

Accelerated hypo-fractionated Whole Breast Irradiation with Concurrent Tumor Bed Boost Feasibility study

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Abstract: Background: Interest in hypofractionated postoperative whole breast irradiation (WBI) has risen in the last few decades, in an attempt to reduce overall treatment time, thus reducing the work load and the cost of post-operative WBI. However, the schedule of tumor bed (TB) boost within the context of this hypofractionated schedule is still unclear. **Patients and Methods:** This is a prospective phase II study conducted at Kasr El-aini Center of Clinical Oncology and Nuclear Medicine (NEMROCK). Patients who underwent breast conservative surgery were recruited. Recruited patients received a hypofractionated radiation schedule using 3DCRT at a dose of 40 Gy in 15 fractions to the whole breast with a concurrent TB boost at a dose of 8.0 Gy (0.5 Gy) per fraction over 3 weeks. All patients were evaluated for acute toxicity and cosmetic outcome. **Results:** During the period from June 2014 to January 2017, a total of 63 patients with a median age of 51 years were included. Regarding acute skin toxicity, 20% of patients developed GII skin toxicity, while 68% of patients developed GI skin toxicity, none of the patients developed GIII or more skin toxicity. The overall cosmetic outcome was excellent in 80.95 % of patients and good in 19% of patients. **Conclusions:** Hypofractionated radiotherapy in three weeks to the Whole breast with a concomitant boost in patients undergoing breast conserving surgery (BCS), allows acceptable outcomes in terms of acute toxicity and early cosmetic results and is a feasible strategy to reduce the cost and work load in radiotherapy departments as well as improve patient compliance. However, long-term follow up is needed to assess late toxicity, cosmesis and clinical outcomes.

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1. Introduction

Breast conservative therapy has become a standard alternative to mastectomy in early breast cancer patients eligible for breast conservation (1). It has been shown that postoperative radiotherapy for breast cancer patients treated with breast conserving surgery improves local control as well as breast cancer mortality (2, 3, and 4). The Oxford group meta-analysis of 17 randomized trials of radiotherapy versus no radiotherapy after breast conserving surgery, enrolling more than 10000 patients, proved reduction in five year local recurrence rate with the use of radiotherapy, as well as an improvement in long-term survival (5). Therefore, post-operative radiotherapy following breast conserving surgery has become a standard of care. This entails a postoperative radiotherapy course of 50 Gy in 5 weeks to the whole breast followed by a tumor bed boost of 10-16 Gy in 5-8 fractions.

There has been an interest in hypo-fractionating postoperative radiotherapy in breast cancer patients, in an attempt to reduce the overall

treatment time. In that context, four large prospective randomized controlled clinical trials were conducted to compare hypofractionated WBI (at different biologically equivalent doses in each trial) to the standard fractionation schedule of WBI at a dose of 50 Gy in 25 fractions (2 Gy per fraction). Long term follow-up data from these studies revealed comparable local control rates with acceptable toxicity and cosmetic outcomes between the hypofractionation arms and the standard arms. Based on these data, hypofractionated postoperative WBI has been adopted as a standard of care option as an alternative to standard fractionation WBI (6, 7, 8, 9, 10).

In altered fractionation schedules, the linear quadratic model is commonly used for predicting the response of different tissues (acute or late-reacting) to different schedules of radiation. For that purpose, the α/β ratio is used to account for the inherent radio-sensitivity of different tissues (11). In the case of breast cancer, Yarnold et al tested the sensitivity of breast tissue to modest increases in

fraction size proving an α/β ratio for late change in the breast of 3.6 Gy (95% CI, 1.8-5.4), and of 3.1 Gy for breast induration (95% CI, 1.8-4.4 Gy), while it was estimated to be 4 for tumor recurrence (95% CI, 1.0-7.8 Gy) (12). Hence, in view of having a relatively low α/β ratio, breast cancer is speculated to be more sensitive to increasing the dose per fraction (fraction size). Thus the delivery of hypofractionated post-operative radiotherapy results in the delivery of a potentially more effective biological dose to the breast and tumor bed, in addition to its other advantages of reducing the financial burden of radiotherapy and improving patient convenience.

