RESEARCH ARTICLE

Estimated Risk of Radiation Induced Contra Lateral Breast Cancer Following Chest Wall Irradiation by Conformal Wedge Field and Forward Intensity Modulated Radiotherapy Technique for Post-Mastectomy Breast Cancer Patients

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Abstract

Background: Epidemiological studies have indicated an increasing incidence of radiation induced secondary cancer (SC) in breast cancer patients after radiotherapy (RT), most commonly in the contra-lateral breast (CLB). The present study was conducted to estimate the SC risk in the CLB following 3D conformal radiotherapy techniques (3DCRT) including wedge field and forward intensity modulated radiotherapy (fIMRT) based on the organ equivalent dose (OED). **Material and Methods:** RT plans treating the chest wall with conformal wedge field and fIMRT plans were created for 30 breast cancer patients. The risks of radiation induced cancer were estimated for the CLB using dose-response models: a linear model, a linear-plateau model and a bell-shaped model with full dose response accounting for fractionated RT on the basis of OED. **Results:** The plans were found to be ranked quite differently according to the choice of model; calculations based on a linear dose response model fIMRT predict statistically significant lower risk compared to the enhanced dynamic wedge (EDW) technique (p-0.0089) and a non-significant difference between fIMRT and physical wedge (PW) techniques (p-0.054). The widely used plateau dose response model based estimation showed significantly lower SC risk associated with fIMRT technique compared to both wedge field techniques (fIMRT vs EDW p-0.013, fIMRT vs PW p-0.04). The full dose response model showed a non-significant difference between all three techniques in the view of second CLB cancer. Finally the bell shaped model predicted interestingly that PW is associated with significantly higher risk compared to both fIMRT and EDW techniques (fIMRT vs PW p-0.0003, EDW vs PW p-0.0032). **Conclusion:** In conclusion, the SC risk estimations of the CLB revealed that there is a clear relation between risk associated with wedge field and fIMRT technique depending on the choice of model selected for risk comparison.

Keywords: Organ Equivalent Dose- contra lateral breast- second Cancer Risk

Introduction

A global comparison of breast cancer in India with other countries like United States and China in 2012 gave a data that collectively the above countries including India account for almost one third of global breast cancer burden. According to this report for every two women newly diagnosed with breast cancer in India, one women is dying of it.In India significant proportion of breast cancer patients are below 35 years of age and it varies between two familiar institutes 11%(Tata memorial Hospital-Mumbai) to 26% (Post Graduate Institute, Lucknow)(Dinshaw et al., 2006; Agararwal et al., 2007). As a part of the curative treatment almost 70% of the breast cancer patients undergo RT. The life span of woman with breast cancer has greatly lengthened due to advancement in the treatment techniques. Meanwhile the curative RT

for breast cancer treatment associated with scattered and leakage radiation exposure to critical organs like heart, CLB, lungs etc .This may induce second cancer in breast cancer patients who survive long enough to develop second malignancy.

According to Connecticut report in patients treated with breast cancer, the SC in CLB is the most common among others and accounts for 50% (Harvey and Brinton, 1985). Radiation is one of the well known carcinogen of breast due its high radiosensititvity (Obedian et al., 2005; Haffty et al., 2002; Boice et al., 1991).To what extent radiation to CLB increase the risk of second breast cancer is still not clear. Some large studies of follow up period more than five years concluded that the significant risk is associated with young women of age less than 45 and who treated for breast cancer by RT (Boice et al., 1992; Gao et al., 2003). A large epidemiological study done by

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Stovall et al., (2008) concluded that the CLB cancer risk is elevated for breast cancer patients of age less than 40 years and if healthy breast receives more than one Gy. Hence its necessary to evaluate dose response effect of CLB for breast cancer patients who received more than one Gy. The dosimetric study on estimation of scatter and leakage dose to CLB done by Chougule in India for conventional treatments also resulted in mean dose of more than 1 Gy for healthy breast (Chougule, 1999).

