated using either mono isocentre or dual matched isocentre. Whole Breast Clinical Target Volume (WBCTV): the soft tissues of the entire breast, from 3 mm under the skin's surface to the deep fascia, are included in CTV; the rib cage and muscles are not. Chest Wall Clinical Target Volume Skin flaps and soft tissues up to the deep fascia are included in the clinical goal volume, but the muscle and rib cage are not, lymph Node Clinical Target Volumes: the SCV and/or the axillary chain. It is possible to treat the full axillary chain or just the levels that the clinician and PTV specify. A margin must be applied to the whole breast/chest wall, lymph node, and tumour bed CTV, considering breathing, breast swelling, and set-up error. The standard PTV margin is 10 mm for all PTV volumes, but a maximum of 5 mm must be added medially for the SCV field and medial margins PTV to restrict the dose to midline structures.

Control arm: The volume of the heart at 2.0 Gy and 10.0 Gy must be less than 35% and 5%, respectively, whereas the volume of the ipsilateral lung at 12.0 Gy must be less than 20%.



Experimental arm: The volume of the heart getting 1.5 Gy and 7.0 Gy should be less than 35% and 5%, respectively, whereas the volume of the ipsilateral lung receiving 8.0 Gy should be less than 20%.

The primary outcome was to assess the difference of acute and late toxicity reports between the two treatment groups and to define two-year ipsilateral local tumor recurrence. The secondary outcomes were the assessment of two years OS between both groups, assessment of two years disease free survival in months between both groups and patient compliance between both groups.

Sample size calculation

The sample size calculation was performed using G.power 3.1.9.2 (Universitat Kiel, Germany). The sample size was calculated based on the following considerations: 0.05 α error and 80% power of the study to demonstrate a 45% decrease in breast pain according to toxicity scores using CTCAE with experimental arm than control arm (62.5 % according to a previous study (17). Two cases were added to overcome dropout. Therefore, 100 patients will be allocated in this study.

Statistical analysis

Statistical analysis was performed by SPSS v26 (IBM Inc., Chicago, IL, USA). Histograms and the Shapiro-Wilk test were used to evaluate the data distribution's normality. The mean and standard deviation (SD) of quantitative parametric variables were used to compare the two groups using the unpaired Student's t-test. The Chi-square test or Fisher's exact test, as appropriate, was used to examine the qualitative variables, which were displayed as frequency and percentage (%). Two-tailed P values were used to designate statistical significance as a value less than 0.05.

Results

Age, size of tumour, comorbidities, side, type of surgery, axilla, T stage, N stage, total lymph node, pathology and focality were statically non significantly different among both groups (Table 1).

ER, PR, Her2, Ki67, PNI, tumour grade, chemotherapy, Targeted therapy, adjuvant hormonal and lymphedema were not significantly differ among both groups. LVI, Adjuvant, CTV, level1, level2 and level3 were statically reduced in boost group than non-boost group ($P < 0.05$).



Table 1 - Age, size of tumour, comorbidities, side, type of surgery, axilla, T stage, N stage and total lymph node, pathology and focality of the studied groups

		Boost group (n=25)	Non boost group (n=25)	P
Age (years)		57 ± 7.21	60.36 ± 6.76	0.096
Size of tumour (cm)		2.13 ± 1.23	2.85 ± 1.52	0.070
Comorbidities				
DM		9(36%)	8(32%)	0.765
HTN		8(32%)	7(28%)	0.758
Other	Liver disease	3(12%)	1(4%)	0.404
	Peptic ulcer	1(4%)	0(0%)	
	IHD	0(0%)	1(4%)	
	Cardiac	1(4%)	0(0%)	
	DVT	0(0%)	1(4%)	
Side	Right	11(44%)	12(48%)	0.777
	Left	14(56%)	13(52%)	
Type of surgery	Breast-conserving surgery	19(76%)	14(56%)	0.136
	Modified radical mastectomy	6(24%)	11(44%)	
Axilla	Axillary LN	15(60%)	21(84%)	0.059
	Sentinel lymph node	10(40%)	4(16%)	
T stage	T1	14(56%)	10(40%)	0.352
	T2	9(900%)	14(56%)	
	T3	2(8%)	1(4%)	
N stage	N1	3(12%)	1(4%)	0.069
	N2	4(16%)	8(32%)	
	N3	2(8%)	7(28%)	
Total lymph node		10±7.08	12.76±6.61	0.169
Pathology	IDC	25(100%)	22(88%)	0.202
	ILC	0(0%)	2(8%)	
	Mucoid carcinoma	0(0%)	1(4%)	
Focality	1	22(88%)	2 (92%)	0.837
	2	2(200%)	1(100%)	
	3	1(4%)	1(4%)	

Data are presented as mean ± SD or frequency (%). DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischemic heart disease, DVT: Deep vein thrombosis, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, LN: lymph node.

