Evaluation of Toxicity of Three Dimensional Conformal Whole Breast Radiotherapy in the Prone Position

Ibrahim A. Awad [a], Azza M. Abd El-Naby [a], Fatma M. Akl [a], Maram T. Abd Elrahman [b]

[a] Department of clinical oncology and nuclear medicine, Faculty of medicine, Mansoura university, Egypt. [b] Department of Clinical oncology, Damietta cancer center, Damietta, Egypt.

Correspondence to: Maram T. Abd Elrahman, Department of Clinical oncology, Damietta cancer center, Damietta, Egypt.

Email:

maram.talaat@yahoo.com

Received: 3 April 2021

Accepted: 15 November 2021

Abstract

Objective: To investigate the toxicity of prone position in whole breast radiotherapy after breast conserving surgery (BCS) in breast cancer patients with large pendulous breasts**. Patient and methods:** Thirty patients (stage I-II) with large pendulous breast were simulated in both supine and prone positions. Target volumes and organs at risk were contoured on CT images. For each patient, the two planes were calculated and dose volume histograms were compared. The prescribed dose was 40 Gy in 15 fractions over 3 weeks to whole breast with 6-10 MV photon followed by 10 Gy in 5 fractions over one week boost to the tumor bed. The selection of treatment position was based on best target coverage and optimal sparing of organs at risk. **Results:** Among 30 patients, 13 patients (43.3%) were treated in the prone position, while the remaining 17 patients (56.7%) were treated in supine position. Higher grades of acute dermatitis were significantly reported in supine position (p=0.01).Grades 1 and 2 chronic radiation dermatitis were more in supine position, but no statistically significant difference (p=0.41). Grade I radiation pneumonitis was developed in 2 patients (14.3%) in supine group which was not significantly different (p=0.49). No cardiac symptoms were noted among both groups. Grade I lymphedema was noted in (11.8%) in supine group versus (23.1%) in prone group (p=0.6). **Conclusion:** Prone position is a suitable alternative to supine position in large pendulous breast with accepted toxicity profile.

Key words: Breast cancer, Breast irradiation, large breast, prone position, Radiation toxicity.

Introduction

Breast cancer remained the most frequently diagnosed cancer in women and the leading cause of cancer death worldwide. Almost there was 2.3 million new cases 25%% of all female cancers) and 685,000 deaths (15% of all female cancer deaths) in 2020 **(1).**

Most of early-stage breast cancer patients are candidates for conservative breast surgery (CBS) followed by whole breast irradiation (WBI). Long term local control and survival rates are equivalent to those with mastectomy, while maintaining an acceptable cosmetic appearance **(2).**

Minimizing radiation toxicity without affecting tumor control or survival is one of the great challenges in breast radiation therapy after CBS **(3).** Cardiac, pulmonary and skin toxicities are the most common complications affecting the quality of life after breast irradiation. Preservation of these organs at risk (OAR) as much as possible is highly recommended **(4)**.

Breast size and treatment position are important factors that may contribute to increase radiation toxicity **(5).** The standard supine position is conventionally used to deliver radiation therapy to whole breast. This position provides patient comfort and reproducibility however it may have disadvantages in patients with large or pendulous breasts **(6)**. Pendulous breast is moved laterally over the chest wall, leading to inclusion of ipsilateral lung and heart in treatment field, and increasing skin fold under breast. This allows for significant complications including lung and heart toxicities, radio-dermatitis and poor cosmesis **(7).**

Prone position has been suggested to be a substitute to the standard supine position in patients who have large pendulous breasts. This position allows to spare OARs **(8)** and to reduce skin toxicities by reducing the bolus effect at the inframammary fold **(9)**. In this study, we aimed to investigate the toxicity of whole breast radiotherapy in prone position compared to supine position.

Patients and methods

This is a prospective study which included female patients with early stage breast cancer who underwent conservative breast surgery and treated at the Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital from January 2016 to June 2018.

Patients' selection:

Eligibility criteria: This study included 30 patients with histologically confirmed breast carcinoma, patients with early stages who underwent CBS with negative margins, negative lymph node, large or pendulous breast defined by bra cup size C or more and ability to lie prone.

Exclusion Criteria: Exclusion criteria were pervious radiotherapy to the same breast, evidence of metastatic disease, positive lymph nodes that indicated of irradiation, and presence of connective tissue disease.

Ethical consideration: Informed written consent was obtained from every patient who participated in the study and the study was approved by Medical Research Ethics Committee, Faculty of Medicine, and Mansoura University.

