Dosimetric planning study for 3D hypofractionated radiotherapy in early breast cancer patients

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Abstract: Background: Breast-conserving surgery and radiotherapy are standard alternatives to mastectomy for eligible patients with early stage invasive breast cancer**.** However, one drawback with conventional RT to the whole breast is the 6-7 weeks length of treatment involves treatment of the whole breast at 1.8 - 2 Gy daily fractions for 46 - 50.4 Gy, followed by a sequential boost to the tumor bed for 10-18 Gy. **Patients and Methods:** Our prospective phase II study conducted at Kasr El-aini Center of Clinical Oncology and Nuclear Medicine (NEMROCK). Early stage breast cancer who underwent BCS were recruited and planned using 3D conformal technique to receive a hypofractionated radiation schedule using 40 Gy/2.67 Gy per fraction over 3 weeks to the whole breast with Concurrent boost 8.0 Gy/0.5 Gy per fraction over 3 weeks. Dosimetric parameters for the coverage of the breast CTV were set using V38, V36 Gy and the homogeneity using the Dmax and the Dmin. For the coverage of the boost PTV V45.6Gy and V43Gy were used and for dose homogeneity Dmax and Dmin. As regard dose constrain for organ at risk (OAR), no more than 20% of the ipsilateral lung exceeds 16 Gy, no more than 5% of the whole heart exceeds 20 Gy. **Results:** During the period from June 2014 to January 2017, a total of 63 patients were included. The dosimetric parameters for the coverage of target volumes and dose constrain for OAR were in compliance with our protocol. **Conclusions:** Hypofractionated radiotherapy in three weeks to the whole breast with a concomitant boost in patients undergoing breast conserving surgery (BCS), allows acceptable and feasible outcomes in terms of dosimetric parameters.

Key words: Dosimetric planning - Hypofractionation - Concomitant boost - Breast conserving therapy - Tumor bed.

1. Introduction

Over 20 years ago large randomized controlled trials proved that breast conserving surgery (BCS) followed by postoperative radiotherapy (breast conserving therapy, BCT) could be an alternative treatment for women with early breast cancer. Women treated with breast conserving surgery followed by radiotherapy showed a significant decrease in local recurrences rates, as compared to breast conserving surgery alone. Moreover, breast conserving therapy (BCT) showed equal overall survival rates compared to radical mastectomy in long-term follow-up**.** Other studies have shown that quality of life is enhanced in women who undergo breast-conserving therapy**.** Consequently, breast-conserving therapy has become the recommended option for women with early breast cancer (2,3,4)**.**

All these problems have resulted in many centers developing a hypofractionated schedule to optimize resources. Thus, clinical and theoretical evidence has shown that a small increase in the dose per fraction, together with a decrease in the total administered dose,

will be as effective as a traditional scheme. This is in agreement with the hypothesis regarding the potential benefit of hypofractionation in tumors with a low (α\β) ratio (5).

prospective randomized clinical trials have shown promising results with hypofractionated schedules for WBI in each of these studies, the goal was to deliver a hypofractionated dose schedule that is biologically equivalent to the standard fractionation breast dose of 50 Gy in 25 fractions of 2 Gy. With 5-10 year follow-up of these studies, there has been similarity in breast local control and cosmetic outcomes between the hypofractionated and standard fractionated arm (6,7,8,9,10).

Optimum fractionation can be defined as a schedule providing the maximum tumor control for the minimum normal-tissue complications. It depends critically on the proliferative state of the tumor cells relative to that of the normal tissue at risk. This is where basic biology, particularly the understanding of cell proliferation, and clinical radiation oncology join hands. The linear-quadratic concept is the most

commonly used radiobiologic model to predict the differential response of the acute and the late reacting tissues to radiotherapy. (11).

2. Patients and Methods

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

Patients were positioned supine with breast boards. Radio-opaque markers (guide-wire) were placed on external landmarks at the acquisition of the CT scan to facilitate contouring of target volumes. A CT scan image thickness of ≤ 0.5 cm was done. External skin localizing marks i.e., permanent tattoos, were used for daily localization and set-up accuracy.

Targets volumes and Organs at Risk (OAR) Contouring; was delineated following the consensus guidelines from The RTOG Breast Cancer Atlas for Radiation Therapy Planning (12).