In the context of hypofractionated postoperative WBI, there is marked variation in the delivery of the tumor bed boost; whether or not to adopt its delivery and if adopted at what schedule. Among the trials testing hypofractionated WBI, some trials adopted a no boost strategy, while others allowed the sequential delivery of a tumor bed boost following the hypofractionated schedule with the drawback of a partial loss of the reduced overall treatment time. In the current study, the aim was to test the feasibility of delivering a concomitant tumor bed boost within an accelerated hypofractionated WBI schedule regarding toxicity and cosmetic outcome.

2. Patients & Methods

This study was conducted at Kasr Al-Aini Center of Clinical Oncology & Nuclear Medicine (NEMROCK). Eligible patients were recruited over the period between June 2014 and January 2017. A total of 63 patients were recruited according to the pre-specified inclusion & exclusion criteria as follows:

Inclusion criteria female breast cancer patients between the age of 18-70 years were recruited if they had histologically proven breast adenocarcinoma, had undergone conservative breast surgery with negative surgical margins, pathological stage pT1 -T3 pN0 according to the America Joint Committee- Union Internationale Contre le Cancer staging system (7th edition AJCC- TNM) and had no evidence of distant metastases at diagnosis.

Exclusion criteria included positive resection margins, contraindication to breast conservative surgery e.g. locally advanced disease (T4, N3 breast cancer), metastatic disease, prior radiation to the thoracic region, pregnancy, and double primary disease.

Patient Positioning, Immobilization & CT Scanning:

Each patient was positioned comfortably on a breast board elevated at 10 degrees with both hands grasping the middle column. A treatment planning

CT scan in that treatment position was acquired with radio-opaque markers (guide-wire) placed on external landmarks - around the breast and over the palpable tumor bed cavity - to guide the contouring of target volumes. A CT scan image thickness of 0.5 cm was acquired from the mandible down to the diaphragm. External skin localizing marks i.e., permanent tattoos, were used to aid in reproducibility of daily patient set-up and localization.

Contouring of Target Volumes: Breast CTV was delineated following the consensus guidelines from **The RTOG Breast Cancer Atlas for Radiation Therapy Planning**. Contouring of the **lumpectomy CTV** was done guided by the wires placed over the palpable cavity during CT scan and with the aid of available pre-operative mammography, the seroma as seen in CT cuts, and surgical clips placed during surgery if available. Surgical details as well as histopathological reports of surgical specimen were also used to aid the determination of the size of the tumor bed as well its distance from the skin. **Lumpectomy PTV** was generated by adding 5mm 3D symmetrical expansion around the lumpectomy CTV.

Contouring of Organs at Risk (OAR): The Ipsilateral lung and the Contralateral lung were each contoured separately using auto-segmentation with manual verification. **The Heart** was contoured beginning just inferior to the level of bifurcation of the pulmonary trunk into the left and right pulmonary arteries (PA). The heart was contoured on every contiguous slice thereafter down to its inferior-most extent near the diaphragm. The pericardium was excluded at delineation. **The Contralateral breast** was contoured to include the apparent glandular breast tissue visualized by CT including the overlying skin and excluding the pectoralis muscles, serratus anterior muscles, ribs and bony thorax.

Dose prescription:

Each treatment plan was calculated to deliver a dose of 40 Gy in 15 daily fractions (2.67 Gy per fraction) over 3 weeks to the whole breast, with a concomitant tumor bed boost dose of 8 Gy in 15 daily fractions. This prescribed dose was calculated according to the linear quadratic model to be a radiobiologically equivalent dose to a conventionally fractionated WBI dose of 50 Gy in 25 fractions and a TB boost of 10 Gy in 5 fractions.

