Dosimetric planning study of hypofractionated radiotherapy with a concomitant boost after breast conserving surgery

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Abstract: Background: Whole breast irradiation followed by a tumor bed boost is the standard of care after breast conserving surgery (BCS). This entails a protracted radiotherapy course over 6-7 weeks with a consequent increase in work load and cost of radiotherapy, as well as reduced patient compliance. **Patients and Methods:** This dosimetric study was conducted at Kasr El-aini Center of Clinical Oncology and Nuclear Medicine (NEMROCK) to elicit the feasibility of applying an accelerated hypofractionated course of whole breast irradiation with a concurrent tumor bed boost. Radiotherapy planning using 3DCRT was done for breast cancer patients eligible for post-operative radiation following BCS, aiming to deliver a hypofractionated radiation schedule of 40 Gy in 15 fractions (2.67 Gy per fraction) over 3 weeks to the whole breast with a concomitant tumor bed boost of 8.0 Gy in 15 fractions(0.5 Gy per fraction) over 3 weeks. Dosimetric parameters for the coverage of the breast CTV were evaluated using V38, V36 Gy and the homogeneity using the Dmax and the Dmin. For the coverage of the boost PTV V45.6 Gy and V43Gy were used as well as Dmax and Dmin for dose homogeneity. As for the organs at risk (OAR), doses to the ipsilateral lung, heart and contralateral breast were evaluated aiming to meet the pre-specified constraints. **Results:** A total of 63 plans were performed. 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) is feasible from a dosimetric point of view, with acceptable coverage and doses to OAR parameters.

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1. Introduction

Breast conserving surgery (BCS) followed by postoperative radiotherapy (breast conserving therapy, BCT) has been proved as an alternative treatment to modified radical mastectomy for women with early breast cancer as proved by several randomized controlled trials... Breast conserving surgery followed by post-operative radiotherapy resulted in significantly lower local recurrence rates compared to breast conserving surgery alone. Long term follow-up showed equivalent overall survival rates among patients who received breast conserving therapy compared to those who underwent radical mastectomy. Moreover, studies have shown an enhanced quality of life among women undergoing breast conserving therapy. Consequently, breast-conserving therapy has become the recommended option for women with early breast cancer (2, 3, and 4)**.**

A major drawback of breast conserving therapy is the need to deliver a protracted post-operative radiotherapy course to the whole breast over 6-7 weeks. This results in a consequent increase in radiotherapy work load, cost and delays, as well as decrease in patient compliance. As a result, there has been great interest in delivering hypofractionated radiotherapy schedules in an effort to optimize resources.

Biologically, optimum fractionation is a schedule that provides maximum tumor control with minimum damage to normal tissues. That depends on the rate of proliferation of targeted tumor cells in relation to that of normal tissues at risk. This is where the linear –quadratic model comes in hand to predict the differential response of acute and late reacting tissues to different doses of radiation (11).

Initial theoretical evidence suggested that a small increase in the dose per fraction- while decreasing total dose delivered- with subsequent reduction in overall treatment time, would be as effective as a conventional radiotherapy scheme. From a radiobiological point of view, the hypothesis behind hypofractionation suggests a preferential benefit from delivering a higher dose per fraction to tumors with a low (α\β) ratio, such as breast cancer (5).

Theoretical evidence was then supported by clinical evidence, where several prospective randomized clinical trials comparing the delivery of a hpofractionated dose schedule-radiobiologically equivalent to conventional schedule- to standard whole breast irradiation at a dose of 50 Gy in 25

fractions over 5 weeks. With long term follow-up, these studies consistently proved equivalent local control and cosmetic outcome between the two schedules with acceptable toxicity (6,7,8,9,10).

An important draw-back of all these studies is the issue of delivering a boost dose of radiation to the tumor bed. While some studies delivered the hypofractionated schedule omitting the tumor bed boost, others allowed the delivery of the tumor bed boost sequentially protracting the delivered hypofractionated scheme another week. The aim of our study is to test the possibility of delivering the tumor bed boost concomitantly with hypofractionated whole breast radiotherapy without significant toxicity from a dosimetric point of view.

2. Patients and Methods

This study was conducted at Kasr Al-Aini Center of Clinical Oncology & Nuclear Medicine (NEMROCK). A total of 63 patients scheduled to receive post-operative radiotherapy following breast conserving surgery for node-negative disease were included.

The aim of this study was to evaluate the feasibility of delivering accelerated hypofractionated whole breast irradiation with a concomitant boost to the tumor bed, from a dosimetric point of view.

Patients were positioned supine on 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 were done following the consensus guidelines from The RTOG Breast Cancer Atlas for Radiation Therapy Planning (12).

