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Review Article

Evaluation and Optimisation of Treatment Plans for Post Mastectomy Patients using Radiobiological Models in a Low-Resource Center, Nigeria

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Keywords

- Mastectomy
- Breast cancer
- Fractionation
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Abstract

Introduction: With a population of over 180 million, Nigeria has only seven radiotherapy centers, four of which have a Linear Accelerator, while the remaining three use Cobalt 60. It is quite unfortunate that most of these centers still embrace manual planning using anatomical landmarks. The study center is the first in Nigeria to embrace the routine use of computerized planning for most of its patients. This study is the first of its kind in Nigeria. It aims at evaluating and optimizing treatment plans of post mastectomy patients using radiobiological models.

Method: This is a retrospective study of forty six (46) post mastectomy patients who have gone through computerised treatment planning from 2012 – 2014. Patients that have undergone chemotherapy were excluded from the study.

Result: The study revealed that the treatment plans had high local tumor control on the target breast (99%); while the NTCP models gave higher complication probability for the lungs than the heart. Using optimized treatment plans, Hyper/Hypo fractionation schemes gave NTCP values below the QUANTEC threshold of 5% and 1% for lung and heart respectively.

Conclusion: This study confirmed that the treatment plans of post mastectomy patients were good; as none of the computed toxicity indices showed any value above the QUANTEC standard. Also the hyper/hypo fractionation schemes gave values below the QUANTEC standard and therefore can be introduced into clinical trials for the treatment of post mastectomy patients.

INTRODUCTION

Radiotherapy (RT) is one of the types of cancer treatment that uses ionising radiation to control malignant cells for either curative or palliative purposes. The history of RT can be traced back to over 100 years ago shortly after the discovery of x-ray. Radioactive isotopes were used in the first few decades, as the source of radiation in radiotherapy. However this has a limitation, in that using radioactive isotopes delivers a much too low energy level and hence the low depth of penetration. In order to treat deep tumours without surgery, a source of high energy x-rays is required [1].

There has been quite a number of technological revolutions in radiotherapy over the years, which have resulted in better treatment outcomes and fewer side effects. Statistics has it that one in every two cured cancer patient is treated or partially treated with radiotherapy [2]. RT has become one of the most effective and widely used methods for cancer treatment. There are basically two primary components of radiotherapy and these are planning and delivery. It is expected that a good plan becomes useless if combined to the inability to deliver it. Likewise, a good and robust delivery system is a waste if coupled to a limited treatment planning. A good radiotherapy structure must have a good plan and a robust delivery system. In modern radiotherapy, the process starts from computerised tomography (CT) simulation, where volumetric CT data of the patient is acquired. Based on the images, a computerised Treatment Planning System (cTPS) is used to create a radiotherapy treatment plan. Once the plan is approved and verified by the medical physicist, the radiotherapy treatment of the patient can be initiated. The total prescription dose is usually divided into many fractions and the patient normally gets one fraction per day, so the entire treatment course may take weeks.

Presently, the plan assessment approach is to evaluate the physical quantities such as the Dose Volume Histogram (DVH) values, which might not be entirely correct. So the need to introduce an assessment approach based on biological responses becomes inevitable. It has been shown that the introduction

of non-dosimetric factors such as normal tissue complication probability, tumor control probability and secondary cancer complication probability in evaluating tumors and organs at risk with dose volume metrics increases the predictive power of incidence of complication and provides a more robust method of comparing different radiotherapy treatment plans [3]. Hence the need for this study is to assess this treatment plans using these indices.

Nigeria, with a population of over 180 million, unfortunately has only seven radiotherapy centers: four of these centers have Linear Accelerator (LINAC), while the remaining three use Cobalt 60. The present study center is the first in Nigeria to embrace the use of computerized planning routinely for most of its patients; unlike other RT centers where manual planning using anatomical landmarks is still in use. Hence, there is the need to carry out an evaluation of the computerized treatment plans in the study center. This study is the first of its kind in Nigeria making use of radiobiological models to evaluate and optimize treatment plans of post mastectomy patients.