The dose response relationship for dose range (one-two Gy) important for radiation protection purpose to induce radiation carcinogenesis has been quantified by several major analyses based on atomic bomb survivors data(Preston et al., 2007; Walsh et al., 2004). Most of the earlier studies evaluated the radiation induced cancer risk based on mean dose to organ. However for doses greater than two-four Gy cell sterilization effects predominates hence the radiation induced SC incidence is not a linear function of dose. So the evaluation of cancer incidence based on average dose needs more attention, specifically when dose distribution is inhomogeneous. As a consequence the concept of OED is introduced to replace average dose by Schneider et al, (2005) OED is denoting that different dose distributions within a organ are equivalent if they cause same cancer incidence rates. For calculation of OED, 3D planning details are essential which is not provided by epidemiological studies.

In this study we estimated the risk of radiation induced CLB cancer associated with EDW, PW field and fIMRT techniques based on OED instead of average dose.

Materials and Methods

Patient's data and treatment planning

The total number of 15 left side breast cancer and 15 right sided post mastectomy breast cancer patients who were treated in Linear Accelerator (Varian, Palo alto, CA, USA) machine by fIMRT plan was selected for this retrospective study. Each of these patients had undergone planning Computed Tomography scan (GE Health Care) to delineate target volume and critical organs. The targets were defined in accordance with Radiation Therapy Oncology Group Guidelines, the Clinical Target Volume (CTV) primary includes surgical bed and Planning Target Volume (PTV) includes CTV plus 0.5 cm margin .The Eclipse (Varian Medical Systems, Palo Alto, CA, USA) Treatment Planning Systems (TPS -V 8.9) was used to perform the treatment plans. Each patient planned for a total dose of 50 Gy at the center of the tumor volume. Treatment plans with PW, EDW and fIMRT techniques were performed for 6 MV photon beam by pencil beam convolution algorithm. The treatment plans which were made by conventional methods for nodal regions are not included in the risk assessment.

Risk assessments

To calculate the risk of radiation induced second breast cancer, all corresponding differential Dose Volume Histogram (dDVH) of wedge field and fIMRT techniques were extracted for CLB from the TPS. From this extracted data the volume of CLB receiving dose in the range of

each dose bin was calculated.

Several studies has been used the OED to estimate the infield organ dose which was proposed by Schneider et al (Paganetti et al., 2012; Schneider et al., 2005; Yoon et al., 2011). OED is a dose in Gray, causes same radiation induced cancer incidence which when uniformly distributed across the organ.

$$OED = \frac{1}{V_T} \sum_i V(D_i) RED(D_i). \quad Eq:1$$

OED accounts for inhomogeniety of clinical dose distributions by breaking the dose distribution into a number of volumes receiving dose Di and multiplying each dose by a dose response variables. Where RED is the Risk Equivalent Dose, which is a dose response weighted variable, and VT is the total organ volume. Four dose response relationships can be considered with RED; including full dose response, bell shaped dose response, plateau dose response and linear dose response.

The full response accounts for the probability of and competition between cell mutations, inactivation, repair and repopulation between fractions.

$$RED(D) = \frac{e^{-\alpha'D}}{\alpha'R}[1 - 2R + R^2 e^{\alpha'D} - (1-R)^2 e^{-\frac{\alpha'R}{1-R}D}] \quad Eq:2$$

Where R - tissue specific factor, which describes the ability of tissue repopulation between fractions. The value becomes 0 if tissue not able to repopulate and becomes 1 if complete repopulation/repair is occurred. Here $\alpha' = \alpha + \beta\ D/D_T$ dT.......Eq: 3. The tissue is irradiated upto dose D by equal number of fractions d. Based on linear quadratic model it is estimated that the cell kill from the number of original cell is proportional to α'. The cellular parameters α, β, R was taken from the study of Schneider et al (Schneider et al, 2011).

The bell shaped dose response relation ship is defined as (R=0)

$$RED(D) = DXe^{-\alpha D} \quad Eq: 4$$

The third dose response relationship, to account for full repopulation between fractions, that is R=1 give plateau shaped dose response relationship is

$$RED(D) = 1 - e^{-\alpha'D}/\alpha' \quad Eq: 5$$

Finally a linear dose response relationship (over the whole dose range) is derived.

$$RED(D) = D \quad Eq: 6$$

For age at exposure X and attained age A the organ specific Excess Absolute Risk (EAR) can be calculated form RED:

$$EAR^{(ORG)} = 1/V_T \sum_i V(Di) X\beta XRED(Di)X\mu(ageX, age\ A) \quad Eq:7$$

Where VT is the total organ volume, V (Di) is the organ volume receiving dose (Di), β is the initial slope of the dose response curve at low doses and μ is a modifying factor dependent on age at exposure, attained age and population age modifying factors.