Treatment Planning:

Three dimensional radiotherapy planning was used, where for each case a plan for WBI was generated then a TB boost plan was generated separately. The isocenter and the dose normalization point for the breast and the boost plan were identical (when possible). Finally, a summation plan of the two previous plans was generated and used for plan acceptance.

Plan acceptance: was done by reviewing the plan for WBI and the boost plan separately, then the plan summation was evaluated. Beam-eye view was revised for each field to ensure proper coverage of the CTV with maximum sparing of the risk organs. Isodose lines on axial CT cuts were revised to evaluate dose homogeneity and adequate CTV coverage. Finally Dose volume histograms (DVH) were evaluated to ascertain that dose coverage of the target volumes and dosimetric constraints regarding (OAR) were abiding with our hypofractionated protocol.

Simulation: is done for each patient to localize treatment portals' iso-center on the skin using its definition in relation to the CT reference point from the treatment planning system data, by means of distances in X, Y & Z directions. The iso-center of the treatment portal is then verified by comparing simulator images to corresponding DRRs obtained from planning computed tomography (CT) scan.

Treatment Verification:

Electronic portal image (EPI) of the set up and for the tangential fields were obtained for each patient in the treatment position before the first session and were matched with digitally reconstructed radiographs (DRRs) obtained from the planning system. Differences of setup in each direction were considered acceptable if <5mm, while any difference of more than 5mm was not accepted. & in that case patients were re-simulated. Plan verification with Electronic portal imaging (EPI) was done at least once weekly to verify setup reproducibility.

Follow-up:

All patients were clinically evaluated on weekly basis during the whole treatment course with assessment of acute toxicity, after which patients were evaluated on monthly basis for recording of late toxicity as well as cosmesis. Late toxicity was scored starting from 6 months after the end of the treatment course. The least follow-up The maximal detected toxicity was scored according to the **RTOG/EORTC Common Terminology Criteria for Radiation Morbidity Scoring Schema, version 3.0** (14).

For the evaluation of cosmetic outcome, two scoring systems were used i.e. subjective patient reported score (Harvard score) as well physician reported score.

Ethical considerations:

This research protocol was presented and accepted by the research ethics committee and the scientific research committee of the department of clinical oncology, Faculty of Medicine, Cairo University.

Statistical analysis:

All data were subjected to statistical analysis using the statistical package for social sciences (SPSS) version 16.

3. Results

I. Patients Characteristics:

Clinical features:

Including age (median age=51 years), menopausal status, side and site of disease. These data are shown in **table 1**

Table 1: Clinical features of patients:

Age (years):	
-median	51
-mean+/-SD	50.85% +/-8.98
-range	(22-65 years)
Menopausal status:	
-pre-menopausal	29 (46.03%)
-post-menopausal	34 (53.97%)
Side:	
-right	29 (46.03%)
-left	34 (53.97%)
Site:	
-UOQ	30 (47.62%)
-UIQ	19 (30.16%)
-LOQ	6 (9.52%)
-LIQ	4(6.35%)
-Retroareolar	4(6.35%)

(UOQ: Upper outer quadrant, UIQ: Upper inner quadrant, LOQ: lower outer quadrant, LIQ: lower inner quadrant),

A. Pathological features: Including the pathological type, grade, T stage of the tumor, ER, PR, Her-2-neu

status, KI-67 and the biological subtypes as shown in **able 2.**

Table2: Pathological features of the tumor:

Pathological types:	
IDC	54 (85.71%)
ILC	4 (6.35%)
Medullary carcinoma	3 (4.76)
Mixed IDC/ILC	2 (4.76)
Tumor grade:	
G1	2 (3.17%)
G2	56 (88.89%)
G3	5 (7.94%)
T stage:	
T1	24 (38.10%)
T2	37 (58.73%)
T3	2 (3.17%)
Maximum diameter:	
Median	2.6
Mean+/-SD	2.27+/-1.11
Range	0.8-6 cm
Surgical management of axillary LNs:	
-ALND:	59 (94%)
Median	17
Mean+/-SD	2.7+/-1.1
Range	8-31
-SLNB	4 (6%)
ER status:	
ER positive	51(80.95%)
ER negative	12 (19.05%)
PR status:	
PR positive	51 (80.95%)
PR negative	12(19.05%)
Her2neu amplification:	
Negative	52 (82.54%)
Positive	11 (17.46%)
KI 67:	
Low i.e. ≤ 14	35 (55.56%)
High i.e. > 14	28 (44.44%)

(ALD) axillary lymph node dissection – (SLNB) sentinel lymph node biopsy- **IDC**: Invasive duct carcinoma, **ILC**: Invasive lobular carcinoma, **ER**: Estrogen receptor, **PR**: Progesterone receptor.

B. Adjuvant systemic therapy: For the current study (65.08%) of the patients received adjuvant chemotherapy while (34.92%) of the patients didn't receive adjuvant chemotherapy, and as regard the adjuvant hormonal therapy (82.54%) of the patients received adjuvant hormonal therapy.

C. Baseline body measures: For the current study Mean +/-SD for tangential separation (cm) was 16.12+/-2.5. Other body measurements e.g. breast volume and width, boost volume are shown in table 3.

II. Received Radiotherapy: The mean duration of the course of radiation was 22+/-2.1days. There was also a lag (delay) in the completion of the course of irradiation in the range of (0-7) days with a mean value of 1.4+/-2.1 days.

III. Acute toxicity: All patients were evaluated clinically on weekly basis throughout the treatment course with recording of acute toxicity. The maximal detected toxicity was scored according to The Common Terminology Criteria for Adverse Events, version 3.0, using the RTOGEORTC toxicity.

Regarding acute skin toxicity (defined as any toxicity recorded within the course of radiation and till 6 months thereafter), (68.25%) of the patients had G1 acute skin toxicity, (20.63%) of the patients had G2 acute skin toxicity, and no patients had G3 nor G4 acute skin toxicity (**Figure 1**). There were no reported acute cardiac nor pulmonary toxicity.

As regard late skin toxicity (71.43%) of the patients had no reported late skin toxicity, and

(28.57%) of the patients had GI late skin toxicity. No patients had G3 nor G4 late skin toxicity as shown in **Figure (2)** . There were no reported cardiac nor

pulmonary late toxicity, however longer follow up is needed to properly evaluate and document late toxicity.

Table 3: Body measures of patients:

Tangential separation (cm):	
-Mean +/-SD	16.12+/-2.5
-Range	11-24.5
Breast width (cm):	
-Mean +/-SD	5.3+/-2.0
-Range	2-13
Breast volume (cm3):	
-Mean +/-SD	929+/-471
-Range	268-2673
Boost volume (cm3):	
-Mean +/-SD	42.2+/-23.6
-Range	3.5-122
CLB volume (cm3):	
-mean +/-SD	1004.7+/-367.7
-Range	330-1895
Heart volume (cm3):	
-mean +/-SD	588.9 +/-144.6
-Range	385-1152
Ipsilateral lung volume (cm3):	
-mean +/-SD	1217.2+/-242.3
-Range	832-2000

CLB: Contra-lateral breast, SD: Standard deviation.

Rtoge acute skin toxicity

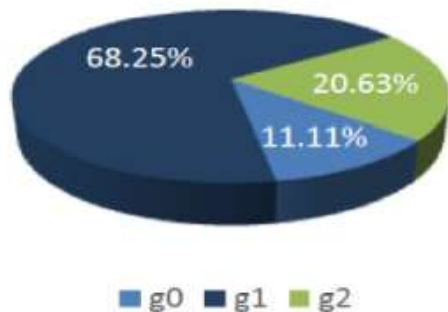


Figure (1): shows that (68.25%) of the patients had G1 acute skin toxicity, (20.63%) of the patients had G2 acute skin toxicity.