Radiobiological equivalent dose: comparing the conventionally fractionated sequential boost schedule, consisting of 60 Gy in 30 fractions, with the concomitant boost accelerated hypofractionated whole-breast radiotherapy employed in the present study (a total of 40 Gy/2.67 Gy per fraction to the whole breast with Concurrent boost 8.0 Gy/0.5 Gy per fraction given in 15 fractions), a conversion into a biologically effective dose (BED) was performed, according to the linear quadratic model (11). For this calculation, we assumed an α/β ratio of 4 Gy for tumor response, 10 Gy for acute responding normal tissues, 3 Gy for late-responding tissues.

Treatment Planning; Doses coverage of the target volumes; Breast CTV V36 defined as the volume that received 36 Gy which represent 90% of the prescribed dose for the whole breast CTV. This was biologically equivalent to V45 Gy in the Standard fractionation. No more than 35% of the breast CTV exceeded 100% of the boost prescribed dose of 48 Gy. Also, no more than 50% of the volume of breast CTV exceeded $\geq$ 44.8 Gy of the boost prescribed dose. These parameters were used to reduce dose heterogeneity. **Lumpectomy PTV** V43.2 defined as the volume that received 43.2 Gy which represent 90% of the prescribed dose for the boost PTV. **Dosimetric constrain regarding (OAR); Ipsilateral lung**: V16 defined as the volume of the ipsilateral lung receiving 16 Gy was used, and was considered acceptable if it didn't exceed 20% of the ipsilateral lung volume. **Contralateral lung**: V4 defined as the volume of the contralateral lung receiving 4 Gy, and considered acceptable if it did not exceed 15% of the contralateral lung volume. **Heart**: V20 defined as the volume of the heart receiving 20 Gy, and considered acceptable only if it did not exceed 5% of the heart volume. **Contralateral breast:** The maximum dose to contralateral breast was considered acceptable if it did not exceed 240 cGy.

Plan acceptance was done by reviewing whole breast plan and boost plan separately, then a plan summation was evaluated. Finally, the isocenter and the dose normalization point for the breast and the boost plan were identical (when possible).

Beam-eye view was revised for each plan 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.

The isocenter of the treatment portal was verified by comparing simulator images with the corresponding DRRs obtained from planning computed tomography (CT) scan.

Plan verification with Electronic portal imaging device (EPID) was done once weekly to verify setup reproducibility.

Follow-up and Cosmetic Evaluation for all patients were evaluated on a weekly basis during the whole treatment course to asses acute toxicity. Late toxicity was scored starting from 6 months after the end of the treatment course. The maximal detected toxicity was scored according to The RTOG/EORTC Common Terminology Criteria for Radiation Morbidity Scoring Schema, version 3.0 (13).

Ethical considerations: The 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 evaluated statistically by the statistical package for the social sciences (SPSS) version 16.

3. Result
Results of dosimetric data:
A)   Dosimetric data on target coverage:

The coverage of the CTV (the whole breast) was assessed using the V38, and V36 Gy. The homogeneity within the target was evaluated by 2 parameters; the Dmax and the Dmin as shown in Table 1.

The Dmax (maximum dose) was defined as the dose received by 2% of the target, while the Dmin (minimum dose) was defined as the dose received by 98% of the target. This is keeping with the ICRU report 83 recommendations *(Grégoire and Mackie, 2011)*.

B) Dosimetric data on coverage of the Boost PTV:

The coverage of the boost ptv was assessed using the V45.6, V43.2 Gy. The homogeneity within the target was evaluated by 2 parameters; the Dmax and the Dmin as shown in **Table 2.**

No boost PTV volume exceeded V52.8 (that represent 110% of the boost prescribed dose of 48 Gy).

C) Dosimetric data on OAR (organs at risk):

The doses received by organs at risk were evaluated by using the following parameters:

● **The dose to the heart**: was evaluated by the V20 Gy, V25 Gy, D35% and MHD.

● **The dose to the ipsilateral lung**: was evaluated by the V20 Gy (considered acceptable below 20%), V16Gy (no more than 20% of the ipsilateral lung exceeded 16 Gy). As well for

contralateral lung no more than 15% of the contralateral lung exceeded 4 Gy.

● **The dose to the contralateral breast**: was evaluated by V2.4Gy and by the Dmax as shown in **Table 3.**

Data on received radiotherapy:

The mean duration of the time between the surgery and the start of the radiotherapy (in days) was 171+/-83.6 days the range was (25-348 days) as shown in Table 4.