The study done by Dasu et al reveal that the inhomogeneous dose distribution plays an important role in predicting the second cancer risk and it must be taken into account through DVH. The study also revealed that the linear dose response relationship is appropriate for doses less than one Gy which is received by organ outside the primary field (Dasu A et al.,2005). Thus it also follows the LNT (Linear No Threshold model) which is commonly extrapolated from atomic bomb survivor data (Preston Dl

Table: 1 Mean, Max and Median Dose to CLB for Wedge and fIMRT Planning Methods

S.No	Planning Methods	Dose to CLB(Mean) in Gy		
		Mean	Max	Median
1	EDW	2.1	48.0	0.4
2	fIMRT	1.8	45.5	0.4
3	PW	1.9	47.1	0.4

et al.,2007;BEIRVII 2006).The cell kill factor becomes important at high dose region and it limits the effect of mutation thereby cancer risk. Thus the information of full dose distribution in the organ and the use of non linear models are expected to results better cancer risk estimations.

Results

The cumulative DVHs of CLB for tangential RT are illustrated in figure 1a, 1b, 1c, 1d; Mean organ dose are highlighted as red solid line in the following images. It proves that mean organ dose values do not adequately describe the dose delivered to the CLB and shows that mean dose of 1.08 Gy in the figure 1a, whereas the dose to the entire volume ranges from 0 to 52.2Gy.

From the DVH data, the following mean, max and median dose to CLB details for 30 patients were calculated and the mean value of 30 patients are given in table.1:

Analysis of mean Dose
To analyze the significant difference between these techniques paired t test is used with confidence level 95% .The fIMRT technique with other two wedge field technique were compared, since fIMRT is mostly adopted technique in our institute. The analysis shows that mean dose of EDW significantly higher when compared to fIMRT (p=0.018), where as fIMRT and PW technique shows insignificant difference. This is due to placement of EDW necessitates the collimator rotation 90 degree, there by increases the primary beam transmission. The average mean dose to CLB delivered by all the above techniques is below 5% of the prescribed dose.

Analysis of OED
The OED which is proportional to risk was calculated using Eq.1 for various dose response models. The calculated OED for different various combination of mean, max and median dose distribution are become equal when the risk is same. The scatter diagram (Fig 2a, 2b, 2c) was plotted by mean dose against calculated OED
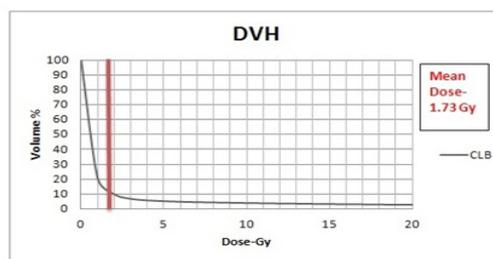

Figure1a. The DVH of CLB for fIMRT plan .The Mean organ dose is displayed as a red solid line
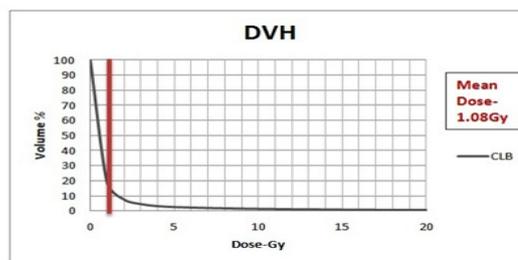

Figure 1b. The DVH of CLB for fIMRT Plan .The Mean Organ Dose is Displayed as a Red Solid Line
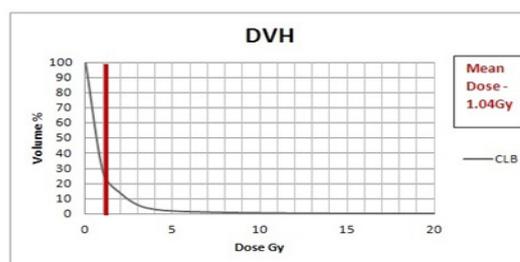