Methods: All included patients underwent conservative breast surgery with negative safety margins and subjected to pretreatment evaluation by history taking and full clinical examination; ECHO for left side breast cancer, abdominal ultrasound, chest X-ray/CT chest and measurement of arm circumference above and below elbow.

1-Patient positioning and CT Simulation:

Patients underwent a computed tomography (CT)-simulation with 3mm slice thickness from the mandible to the diaphragm in both prone and supine position. In supine positioning, the patient placed on the supine breast board with arms above the head. Radio-opaque markers placed in the following manner: the medial marker placed in the midline over the sternum, the lateral marker placed in mid-axillary line, the third marker placed around the contour of the breast. After simulation in supine position, these markers remained in its place and then the patient simulated in prone position. In prone positioning, the patients placed prone on a prone breast board (**Klarity prone breast system R620-BCF4**) with head facing downward and both hands holding a handlebar fixed in the board. The treated breast fall down through an opening in the board as presented in **Figure 1**, while the contralateral breast was placed laterally away from radiation field.

Figure (1): CT simulation for patient with left sided breast cancer in prone Position

2-Planning system and contouring of target volumes and organs at risk :

Both supine and prone images were transferred to the treatment planning system (3D Precise Treatment Planning System version 2.12). We used RTOG contouring guidelines to define target volumes in both supine and prone positions. ***Clinical target volume CTV*:** defined by the following borders: cranially: the caudal edge of sternoclavicular joint, caudally: loss of breast tissue on CT, medially: at the sternal rib junction, laterally: midaxillary line (exclude latissimus dorsi muscle), anteriorly: 5 mm under the surface of the skin, and posteriorly: exclude the pectoralis muscles, muscles of the chest wall and ribs. ***Planning target volume PTV***: obtained by adding 10 mm margin to the CTV except in the skin direction. ***Lumpectomy CTV***: defined by lumpectomy cavity. ***Lumpectomy PTV***: lumpectomy CTV with a margin of 0.5 to 1.0 cm. ***Organs at risk (OAR)*** *include*: a-ipsilateral and contralateral lungs, b-heart in left sided breast cancer, c-contralateral breast.

3-Dose prescriptions and radiotherapy technique:

Total dose was 40 Gy in 15 fractions over 3 weeks to whole breast with 6-10 MV photon beams followed by 10 Gy in 5 fractions over one week boost to the tumor bed. Prescribed dose delivered by 3D conformal radiotherapy using tangential-fields with 6 or 10 photon energy.

4-Treatment position:

For each patient, we choose treatment position (either supine or prone) according to the best target coverage and better sparing

of organs at risk. Linear Accelerator device (Version 5 Linear accelerator, Elekta, Precise Treatment System TM) was used to deliver radiotherapy treatment as in **Figure 2.**

Figure (2): Patient with right breast cancer lies in prone position in Linear accelerator device.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package (version 22.0). **Monte Carlo test,** Chi-**Square test** or **Fischer Exact test** were used to evaluate toxicity in supine treated and prone treated groups. Significance of the obtained results was judged at the (0.05).

Follow up:

Radiation toxicities were assessed in both positions and graded according to Radiation Therapy Oncology Group (RTOG). Acute toxicity was assessed weekly during radiotherapy and every 2 months after treatment completion for six months. Late effects were assessed during follow-up visits every 4 months during the first 2 years and every 6 months during the next 2 years then annually. Arm lymphedema was assessed by measurement of arm circumference before radiotherapy and after 6 months from the end of radiation. Shoulder immobility and brachial plexus injury were evaluated by MRI for symptomatic suspected case only.

Results

1-Patients characteristics:

All patients presented in this study had large pendulous breasts and apparent inframammary folds. Bra cup size was ranging from size C (750-1000 cc) to size D or more (> 1000-1500 cc). The characteristics of 30 patients enrolled in the current study were summarized in **Table 1**

Table (1): Patients characteristics

Patient characteristics	N=30	%
Age/years **Mean ± SD**	50.88±7.08	
BMI(Kg/m^2) **Mean ± SD**	34.30±2.89	
Bra cup size		
• **C**	6	20.0
• **D or more**	24	80.0
Side		
• **Right**	14	46.7
• **Left**	16	53.3
T stage		
• **T1**	17	56.7
• **T2**	13	43.3
Pathology		
• **IDC**	27	90.0
• **Mixed carcinoma**	2	6.7
• **Others**	1	3.3
Surgery		
• **CBS + Axillary dissection**	21	70.0
• **CBS + Sentinel LN biopsy**	9	30.0

4-Treatment position

Each patient was simulated in both supine and prone positions, and had 2 plans which were calculated and compared. According to on dosimetric data from individual DVH, 13 patients (43.3%) were treated in the prone position because it was the ideal position. that achieve both adequate target coverage and better sparing of OARs. In the remaining 17 patients (56.7%), supine position was preferred. All cases completed radiotherapy course without interruption except one case (3.3%) belonged to supine

treated group and required break for one week because of wet desquamation in large area in the fold under the breast.