The mean duration of the whole course of radiation (in days) was 22+/-2.1 days. 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 as shown in **Table** 4.

Table 1: Dosimetric data on coverage of the CTV-WB

Parameter	Value
V38 **(mean +/-SD)**	95.89+/-1.7
-Range	90-100
V36 **(mean +/-SD)**	99.0 +/- 0.8
-Range	96-100
V48 **(mean +/-SD)**	5.2 +/- 3.8
-Range	0-16
V44.8 **(mean +/-SD)**	16.8**+/-** 7.4
-Range	0-34
D max **(mean +/-SD)**	48.5 +/-1.17
-Range	50-43
D min **(mean +/-SD)**	37.26 +/- 1.15
Range	36-45

CTV: *Clinical target volume,* **V38**: *Volume that received 38 Gy,* **V36**: *Volume that received 36 Gy,* **V48**: *Volume that received 48 Gy* **V44.8**: *Volume that received 44.8. Gy* **Dmax**: *maximum dose,* **Dmin**: *minimum dose*

Table 2: Dosimetric data on coverage of the Boost ptv:

Parameter	Value
V45.6 **(mean +/-SD)**	97.28+/-3.5
-Range	90-100
V 43.2**(mean +/-SD)**	99.29 +/- 1.55
-Range	93-100
D max **(mean +/-SD)**	49.53 +/-1.02
Range	47-51
D min **(mean +/-SD)**	45.51 +/- 1.77
Range	40-48

PTV: *planning target volume,* **V45.6**: *Volume that received 45.6 Gy,* **V43.2**: *Volume that received 43.2 Gy,* **Dmax**: *maximum dose,* **Dmin**: *minimum dose.*

Table 3: *Dosimetric data on OAR (organs at risk):*

Ipsilateral Lung	
V20 **(mean +/-SD)**	12.4+/-3.84
-Range	*2-20*
V16 **(mean +/-SD)**	13.87+/-4.16
-Range	*2-20*
D50 **(mean +/-SD)**	1.97+/-0.5
Range	*0.9-3.3*
D35 **(mean +/-SD)**	3.3+/-0.7
Range	*1.5-4.5*
V4CLL **(mean +/-SD)**	0.003 +/- 0.025
-Range	*0-0.2*
Heart	
V20 **(mean +/-SD)**	1.79 +/- 2.47
-Range	*0-10*
V25 **(mean +/-SD)**	1.52 +/- 2.21
-Range	*0-9.5*
D35 **(mean +/-SD)**	1.19 +/- 0.7
Range	*0.3-3.7*
MHD **(mean +/-SD)**	1.7+/-1.2
Range	0.3-4
Contra lateral breast	
V2.4 **(mean +/-SD)**	*0.96+/- 1.1 1*
-Range	0-4.8
Dmax **(mean +/-SD)**	1.78 +/-0.69
-Range	*0.6-3.5*

CLL: *Contra-lateral lung,* **SD**: *Standard deviation,* **V20:** *Volume that received 20Gy,* **V16:** *Volume that received 16Gy,* **V4:** *Volume that received 4Gy,* **D50:** *dose that reach 50% of volume,* **D35:** *dose that reach 35% of volume,* **V25**: *Volume that received 25Gy,* **MHD**: *mean heart dose,* **V2.4**: *Volume that received 2.4Gy,* **Dmax**: *maximum dose.*

Table 4: *Data on received radiotherapy*

Surgery-radiotherapy interval (in days):	
mean +/-SD	171+/-83.6
Radiotherapy duration (in days):	
mean +/-SD	22+/-2.1
Median	21
Range	21-28
Radiotherapy lag (in days):	
mean +/-SD	1.4+/-2.1
Range	0-7

SD: *Standard deviation*

4. Discussion

In our study the dosimetric data for target coverage for the mean breast volume that received ≥ 95% of the prescription dose were 96%. The mean breast volume that received ≥ 90% of the prescription dose were 99%. The parameters for dose homogeneity i.e. the mean Dmax and Dmin, were 48Gy and 37 Gy respectively. These data are similar to those reported in **Valero Albarrán et al** study in which all patients received RT to the whole breast with concomitant boost irradiation of the tumor bed. Prescription dose were 40.5 Gy and 48 Gy respectively, delivered in 15 fractions (2.7 Gy and 3.2 Gy per fraction). This study reported the mean value for breast volume that received ≥ 95% of the prescription dose was 98.3 %. The mean maximum dose to the breast was 52.8 Gy, and by **Chadha, et al** study in which the RT dose to the WB was 40.5 Gy in 2.7 Gy/ fraction over 15

fraction, and concomitantly to the lumpectomy site was 45 Gy in 3 Gy/ fraction over 15 fraction using a concomitant boost. They reported the mean breast volume that received ≥ 95% of the prescription dose was 99.4% (14,15).