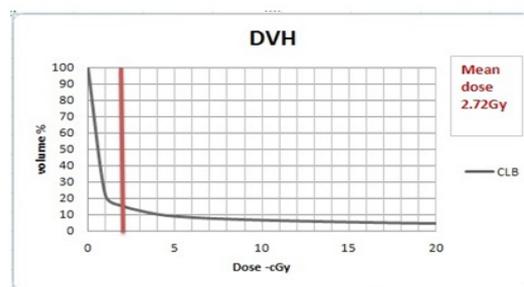Figure 1c. The DVH of CLB for fIMRT Plan .The Mean Organ Dose is Displayed as a Red Solid Line

Figure 1d. The DVH of CLB for fIMRT Plan .The Mean Organ Dose is Displayed as a Red Solid Line

corresponding to various dose response curves given in the Eq 2-6.

From the figure 2a, 2b, 2c the linear model predicts continuously increasing OED (proportional to risk) with dose. The non linear models (full dose response, plateau

Table. 2 EAR Calculated for Wedge and fIMRT Techniques by Four Dose Response Models

S.No	Models	EAR /10,000 PY*			Paired t test-P value(95% confidence level)		
		EAR	/10,000	PY	fIMRT vs EDW	fIMRT vs PW	EDW vs PW
1	Linear response	10.3	9.3	9.6	0.0089	0.054	0.05
2	Plateau shaped	5.4	5.1	5.3	0.0013	0.04	0.14
3	Full dose response	4.6	4.6	4.6	0.606	0.855	0.53
4	Bell shaped	3.7	3.7	3.8	0.12	0.0003	0.0032

*EAR, Excess Absolute Risk; PY, Person Years

and bell shaped) predicts increasing risk with initial doses and then it shows levelling off of risk or even reduction at higher mean dose corresponds to higher maximum point dose. The calculated OED are indistinguishable for small doses that are below 1 Gy. Also the calculated OED by linear response model is approximately 2.5-3.5 times higher than non linear models. The plateau response at higher doses may be due to the predominant effect of cell kill rather than radiation induced mutation resulting in lower OED than mean dose. Thus the linear model also does not take into account the non uniform dose distribution in the organ.

Risk estimation using calculated OED

The estimated EAR by four different dose response models for wedge and fIMRT techniques are given in table 2 and in figure 3. Here the age modelling is centred on 30- 70 years

To analyze the radiation induced second cancer risk from the figure3 and table2, the first model to be considered is a linear response model. According to this model ,when compared to fIMRT the EDW technique leads to significantly higher risk (p-0.0089),whereas PW and fIMRT technique shows insignificant difference(p-0.054). Then the calculation based on plateau shaped dose response model resulted that fIMRT associated with statistically significant lower risk compared to both EDW (p-0.0013),and PW (paired t test ,p-0.04) techniques .The bell shaped dose response model based calculation

Figure:2a

Figure:2b

Figure:2c

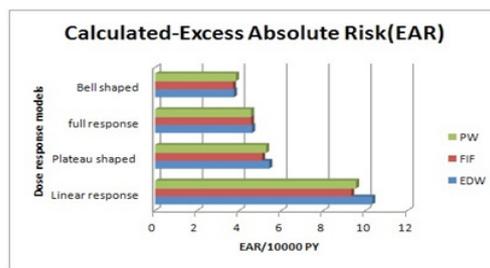Figure 2a, 2b, 2c. Scatter Diagram for Organ Equivalent Dose Calculated by Various Dose Response Models

Figure 3. Mean Excess Absolute Risk of CLB for 30 Patients

resulted differently in such a way that insignificant difference between fIMRT and EDW field technique. (p-0.12),and significantly lower risk offered by fIMRT compared to PW (p-0.0003). Finally the full dose response model based analysis shows that insignificant difference between fIMRT-EDW (p-0.606), fIMRT-PW (p-0.855) techniques. The competition between initiation, proliferation and inactivation of cells resulted in reduction in risk compared to other dose response curves. Hence the risk equivalent dose varies less significantly with dose bins. The difference between bell shaped and plateau shaped dose response are attributed to cellular repopulation becoming important at higher doses. It is also interested to note that except bell shaped model (p-0.0032) all other model predicts insignificant difference between PW and EDW associated risk in CLB.