MATERIALS AND METHODS

Forty six (46) patients treated in the Radiotherapy Center, Nigeria, between January 2012 and March 2014 for Breast Cancer after simple mastectomy were included in this study. All patients underwent CT-simulation in supine position on an angled board, with both arms placed above their head, which was rotated to the contra lateral side (GET Bright speed CT-scanner, GE Medical Systems). Patients received 50 Gy in 25 fractions over 5 weeks to the primary and axillae chest walls and the corresponding supra clavicular region, using tangential field (AP-PA) and direct anterior respectively. The Elekta Precise Plan was used for this process.

Computerized Treatment Plans are mostly evaluated using the following radiobiological models: Normal Tissue Complication Probability (NTCP) and Tumour Control Probability (TCP). Based on the objective of radiotherapy, a good treatment plan is expected to have high local tumour control with low normal tissue complication probability.

THEORY

Control probability model

Tumour control probability was calculated using the Webb and Brenner model [3-5].

$$TCP = \prod_i TCP_i \tag{1}$$

$$TCP_i = e^{-NSF_i} \tag{2}$$

where SF is the surviving fraction and N is clonogen number ≈10^7

$$SF_i = e^{-\alpha D_i - G\beta D_i^2} \tag{3}$$

$$G = \frac{1}{n} \tag{4}$$

where *n* is the number of fractions

TCP parameter values

α is the rate of lethal cell damage and is 0.51 $Gy^{-1;}$ while β is the rate of sub-lethal cell damage and is 0.061 Gy^{-2} [6].

Equivalent uniform dose (EUD)

This is defined as the uniform dose that, if delivered over the same number of fractions as the non-uniform dose distribution of interest, yields the same radiobiological effect [7].

The phenomenological formula for the generalized EUD (i.e. Normal and Tumor cells) as proposed by [8] is

$$gEUD = \left(\sum_i^i v_i D_i^a \right)^{\frac{1}{a}} \tag{5}$$

Where $_i$ is fractional organ volume receiving a Dose of D_i and α is tissue-specific parameter that describes the volume effect.

NTCP models

The Lyman-Kutcher Burman (LKB) model: A four-parameter model was proposed [9]. In this model, the complication probability P (D,υ) for a uniform irradiation of a normal tissue volume V with a dose D is given [9-12].

$$P(D,v) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx = \frac{1}{2}\left\{1 + erf\left(\frac{t}{\sqrt{2}}\right)\right\} \tag{6}$$

$$t = \frac{1}{m}\left(\frac{EUD}{TD_{50}(v)} - 1\right) = \left(\frac{EUD - TD_{50}(v)}{mTD_{50}(v)}\right) \tag{7}$$

$$v = \left(\frac{V}{v_{ref}}\right) \tag{8}$$

The four parameters of the model are given by TD_{50}, m, n and υ_{ref} which have to be adjusted to clinical data for each tissue type using a specified biological end point. TD_{50} is the tolerance dose for the fractional volume , *m* is the slope of the dose-response curve, n is the volume effect and υ_{ref} is the reference volume to which the fractional volume is compared.

Relative Seriality (RS) model: According to this model for the homogenous dose distribution in the organ at risk, the NTCP is given by the following equations [13]:

$$NTCP = \left[1 - \prod_{i=1}^{n}\left[1 - P(D_i)^s\right]^{Äv_i}\right]^{\frac{1}{s}} \tag{9}$$

where

$$(D_i) = 2^{-e\cdot\gamma\left(1-\frac{D_i}{D_{50}}\right)} \tag{10}$$

The meanings of the $\Delta\upsilon_i$, $D_{i,}$ and D_{50} are analogous to the parameters of the LKB model. γ is the slope parameter with impact on the steepness of the sigmoid-shape dose-response curve- is the parameter of relative seriality of the organ/tissue (serial organ; S ≈1 parallel organ S ≈0.