Rtoge late skin toxicity

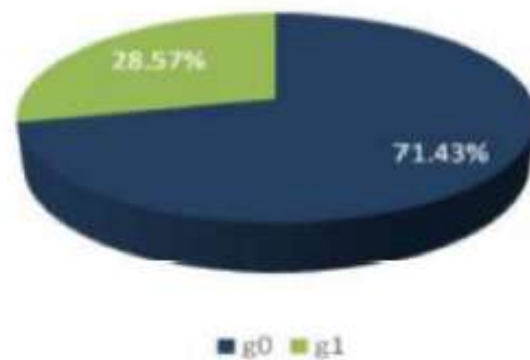


Figure (2): shows that (28.57%) of the patients had G1 late skin toxicity no patients had G3 nor G4 late skin toxicity.

IV. Cosmetic result:

Patient reported cosmetic scores according to Harverd criteria as following: Excellent cosmesis (defined as designating little or no change) was reported by 51 (80.95%) of the patients. Good cosmesis (defined as minimal but noticeable change) was reported by 12 (19.05%) patients as shown in

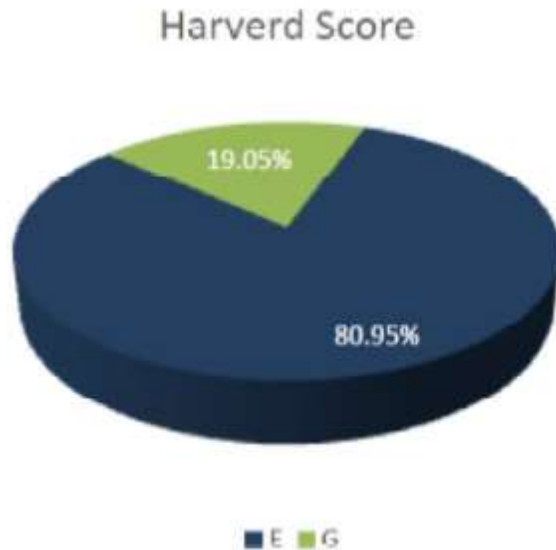


Figure (3): Shows excellent cosmesis in (80.95%) of patients and good cosmesis in (19.05%) of patients.

Figure (3). None of the recruited patients reported poor cosmesis. Similarly, physician reported cosmetic scores (according to objective score) was as follows: excellent cosmesis was noted in (80.95%) of the patients and good cosmesis was noted in (19.05%) patients as shown in **Figure (4).**



Figure (4): Shows excellent cosmesis in (80.95%) of patients and good cosmesis in (19.05%) of patients.

V. Clinical outcomes: local control and disease free survival:

In our study, A total of 63 patients were recruited and followed for a median period of 24 months (ranging from 18 to 32 months). No local recurrences nor distant metastasis were reported during the follow up period.

4. Discussion

With the expanded use of postoperative whole breast irradiation among breast cancer patients undergoing breast saving surgery, interest has grown in contracted radiation schedules as they carry several advantages including owing to the shorter duration of radiation. These advantages include improvement of patient convenience with subsequent higher compliance and adherence to postoperative radiotherapy as well as reduction of machine load and the cost of radiation thus leading to optimizing the utility of available radiotherapy facilities.

At the department of clinical oncology-Cairo university, we conducted a study comparing

conventionally fractionated post-operative radiotherapy with concomitant boost versus sequential boost after breast conservative surgery among early breast cancer patients in the period between July 2010 and December 2012 in an aim to shorten the radiotherapy course from six weeks to five weeks. At that time, hypofractionated radiotherapy was not yet adopted as a standard of care in our department. Consequently, with the adoption of hypofractionated post-operative radiotherapy the current study was conducted to evaluate the feasibility of delivering a hypofractionated radiation schedule of 40 Gy/2.67 Gy per fraction over 3 weeks to the whole **breast** with a concurrent tumor bed boost of 8.0 Gy/0.5 Gy per fraction over 3 weeks for further reduction of the overall treatment time. Here we report on the early outcomes of the first 63 patients enrolled with a median follow-up period of 24 months (ranging from 18 to 32 months).