Discussion

In this study we have evaluated the risk of second CLB cancer associated with three common techniques used in most of the RT centres for planning. This evaluation was completed with Schneider et al EAR model that incorporates inhomogeneous dose distribution and four dose relationships.

The availability of multi leaf collimator and superior dose distribution made fIMRT technique to replace the wedge field which necessitates manual handling. There are many studies on dosimetric comparison between these techniques are available. The study done by Cavey ML et al on dosimetric comparison between fIMRT technique and conventional tangential field technique shows that fIMRT resulted in improved dose homogeneity , target volume coverage and reduced dose to OAR compared to conventional field techniques(Cavey et al, 2005).The study done by Morganti et al on application of fIMRT for whole breast post operative RT reviewed that fIMRT technique associated with superior dose distribution than standard wedge field technique, and the results are independent of nodal irradiation and size of the breast(Morganti et al, 2005).Similarly in this study the dose distribution calculated for same normalization point results in lesser mean and max dose to CLB with fIMRT technique compared to other wedge field techniques.

The various studies on mantle field treatment of Hodgkin Disease resulted in EAR= 21.5/10,000PY by Hancock and Hoppe et al, 10.5/10000PY by Dores et al and from Swerdlow et al 3.1/10000PY for CLB(Hancock SL et al.,1996;Dores GM et al.,2002;Swerdlow et al.,2000) . In the same way the estimated EAR by this study and given
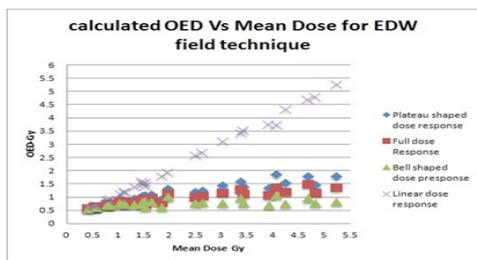
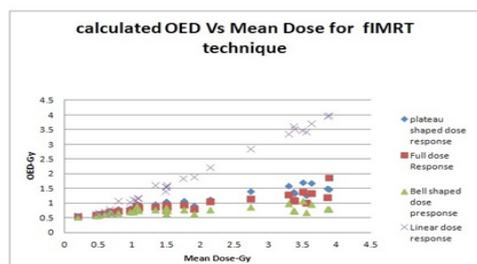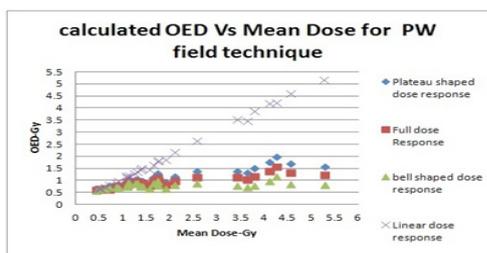in Table 3 is comparable with the published values. The dose response analyses for population based, multicenter and case control study was designed by Stovall M et al to examine the radiation induced breast cancer and genetic factors. The risk analysis was based on dose to specific quadrant of CLB due to breast irradiation and resulted that 2.5 fold greater risk associated for women <40 years of age and who received dose > 1Gy when compared to unexposed women.The study done by Safora Jhoansen et al on risk estimation of second cancer on CLB following 3DCRT concluded that the Excess Relative Risk (ERR) calculated by linear and non linear dose response models are indistinguishable for low doses and also reviewed that linear dose response models are lacking to account complex mechanism underlying the development of second malignancies particularly when dose distribution is highly inhomogeneous. From this study the calculated ERR /Gy for mean dose less than 2 Gy to CLB was 0.5 irrespective of the model selected and for higher dose the ERR/Gy is 1.2-1.8 using linear model(Jhoansen et al.,2008). Similarly the analysis of OED by scatter diagram (Figure;2) in our study results that, at a lower mean dose range of 2 Gy the dose response is indistinguishable for both linear and non linear dose response models. At higher mean dose which corresponds to maximum point dose, the dose response gets levelling off or even reduction.

In conclusion, the SC risk estimations for the CLB resulted that there is a clear relation between risk associated with wedge field and fIMRT techniques depending on the choice of model selected for risk comparison.

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