5-Radiotherapy related Toxicity:

All patients (30 patients) completed the follow up period with a median of 20 months. Toxicity was assessed and graded according to Radiation Therapy Oncology Group (RTOG).

- **Fatigue and breast pain:**

In all 30 patients (100%) mild fatigue and mild breast pain were reported. But, this did not interfere with continuation of sessions and did not require medical treatment.

- **Skin toxicity:**

There was a statistically significant higher proportion of grade 1 in prone position and a statistically significant higher proportion of grade 2 in supine position (p=0.01). There was only one case with grade 3 belonged to supine positions and required one week break of radiotherapy. Pigmentation was the most common late toxicity reported in both groups, grades 1 and 2 were more in supine position with no statistically significant difference (p=0.41) (**Table 2)**

- **Pulmonary toxicity:**

Acute radiation pneumonitis: Grade I was developed in only 2 patients (14.3%) in supine group which was not significantly different (p=0.49). Patients experienced mild cough and did not require medical treatment. Radiation opacities in chest x-ray reported only in 2 patients (11.8%) in the supine group **(Table 2)**.

- **Cardiac toxicity:**

Sixteen left sided breast cancer patients were assessed for the cardiac function by echocardiography and estimating the reduction in the ejection fraction (EF) by 10%. For all 16 patients, no remarkable changes in EF values were noted.

- **Lymphedema and brachial plexus injury*:***

Grade I lymphedema was noted in 2 patients (11.8%) in supine group versus 3 patients (23.1%) in prone group (p=0.6). All cases in both groups did not experienced any symptoms suggesting a brachial plexus injury. **(Table 2)**

Table (2): Radiation toxicity in supine treated and prone treated cases .

Toxicity	Total number =30	Ideal radiography position				Test of significance
		Supine position N=17		Prone Position N=13		
		N	%	n	%	
Acute dermatitis						
G1	15	4	23.5	11	84.6	MC P=0.01*
G2	11	9	52.9	2	15.4	
G3	1	1	5.9	0	0.0	
Chronic dermatitis						
G1	7	5	29.4	2	15.4	FET P=0.41
G2	1	1	5.9	0	0.0	
Acute pneumonitis						
G1	2	2	11.8	0	0.0	FET P=0.49
Lymphedema						
G1	5	2	11.8	3	23.1	FET P=0.63

MC: Monte Carlo test FET: Fischer exact test * statistically significant (p<0.05

Discussion

Conventionally, the whole breast irradiation is delivered to the patient in the supine position. This standard position may be not suitable for all patients especially those with large pendulous breast who may suffer from acute and late toxicity resulting from dose inhomogeneity in the target and increased dose to OARs **(10).** Trying to overcome this obstacle, Merchant and McCormick in 1994 were the first to describe the prone breast technique as substitute to supine position after BCS **(11).** Multiple subsequent studies were conducted to investigate the role of prone technique in reducing the exposure of OAR to radiation and minimizing radiation toxicity, particularly in patients with large breasts and yielded promising results **(12), (13), (14), (15).**

Radiation dermatitis is the most common toxicity reported in breast radiotherapy **(4)**. In supine position, large breast rests against the skin of the abdomen making an inframammary fold. The skin on skin contact increases the radiation dose to this area and lead to moist desquamation and subsequent skin infection **(16).** In our study, higher grades of acute dermatitis were more observed in supine group than in prone

group. Grade 2 was reported in 9 (52.9%) supine cases versus 2 (15.4%) prone cases, (p=0.01). Grade 3 reported in only one supine case (5.9%) vs. no prone cases. Elimination of inframammary fold in prone position may explain low incidence of high grades of toxicity. Similarly, another study reported a 2-fold reduction in dermatitis grade ⩾2 was (38%) in the prone group vs. (80%) the supine group. Grade 3 dermatitis occurred only in 4% of the supine group and in none of the prone group **(17).** On the contrary, different results were reported by observing higher incidence of grade 2 acute dermatitis in (41%) prone group vs. (20%) in supine group. These different results were referred to the effect of prone board on skin areas where the breast pressed against the board in addition to using low energy (4 MV) photon that increase this effect **(18).**

Regarding chronic dermatitis, hyperpigmentation was the most common toxicity reported in both groups but not statistically significant (p=0.41). Grade 1 hyperpigmentation was reported in 15.4% of prone patients with no cases of grade 2. Although small sample size in our study, but our findings were relatively in agreement with a single institutional study that investigated the prone position on 110 cases and reported grade 1 hyperpigmentation in 22% of patients and only 1 patient with grade 2 hyperpigmentation **(16)**.