Treatment radiotherapy planning was done using 3DCRT to the whole breast and an additional plan for tumor bed boost was also made, and a final summation of both plans was done for evaluation of dosimetric parameters. For each patient, two plan sets were generated, one employing a conventionally fractionated dose of 50 Gy in 25 fractions to the whole breast followed by a sequential boost of 10 Gy in 5 fractions over a total treatment time of 6 weeks, while the other was set at an accelerated hypofractionated scheme of 40 Gy in 15 fractions (2.67 Gy per fraction) to the whole breast with a concomitantly delivered tumor bed boost of 8 Gy in 15 fractions (0.5 Gy per fraction) over a total treatment time of 3 weeks. The dose of the experimental arm was calculated employing the Linear-quadratic model to achieve a biologically equivalent dose (BED) (11) to the conventional fractionation arm. For this calculation, we assumed an α/β ratio of 4 Gy for tumor response, 10 Gy for acute responding normal tissues, and 3 Gy for late-responding tissues.

Dose 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 was used for the hypofractionation arm. This was biologically equivalent to V45 Gy in the Standard fractionation arm. Also 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 ≥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- was used for the hypofractionation arm.

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, and then a plan summation was evaluated.

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.

Finally dose volume histograms were reviewed for each plan and the aforementioned parameters for target coverage as well as doses to OAR were compared and recorded for each plan evaluated.

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 T**able** 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 and the 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 represents 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 for the 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.**

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

Parameter	**Value**
V38 **(mean +/-SD)** -Range	95.89+/-1.7 90-100
V36 **(mean +/-SD)** -Range	99.0 *+/- 0.8* *96-100*
V48 **(mean +/-SD)** -Range	5.2 *+/- 3.8* *0-16*
V44.8 **(mean +/-SD)** -Range	16.8+/- 7.4 0-34
D max **(mean +/-SD)** -Range	48.5 *+/-1.17* *50-43*
D min **(mean +/-SD)** Range	37.26 *+/- 1.15* *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)** -Range	97.28+/-3.5 90-100
V 43.2**(mean +/-SD)** -Range	99.29 *+/- 1.55* *93-100*
D max **(mean +/-SD)** Range	49.53 *+/-1.02* *47-51*
D min **(mean +/-SD)** Range	45.51 *+/- 1.77* *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)** -Range	12.4*+/-3.84* *2-20*
V16 **(mean +/-SD)** -Range	13.87*+/-4.16* *2-20*
D50 **(mean +/-SD)** Range	1.97*+/-0.5* *0.9-3.3*
D35 **(mean +/-SD)** Range	3.3*+/-0.7* *1.5-4.5*
V4CLL **(mean +/-SD)** -Range	0.003 *+/- 0.025* *0-0.2*
Heart	
V20 **(mean +/-SD)** -Range	1.79 *+/- 2.47* *0-10*
V25 **(mean +/-SD)** -Range	1.52 *+/- 2.21* *0-9.5*
D35 **(mean +/-SD)** Range	1.19 *+/- 0.7* *0.3-3.7*
MHD **(mean +/-SD)** Range	1.7*+/-1.2* 0.3-4
Contra lateral breast	
V2.4 **(mean +/-SD)** -Range	*0.96+/- 1.1 1* 0-4.8
Dmax **(mean +/-SD)** -Range	1.78 *+/-0.69* *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.*

4. Discussion

In the current 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 was 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 to be 98.3%, while the mean maximum dose to the breast was 52.8 Gy. In another study conducted by **Chadha, et al** in which the RT dose to the WB was 40.5 Gy in 2.7 Gy/ fraction over 15 fractions and the dose concomitantly delivered to the lumpectomy site was 45 Gy in 3 Gy/ fraction over 15 fraction, they reported the mean breast volume that received ≥ 95% of the prescription dose to be 99.4% (14, 15).

As for the Boost-PTV, The mean boost volume in our study 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 not far from those reported by **Chadha, et al;** where the mean boost volume that received ≥ 95% of the prescription dose was 99.7% ***(15)*.**

For dose homogeneity within the breast CTV, 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 accepted outside the regions of the lumpectomy PTV.

The dosimetric data on the doses received by the risk structures: 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%. **Albarrán et al** used the mean heart V16 which is biologically equivalent to V20 in the standard fractionation, and reported a mean heart V16 of 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 used and found to be 13.8%. In **Albarrán et al study** the reported mean value for ipsilateral lung V16 was 12.1 %(14).

Conclusion and Recommendation

The delivery of hypofractionated whole breast irradiation at a total dose of 40 Gy (2.67 Gy per fraction) with a Concurrent boost of 8.0 Gy (0.5 Gy per fraction) given in 15 fractions over 3 weeks is feasible from a dosimetric point of view with acceptable target volumes coverage and risk structures dose constrain. Clinical trials to further test this radiation therapy schedule is encouraged in an aim to shorten the duration of the treatment course.

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