Heart v5, contralateral breast max ,105hot, late toxicity, lung changes, echo pre, post, compliance and wet and dry desquamation did not differ significantly among the two groups.

SCV ipsilateral lung v5, mean lung, mean heart, pigmentation and erythema were significantly decrease in boost group than in non-boost group (P<0.05).



Table 2 - ER, PR, Her2 markers, Ki67, LVI, PNI, tumour grade, chemotherapy, Targeted therapy, adjuvant hormonal, adjuvant, neoadjuvant, lymphedema, CTV, level 1, level2 and level3 of the studied groups

		Boost group (n=25)	Non boost group (n=25)	P
ER	Mild strong	2(8.0%)	1(4.0%)	0.343
	Moderate strong	1(100.0%)	4(400.0%)	
	High strong	19(76.0%)	18(72.0%)	
PR	Mild strong	22(88.0%)	23(92.0%)	0.942
	Moderate strong	2(200.0%)	1(100.0%)	
	High strong	1(4.0%)	1(4.0%)	
Her2	Mild strong	1(4.17%)	0(0.0%)	0.361
	Moderate strong	0(0.0%)	0(0.0%)	
	High strong	2(8.33%)	2(8.0%)	
Ki67		53.85±39.67	38.79 ± 34.01	0.178
LVI		13(54.17%)	15(60.0%)	0.002*
PNI		2(9.09%)	3 (12.0%)	0.667
Grade of tumour	Grade I	2(8.0%)	0.759	0.759
	Grade II	18(72.0%)	20(80.0%)	
	Grade III	5(20.0%)	4(16.0%)	
Chemotherapy		16(69.57%)	21(84.0%)	0.310
Targeted therapy		3(14.29%)	1(4.55%)	0.344
Adjuvant hormonal		20(86.96%)	23(92.0%)	0.660
Adjuvant		15(60.0%)	22(88.0%)	0.050*
Neoadjuvant		10(40.0%)	3(12.0%)	
Lymphedema		6(24.0%)	3(12.0%)	0.463
CTV		25.52±0.3	38.47±1.95	<0.001*
Level 1		21.87±2.5	33.36±4.35	<0.001*
Level 2		18.29±4.97	30.35±6.26	<0.001*
Level 3		14.47±8.24	28.2±11.96	<0.001*

Data are presented as mean ± SD or frequency (%). *: significant as P value<0.05, CTV: clinical target volume, SCV: Short comment volume, CRC: colorectal cancer, LVI: lymphovascular invasion, PNI: perineural invasion.

Skin toxicity, recurrence and distant recurrence did not exhibit a significant difference between the two groups. OS was significantly lower in boost group than in non-boost group (P<0.05) (Table 4).



Table 3 - SCV, ipsilateral lung v5, mean lung, heart v5, mean heart, contralateral breast max, 105 hot, late toxicity, lung changes, Echo, compliance, pigmentation, wet and dry desquamation and erythema of the studied groups

		Boost group (n=25)	Non boost group (n=25)	P
	SCV	13±12.2	23.62±17.38	0.023*
	Ipsilateral lung v5	22.16±7.41	30.57±6.6	<0.001*
	Mean lung	4.24±1.31	7.45±1.52	<0.001*
	Heart v5	1.94±2.35	3.57±4.05	0.087
	Mean heart	0.93±0.43	1.48±0.88	0.007*
	Contralateral breast max	3.9±2.42	4.21±2.29	0.643
	105 hot area	1.56±1.48	1.99 ± 2.67	0.479
	Late toxicity	7(29.17%)	5(20.0%)	0.456
	lung changes	5(20.0%)	2(8.0%)	0.221
Echo	Pre echo	67.19±11.91	66.75±17.83	0.924
	Post echo	66.23±10.54	75.33±14.71	0.087
Compliance	Mild	4(16.0%)	5(20.0%)	0.135
	Moderate	2(8.0%)	7(28.0%)	
	Non-compliant	1(4.0%)	3(12.0%)	
	Pigmentation	5(20.0%)	12(48.0%)	0.037*
	Wet desquamation	5(20.0%)	6(24.0%)	0.733
	Dry desquamation	6(24.0%)	12(50.0%)	0.059
	Erythema	13(52.0%)	20(80.0%)	0.037*