As for the Boost-PTV, The mean boost volume that received ≥ 95% of the prescription dose was 97% and the mean boost volume that received ≥ 90% of the prescription dose was 99 %. The parameters for dose homogeneity i.e the mean values for Dmax and Dmin, were 49 Gy and 45 Gy respectively. Data are similar to those reported in **Chadha, et al;** where the mean boost volume that received ≥ 95% of the prescription dose was 99.7% **(15).**

For dose homogeneity boost dose received by the breast CTV as regard the mean value for V48 i.e the total prescribed dose to the tumor bed was 5.2%. This was compatible with dose constrain in our protocol no more than 35% of the breast CTV exceeded 48 Gy, also there were no isolated hot spots found outside the regions of the lumpectomy PTV.

The dosimetric data on the doses received by the risk structures: the mean for the heart we used V20 which is biologically equivalent to V25 used by the QUANTEC as a constrain dose in the standard fractionation. The mean heart V20 was 1.4%. **Valero Albarrán et al** they used the mean heart V16 which is biologically equivalent to V20 in the standard fractionation The mean heart V16 was 2.13%.

And in our study for the mean value for ipsilateral lung V16 which is biologically equivalent to V20 in the standard fractionation was 13.8%. In **Valero Albarrán et al** as regard the mean value for ipsilateral lung V16 was 12.1%(14).

As regard radiotherapy lag; the mean+/- SD was 1.4+/-2.1. Most of these disruptions of our patients' radiotherapy courses are attributed to machine breaks and long holidays (e.g. feast holiday), and no patient was disrupted due to toxicity necessitating holding treatment*.*

Conclusion and Recommendation

The hypofractionated 3D planning for a total of 40 Gy/2.67 Gy per fraction to the whole breast with Concurrent boost 8.0 Gy/0.5 Gy per fraction given in 15 fractions) is feasible with acceptable target volumes coverage and risk structures dose constrain, with the advantage of shorting the length of treatment course and compliance of patient.

References

1. National Comprehensive Cancer Network: *NCCN* Clinical Practice Guidelines in Oncology 2010.
2. Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. J Natl Cancer Inst 1996 Nov 20;88(22):1659-1664.
3. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002; 347:1233-1241.
4. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002; 347:1227- 1232.
5. Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomized trial. *Radiother Oncol* 2005;75:9–17.
6. Whelan T, Pignol JP, Levine MN, et al. Longterm results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513-20.
7. Yarnold J, Haviland J, Bentzen SM, et al. Estimation of an overall treatment time factor for local relapse after adjuvant radiotherapy for early breast cancer by the UK START Trialists' Group. Eur J Cancer 2013;49(2):S2405.
8. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patient with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006;7:467–71.
9. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial. Lancet Oncol 2008;9:331-41.
10. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial. Lancet 2008;371:1098-107.
11. linear quadratic model S.M. Bentzen, M. Baumann. The linear-quadratic model in clinical practice G.G. Steel (Ed.), Basic Clinical Radiobiology (third ed.), Arnold, London (2002), pp. 134-146.
12. Breast Cancer Atlas for Radiation Therapy Planning.
13. The Common Terminology Criteria for Adverse Events, version 3.0, using the RTOG⁄EORTC

toxicity. J.D. Cox, J. Stetz, T.F. Int. J. Radiat. Oncol. Biol. Phys., 31 (1995), pp. 1341-1346.

14. Valero Albarrán Ciervide Jurio1 et al. Hypofractionated radiotherapy and concomitant boost in breast cancer patients using 3-D conformal radiotherapy. ESTRO (33), 2014.

15. Chadha M, Woode R, Sillanpaa J, et al. Earlystage breast cancer treated with 3-week accelerated whole-breast radiation therapy and concomitant boost. Int J Radiat Oncol Biol Phys 2013;86:40-47. http://dx.doi.org/10.1016/j.ijrobp.2012.11.010.

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