Radiation pneumonitis results from exposure of the ipsilateral lung to radiation in breast cancer. The incidence of pneumonitis has been related to large breast size and volume of lung included within the tangential fields **(5)**,**(19)**. In our study, no significant pulmonary symptoms were reported during 20 months of follow up period. Only 2 patients in supine group complained of mild cough that resolved spontaneously without medical treatment. After 6 months, no late pulmonary symptoms among both groups were reported. Similarly, the severity of acute and late toxicities in both positions was analyzed; there was no significant radiation pneumonitis during the follow-up period of 58 months in both groups **(18).**

Pericarditis and pericardial effusion are considered as the most reported acute side effects of radiation therapy to left breast **(20)**. In the current study, cardiac function were assessed by detecting the changes in echocardiography. Among 16 patients with left side breast cancer included, no one reported any cardiac symptoms or changes

in EF values in both groups. Our findings was comparable to what reported by a pervious study analyzed cardiac toxicity (**18**). Cardiac complications can manifest late 10-15 year after initial radiation exposure **(20)**. This indicates the need for long term follow up period to evaluate late cardiac outcome.

Lymphedema and brachial pleuxopathy from breast radiotherapy can have harmful effects on patient quality of life. The combination of both axillary surgery and axillary radiotherapy may increase the risk of brachial pleuxopathy **(21).** In our study, only grade I arm lymphedema was reported in both positions with no significant difference (p=0.65). There were no cases suspicious for brachial pleuxopathy. Such findings were expected as all our cases were node negative and they did not require regional nodal irradiation which helps to reduce incidence of such toxicity. Also the prescribed dose for breast radiation in our study was within the brachial plexus tolerance dose.

Regarding to comfortability and patient compliance, in our study, we used delicate prone breast board, so most patients were comfortable and only 3 patients did not tolerate this position. Some studies reported difficulty in prone positioning especially in elder women **(22).**

The major limitation of our study is the small number of included patients. This was because of selection criteria of the study that require inclusion of early cases with negative lymph nodes, large pendulous breasts with the ability to lie prone comfortably on the prone board.

In conclusion, the results of our study encourage the use of prone position as a suitable alternative to the standard supine position in patients with large pendulous breast when there is high exposure to ipsilateral lung and/or heart. Toxicity was comparable in both positions except for acute dermatitis which was reduced significantly in prone position. Further studies with long term follow up are needed to evaluate incidence late toxicity in prone position.

References

1-Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021. https://doi.org/10.3322/caac.21660

2-Gu J, Groot G, Boden C, Busch A, Holtslander L, Lim H. Review of Factors Influencing Women's Choice of Mastectomy Versus Breast Conserving Therapy in Early Stage Breast Cancer: A Systematic

Review. *Clinical Breast Cancer.* 2018;18 (4):539-554.

3-Wang X, Fargier-Bochaton O, Dipasquale G, Laouiti M, Kountouri M, Gorobets O, et al. Is prone free breathing better than supine deep inspiration breath-hold for left whole-breast radiotherapy? A dosimetric analysis. *Strahlenther Onkol* 2021; https://doi.org/10.1007/s00066-020-01731-8.

4-Javadinia S A, Dehghani M, Ferns G A, Sales S S, Avan A. Toxicity of Adjuvant Radiotherapy in Patients with Breast Cancer: A Review Study. Rep *Radiother Oncol*. 2018 ; 5(1):e89328.

5-Ratosa I, Jenko A, and Oblak I. Breast size impact on adjuvant radiotherapy adverse effects and dose parameters in treatment planning. *Radiol Oncol* 2018; 52(3): 233-244.

6-Krengli M, Masini L, Caltavuturo T, Pisani1 C, Apicella G, Negri E, et al. Prone versus supine position for adjuvant breast radiotherapy: a prospective study in patients with pendulous breasts. *Radiat Oncol*. 2013;8:232-237.

7-Yu T, Xu M, Sun T, Shao Q, Zhang Y, Liu X, et al. External-beam partial breast irradiation in a supine versus prone position after breast-conserving surgery for Chinese breast cancer patients. *Scientific Reports*. 2018; 8:15354.