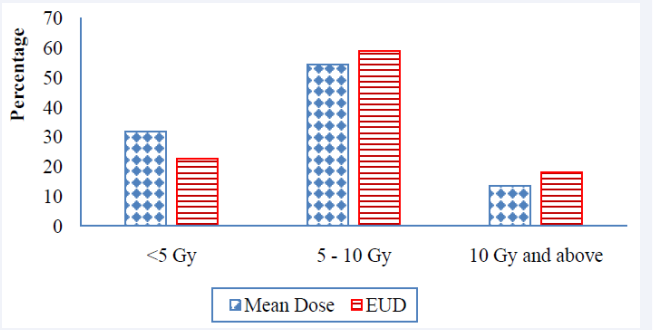

Figure 1 Mean Dose and EUD distribution in the Lungs.

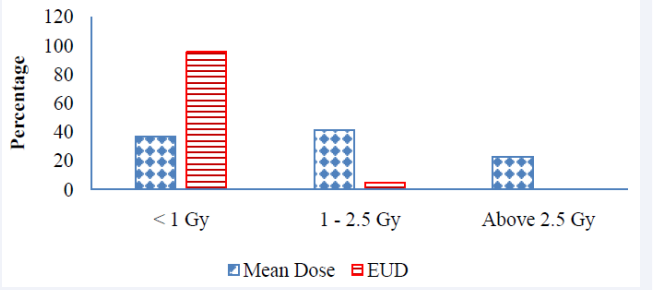

Figure 2 Mean Dose and EUD distribution in the Heart.

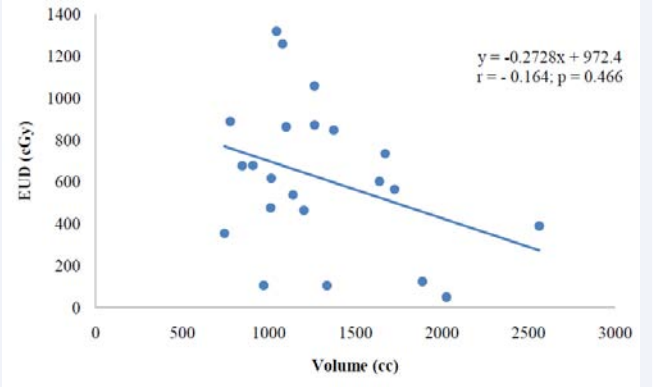

Figure 3 Relationship between EUD and volume of Lungs irradiated.

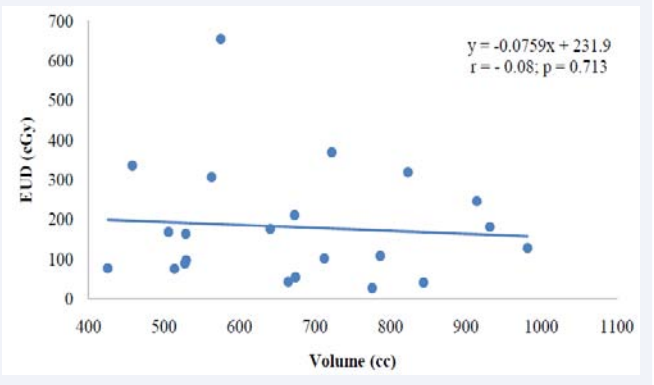

Figure 4 Relationship between EUD and volume of Heart irradiated.

Table 1: Patients characteristics (N=46).