Data are presented as mean ± SD or frequency (%). *: significant as P value<0.05, Scv: Short comment volume, Echo: echocardiogram.

Table 4: Skin toxicity, recurrence, distant recurrence and OS (months) of the studied groups

		Boost group (n=25)	Non boost group (n=25)	P
Skin toxicity	Skin pigmentation	2(8.0%)	4(16.0%)	0.344
	Wet desquamation	0(0.0%)	5(20.0%)	
	Dry desquamation	6(24.0%)	8(32.0%)	
	Erythema	7(28.0%)	10(40.0%)	
	Recurrence	0(0.0%)	2(8.0%)	0.149
	Distant recurrence	3(12.0%)	3(12.0%)	1.000
	OS (months)	35.92±6.38	40.16 ±7.59	0.038*

Data are presented as mean ± SD or frequency (%). *: significant as P value<0.05. OS: overall survival.



Discussion

One of the most prevalent malignancies affecting women globally, breast cancer is the primary reason of cancer-related mortality in this population (18). The features of the tumour determine the therapy to be used (19).

Our study shows that side, type of surgery and axilla was insignificantly different between both groups. These results are supported by Meloot et al. (20) found that side of breast cancer was indifferent between conventional therapy and boost groups . Moreover, Lertbutsayanukul et al.(21). found the same as they revealed that the laterality was indifferent between conventional and boost group.

Concerning our study, T stage, N stage and total lymph node were insignificantly different between both groups. These findings are agreed with Meloot et al. (20) demonstrated that out of 317 patients, 194 received hypo fractionated while 123 received RT. T2, T3, and T4 tumours were present in the majority of patients in the two groups. In total, 43% of the patients were diagnosed with T2 disease. There was only one patient with unknown T status. There was insignificant difference among the groups, $P=0.777$. status: nodal involvement, 11 % had N3 status; most were N0, N1, or N2. Nodal status was unknown in only three cases. The noted change did not indicate significance. at $P=0.250$. Grade II tumours constituted most patients in both hypo fractionated and conventional RT, with a fraction of 0.8. No significant difference was found between both groups.

Our work found that pathology and focality were not significantly different between the two groups. These findings are comparable to the results of Amouzegar Hashemi et al.(22) stated that 52 patients were included in the study (hypo fractionated group, $n = 30$; conventional group, $n = 22$). Histologic grading and tumour staging were not statistically significant differences between groups.

Concerning our study, Er, Pr and Her2 were insignificantly different between both groups. These finding are consistent with Yadav et al. (23) found that hypo fractionated and conventional groups had insignificant different hormone receptors as Her2-neu positive .Added to that, Amouzegar Hashemi et al. (22) agreed to ours as in their study there were 30 patients had hypo fractionated and 22 patients had conventional therapy. hormone receptors (ER, PR, HER-2 receptors) were not significantly differences between both groups.

According to our research, Ki67, PNI and grade weren't significantly different between both groups while LVI was significantly reduced in booster group in comparison with booster group .These results matched with Saksornchai et al. (24) found that Ki67 was insignificantly different between participants who received conventional radiation and those who received hypo fractionated radiation groups. Further, Ahn et al. (25) revealed that low Lvi was associated with better modality of therapy of BC and less recurrence so boost group associated with less LVI and better prognosis.



Our results found that the two groups did not differ significantly in adjuvant hormonal, chemotherapy, Herceptin, or lymphedema, while, adjuvant was statically lower in boost group than non-boost group. These outcomes are in agreement with Yadav et al. (23) showed that chemotherapy and hormonal therapy were insignificantly different between boost and conventional groups. Contrary, Meloot et al. (20) noted that adjuvant therapy was indifferent between boost group than non-boost group.