8-Brownlee Z, Garg R, Listo M, Zavitsanos P, Wazer DE, and Huber K.E. Late complications of radiation therapy for breast cancer: evolution in techniques and risk over time. *Gland Surg*. 2018;7(4):371-378.

9-Bolukbasi Y. and Ugur Selek U. Breast Cancer - From Biology to Medicine Modern Radiotherapy. *Era in Breast Cancer*. 2017; Chapter 14: 269-304.

10-Xu H, Lee SW, Guerrero M, Yi BW, Chen S, Becker SJ et al. Dosimetric effects of the kV based image-guided radiation therapy of prone breast external beam radiation: towards the optimized imaging frequency. *J Appl Clin Med Phys.* 2019;20 (1):212–219.

11-Merchant TE, McCormic kB. Prone position breast irradiation. *Int J Radiat Oncol Biol Phys* 1994; 30(1):197–203.

12-Chen JL, Cheng JC, Kuo SH, Chan HM, Huang YS, and Chen YH. Prone breast forward intensity-modulated radiotherapy for Asian women with early left breast cancer: factors for cardiac sparing and clinical outcomes. *J Radiat Res*. 2013; 54:899–908.

13-Fan LL, Luo WK, Xu JH., He L, Wang J, Du X. A dosimetry study precisely outlining the heart substructure of left breast cancer patients using intensity-modulated radiation therapy. *Journal of Applied Clinical Medical Physics.* 2014;15 (5):265-274.

14-Deseyne P, Speleers B, De Neve W, Boute B, Paelinck L, Van Hoof T, et al. Whole breast and regional nodal irradiation in prone versus supine position in left sided breast cancer. *Radiat Oncol.* 2017; 12: 89-100.

15-Speleers BA, Belosi FM, De Gersem WR, Deseyne PR, Paelinck LM, Bolsi A., et al. Comparison of supine or prone crawl photon or proton breast and regional lymph node radiation therapy including the internal mammary chain. *Sci Rep*. 2019; 9, 4755. doi:10.1038/s41598-019-41283-1.

16-Bergom C, Kelly T, Morrow N, Frank Wilson J, Walker A, Xiang Q, et al. Prone whole-breast irradiation using three-dimensional conformal radiotherapy in women undergoing breast conservation for early disease yields high rates of excellent to good cosmetic outcomes in patients with large and/or pendulous breasts. *Int J Radiat Oncol Biol Phys*. 2012; 83, 821–828.

17-Mulliez T, Speleers B, Madani I, De Gersem W, Veldeman L, De Neve W. Whole breast radiotherapy in prone and supine position: is there a place for multi-beam IMRT?. *Radiat Oncol*. 2013;8:151. doi:10.1186/1748-717X-8-151.

18-Takahashi K, Morota M, Kagami Y, Okamoto H, Sekii S, Inaba K, et al. Prospective study of postoperative whole breast radiotherapy for

Japanese large-breasted women: a clinical and dosimetric comparisons between supine and prone positions and a dose measurement using a breast phantom. *BMC Cancer*. 2016; 16: 757-767.

19-Chan TY, Tang J, Tan PW, Roberts N. Dosimetric evaluation and systematic review of radiation therapy techniques for early stage node negative breast cancer treatment. *Cancer Management and Research* 2018:10: 4853–4870.

20-Gkantaifi A, Papadopoulos C, Spyropoulou D, Toumpourleka M, Iliadis G, Kardamakis D, et al. Review: Breast Radiotherapy and Early Adverse Cardiac Effects. The Role of Serum Biomarkers and Strain Echocardiography. *Anticancer Res*. 2019; 39 (4) 1667-1673.

21-Rudra S, Roy A, Brenneman A, Gabani P, Roach M C, Ochoa L, et al. Radiation-Induced Brachial Plexopathy in Patients With Breast Cancer Treated With Comprehensive Adjuvant Radiation Therapy. *Advances in Radiation Oncology*. 2021; 6, (1):100602. Doi:10.1016/j.adro.2020.10.015.

22-Stegman LD, Beal KP, Hunt MA, Fornier MN, McCormick B. Long-term clinical outcomes of whole-breast irradiation delivered in the prone position. *Int J Radiat Oncol Biol Phys*. 2007;68:73–81.

To cite this article: Ibrahim A. Awad, Azza M. Abd El-Naby , Fatma M. Akl , Maram T. Abd Elrahman. Evaluation of Toxicity of Three Dimensional Conformal Whole Breast Radiotherapy in The Prone Position. BMFJ 2021; 38 (3): 1048-1059. DOI: 10.21608/bmfj.2021.70636.1404