Characteristics	Descriptive statistics
Age	
Mean, SD	57.8 ± 8.7 yrs
Median (min/max)	58 (46–83) yrs
Gender	
Female	46(100.0%)
Male	
Histology	
Invasive ductal carcinoma	46(100.0%)
Tubular carcinoma	0(0.0%)
Staging	
I	0(0.0%)
II	4(8.7%)
III	42(91.3%)
PTV volume (cm^3)	
<700	36(78.3)
700-1000	10(21.7)
>1000	0(0.0%)

Abbreviations: SD: Standard Deviation; PTV: Planning Target Volume

Data analysis: BioSuite™ (version 12.2) was used to read the absolute differential DVHs files from the Computerised Treatment planning System; which runs a Linux red hat operating system. Descriptive statistics (Percentage, mean, standard error of mean) were used to analyse the DVH parameters, correlation to test the relationship between DVH parameters and NTCP. Level of significance was set at 0.05. The analyses were done using STATA version 12.

RESULTS AND DISCUSSION

Table 1 shows the patients characteristics. The mean age of patients is 57.8 ± 8.7yrs (46 - 83yrs). They were all female subjects with invasive ductal carcinoma. Majority of the cases are stage III.

Figures 1 and Figure 2 show the distribution of Mean dose and EUD in the Organs at Risk (paired lungs and heart). The majority of patients were exposed to mean dose/EUD of 5 – 10 Gy to the paired lungs; while the majority were exposed to mean dose/EUD of <1 Gy to the heart. This shows that the lungs received a higher dose than the heart.

Table 2 shows the descriptive statistics of Organs at Risk (OARs) and of the contra lateral and ipsilateral breasts of the patients. The volume of the breast, heart, lung and PTV are 1781.19 ± 569.80 cc, 671.27 ± 34.39 cc, 1790.82 ± 496.58 cc, 532.21 ± 31.04 cc respectively. The means of the max dose, min dose, mean dose, EUD of the contra lateral breast are 3925.18 ± 502.76 cGy, 20.43 ± 2.71 cGy; 87.04 ± 14.25 cGy respectively; for the ipsilateral breast (PTV) is 8641.23 ± 2940.89 cGy, 29.21 ± 1.84 cGy; 4057.39 ± 264.95 cGy and 532.21 ± 31.04 cGy. For the organs at risk (OARs), the max dose, min dose, mean dose and EUD to the heart are 3455.29 ± 517.50 cGy, 18.41 ± 2.51 cGy, 238.87 ± 35.09 cGy and 180.95 ± 31.36 cGy; while to the lungs are

Table 2: Analysis of DVH parameters of different Organs at Risk (OARs) and the breasts.

	Breast	Heart	Lung	*PTV
Max Dose (cGy)	3925.18 ± 502.76	3455.29 ± 517.50	5105.45 ± 300.49	8641.23 ± 2940.89
Min Dose (cGy)	20.43 ± 2.71	18.41 ± 2.51	26.08 ± 1.64	29.21 ± 1.84
Mean Dose (cGy)	87.04 ± 14.25	238.87 ± 35.09	719.30 ± 78.66	4057.39 ± 264.95
Volume (cc)	1781.19 ± 569.80	671.27 ± 34.39	1790.82 ± 496.58	532.21 ± 31.04
EUD (cGy)	-	180.95 ± 31.36	618.03 ± 75.52	-

Abbreviations: *PTV: Planning Target Volume (Ipsilateral breast)

Table 3: TCP and NTCP (LKB and RS) indices for different organs.

Models	Breast	Heart	Lung	PTV
TCP (%)	-	-	-	99.00 ± 0.01
NTCP (%)				
LKB	-	0.13 ± 0.03	2.10 ± 0.33	-
RS	-	0.58 ± 0.06	1.35 ± 0.31	-

Table 4: Relationship between DVH parameters and NTCP of Organs at Risk.