Regarding the enrolled patient characteristics; the median age was 51 years with about 50.78% of our patients being premenopausal. Noticeably, our patients have a significantly younger age than

internationally reported for breast cancer. In general, epidemiological data on breast cancer in Egypt hint at this younger age, where the data from the Gharbia cancer registry identifies a median age of breast cancer of 50.1 years similar to that reported in our study (15, 16, 17).

Regarding the disease characteristics; in our study more than 85% of the tumors were IDC, with 83% of the patients having hormone-receptor positive breast cancer, and around 18% had Her2-neu over-expression and 9.5% had TNBC. These numbers are not far from international figures (18,19,20).

With a median follow-up of 24 months, we report here on the acute toxicity profile of our schedule which was generally tolerable. The maximum acute skin toxicity reported among our patients was grade (1) in 43 patients (68.25%), and grade 2 in 13 patients (20.63%), with no grade 3 or higher skin toxicity. Our data are in keeping with those reported by **Albaran et al.**; where out of the 50 patients in their trial of hypofractionated WBI with a concomitant boost, acute toxicity was confined to the skin and Grade 0-1 skin toxicity was detected in 66% of patients. Grade 2 skin toxicity was reported in 28% of patients. No **grade** >3 skin toxicity was observed. The study conducted by **Chadha, et al.** reported similar results among 105 patients receiving a similar radiation schedule with no acute grade 3 or 4 toxicity.

As for acute and late heart and lung toxicities, none were reported in our study, however longer follow up is needed to further evaluate late toxicities among our patients.

In our study, post-treatment patient-reported and physician-reported cosmetic scores were excellent cosmesis in (80.95%) of patients and good cosmesis in (19.05%) of patients. This data was not far different from those reported by the cited studies; where **Valero Albaran et al.** reported good-excellent cosmetic outcome in all patients. **Chadha et al.** documented no significant negative effect reported on cosmesis (21,22).

Regarding the use of accelerated hypofractionation in young patients, 13% of our patient population were under 40 years. We didn't notice any increase in toxicity nor poorer cosmetic outcome among those patients. In the **Canadian study** of hypo fractionated postoperative WBI that delivered RT dose to the WB of 42.5 Gy/16 fractions, 25% of the enrolled women were under 50 years of age and the hypo fractionated treatment was as efficacious as conventional fractionation. The **START-B** delivered hypofractionated radiotherapy (40 Gy in 15 fractions) after either breast

conserving surgery or mastectomy regardless of age at diagnosis (6, 7, 8, 9, 10).

Regarding the use of accelerated hypofractionation in large breast volume, we defined large breast as breast volume to be that above 1500 cm³ as calculated from the planning CT scan, as unfortunately most of our patients could not report their cup size. In our study, 10% of patient population had large breast volume and there was no significant deterioration regarding neither toxicity nor cosmetic outcome in those patients. This is compatible with data reported by the group of **Corbin et al.** who compared the acute toxicity observed in 93 large breasted women with early stage disease treated with hypofractionated whole breast radiotherapy (42.56 Gy in 16 fractions of 2.66 Gy versus conventionally whole breast fractionated radiotherapy. No differences were observed in acute toxicity related to fraction size (23).

Conclusion

Among patients undergoing breast saving surgery going into hypofractionated post-operative whole breast irradiation, the delivery of the tumor bed boost- when indicated- concomitantly to avoid prolongation of the schedule of radiation, appears to be feasible with acceptable toxicity and cosmetic outcome. However, we acknowledge the need for longer follow-up to observe late toxicity and local control. Larger prospective randomized trials are needed to compare the proposed schedule of accelerated hypofractionation to standard of care.

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