Our study reveals that CTV, level1, level2 and level3 were significantly decreased in boost group than non-boost group.

The present study reported that SCV, ipsilateral lung v5, mean lung and mean heart were significantly reduced in boost group than non-boost group. Similarly, Yadav et al. (26).found the same results as they declared that mean dosage in the right lung was notably lower in mastectomy than patients with BCS, 0.29Gy *vs.* 0.51Gy, respectively. Mean dosage to the opposite breast was notably raised in BCS patients compared to mastectomy (0.54Gy *Vs* 0.37Gy, $p = 0.007$). On the other hand, BCS patients had a higher V2 to the right breast (1.43%) than mastectomy patients (0.26%) though this difference was not statistically significant. The mean dosages to the heart, LAD, proximal LAD and distal LAD were 3.364Gy, 16.06Gy, 2.7Gy, 27.5Gy; and 4.219Gy, 14.653Gy, 4.306Gy, 24.6Gy, respectively for mastectomy and BCS patients. The dosages given to the heart by BCS and mastectomy patients did not differ significantly. The mean dose of the left lung, V5, V10 and V20 were 5.96Gy, 16%, 14%, 12.4%; and 7.69Gy, 21%, 18%, 16% in mastectomy and BCS patients, respectively. These weren't also significantly different between both techniques.

Our study showed that late toxicity, lung changes and Echo pre and post were insignificantly different between both groups. Also, there was not significantly different between both groups as regard skin toxicity. These results are like Saksornchai et al.(24) concluded that there wasn't significant difference in late toxicity between the conventional and hypo fractionated groups ($p = 0.072$). Moreover, Amouzegar Hashemi et al. (22) supported our findings as they showed that the difference between the conventional and hypo fractionated groups in terms of distant metastasis didn't reach statistical significance either. In opposing side, Butler-Xu et al.(27) stated that patients receiving HFRT had a noticeably lower skin reaction rate than patients treated with CFRT. Grade ≥ 2 skin toxicity was experienced by only 28% of patients treated with HFRT, compared to 76% of patients treated with CFRT. One patient experienced grade 3 cutaneous toxicity (CFRT group). A tendency toward greater rates of grade ≥ 2 toxicity for CFRT (73% *vs.* 38% with HFRT; $P = .057$) was noted in patients with breast volumes ≥ 1000 cm³. Grade ≥ 2 skin toxicity did not differ significantly among patients with posterior breast separation more than 25 cm (57% for CFRT; 43% for HFRT; $P = .67$). Regardless of whether a boost was used or not, CFRT was associated with a noticeably increased rate of acute grade 2 skin toxicity.

Concerning our results, compliance, wet desquamation, dry desquamation wasn't significantly different between the two groups. Nevertheless, Pigmentation and erythema were significantly lower in boost group than non-boost group. These findings are different with the results of Chu et al.(28) discovered that 421 breast cancer



survivors finished the survey overall. Of them, 340 (80.76%) reported having dry skin, 184 (43.71%) reported having itchy skin in addition to dry skin, 336 (79.81%) had severe or mild skin colour deposition, 76 (18.05%) had eczema or contact dermatitis, and 331 (78.62%) reported sweating infrequently. The lack of perspiration, dryness in the irradiated area, severe skin disorders after radiation therapy, and changes in skin pigmentation were the causes of dry skin problems.

Our work reported that recurrence and distant recurrence weren't significantly different between two groups. Yet, OS in months was significantly lesser in boost group than non-boost group.

In the same line of our results, Amouzegar Hashemi et al.(22) concluded that the 5-year OS rate was 100% for the conventional group whereas the hypo fractionated group's was 95.2%, which wasn't significantly different among groups.

The limitations of our study are that small sample size. Short duration of follow-up and single center study may yield different results compared to studies conducted in other locations.

Conclusions

Boost group have statically significant lower LVI, Adjuvant, CTV, level1, level2, level3, SCV, ipsilateral lung v5, mean lung, and mean heart than non-boost group and complication of radiation after mastectomy of breast cancer are less pigmentation, erythema and OS while recurrence and distant recurrence are indifferent to conventional surgery without post radiation.

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