	LKB		RS	
	r	p	r	p
Heart				
Max Dose (cGy)	0.40	0.06	0.52*	0.01
Min Dose (cGy)	0.40	0.07	0.48*	0.02
Volume	-0.20	0.38	-0.07	0.74
Mean Dose (cGy)	0.89**	0.00	0.95**	0.00
EUD (cGy)	0.90**	0.00	0.96**	0.00
Lungs				
Max Dose (cGy)	0.39	0.08	0.32	0.14
Min Dose (cGy)	0.50*	0.02	0.44*	0.04
Volume	-0.22	0.33	-0.21	0.35
Mean Dose (cGy)	0.93**	0.00	0.89**	0.00
EUD (cGy)	0.79**	0.00	0.75**	0.00

**P<0.01; *P<0.05

Table 5: Fractionation Schemes of different OARs using LKB and RS NTCP models.

	Fractionation Scheme				
	Hyper	Conventional	Hypo		
	1.5 X 33	2 X 25	2.5 X 20	3 X 17	4 X 13
LKB					
Heart (%)	0.56 ± 0.05	0.13 ± 0.03	0.61 ± 0.07	0.50 ± 0.04	0.67 ± 0.10
Lung (%)	1.52 ± 0.24	2.10 ± 0.33	2.15 ± 0.44	3.02 ± 0.58	3.56 ± 0.68
RS					
Heart (%)	0.13 ± 0.03	0.58 ± 0.06	0.15 ± 0.04	0.16 ± 0.05	0.19 ± 0.07
Lung (%)	1.05 ± 0.24	1.35 ± 0.31	1.61 ± 0.41	2.06 ± 0.50	2.72 ± 0.73

5105.45 ± 300.49 cGy, 26.08 ± 1.64 cGy, 719.30 ± 78.66 cGy and 618.03 ± 75.52 cGy.

In establishing the relationship between volume of organs at risk and EUD, the results in Figure 2 and Figure 3 show that there is a negative relationship between volume of organs irradiated and EUD which was not statistically significant.

Table 3 gives an evaluation report of the treatment plans using different radiobiological models. An evaluation of the treatment plans using the radiobiological indices (NTCP and TCP) reveals that the treatment plans have high local control, with small normal tissue complication probability. The RS model gave a higher NTCP value for the heart while the LKB model reported a higher value for the lungs. These reported values are however below the Quantitative Analysis of Normal Tissue Effects in Clinic (QUANTEC) value of 1% for the heart and 5% to the lungs. This high TCP corresponding with low NTCP implies that the treatment plans for the post mastectomy cases handled in this study is very good.

Table 4 assessed the relationship between DVH parameters and NTCP of organs at risk. Pearson correlation coefficient revealed that the mean dose and EUD to the heart showed significant positive relationship with NTCP for the LKB model; while max Dose, min Dose, Mean Dose and EUD showed positive significant relationship with NTCP for RS model.

Table 5 compares the conventional fractionation scheme with the prescribed fractionation schemes by increasing or decreasing the number of fractions to still give a similar prescribed dose (50 Gy). Interestingly, the result shows that the lungs values are below the 5% cut off for Radiation pneumonitis; while the heart values are below the 1% cut off for cardiac mortality as recommended by QUANTEC [14].

CONCLUSION

This study is under taken to evaluate a computerised treatment planning system using radiobiological models. The Lyman Kutcher and Burnam (LKB) and Relative Seriality (RS) models were used in calculating the Normal Tissue Complication Probability (NTCP) of the Paired Lungs, Heart and Contralateral Breasts of post mastectomy breast cancer patients. These indices are function of the toxicity to the Organs at Risk (OARs) due to exposure of high photon radiation energy.

The results show that for both models (RS and LKB), the paired lungs is more at risk, followed by the heart, next is the contralateral breast. Also, there was a significant positive relationship between lung organ volume and Equivalent Uniform Dose (EUD).

Also the hyper/hypo fractionation schemes gave values below the QUANTEC standard and therefore can be introduced into clinical trials for the treatment of post mastectomy patients. This protocol will save time for both the patients and clinicians and reduce failure of the Linear Accelerator (LINAC) machine which is a major challenge in most radiotherapy centers in the country.

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