ESTIMATION OF NORMAL TISSUE TOLERANCE DOSES AND VOLUME EFFECT FOR THE ORGANS AT RISK FOR CERVICAL RADIOTHERAPY

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Abstract- The purpose of this study is to analyze the dose given and volume effect to the organs at risk (OAR_S) for cervical cancer radiotherapy. This retrospective study, carried out in a part of northern Nigeria included fifty patients with different stages of cervical cancer who were treated with external beam radiotherapy technique between March 2012 and November 2013. Patients who had other gynecological malignancies were excluded. All patients underwent a Computed Tomography (CT) scan, imaged supine in treatment position using a flat table top insert. Treatment fields of Anterior-posterior (AP) and Posterior-anterior (PA) fields or a four Field technique (AP, PA, right and left lateral fields) were planned with 2 cm margins defined by the clinician from bony anatomy. Patients were treated with a 100 cm Source to Axis Distance (SAD) isocentric technique. An external beam radiotherapy treatment (EBRT) plan was developed for all patients, based on target volumes and organs at risk, delineated on the CT-scan.

Index terms- Volume effect, External Beam Radiotherapy, OAR_S, Cervical cancer.

I. INTRODUCTION

In today's world, clinical oncologists, radiotherapists and medical physicists are looking for the best method to treat cervical cancer with external beam radiotherapy. Radical dose as a role in radiation therapy has been used as a means in the management of non-metastatic cervical cancer. Some time back, normal structures and organs around the target region were exposed to unwanted radiation as a result of the fact that radiation treatment was matched to the height and width of the target volume. Fowler J.F (2008).Various advancements in radiation therapy has made it possible to locate and treat tumors more precisely. We have moved from conventional radiotherapy using simple rectangular treatment fields to increasingly conformal radiotherapy techniques such as three dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT). (Kirkpatrick J.P et al., 2010).These changes in the delivery of radiotherapy have come about as a result of trying to improve the delivered dose to tumor bearing tissues, and reduce
irradiation of organs at risk (OARs), hence improving the therapeutic ratio of the radiation treatment. High-energy radiation damages genetic material (deoxyribonucleic acid, DNA) of cells and thus blocking their ability to divide and proliferate further (Jackson S.P et al., 2009).
Although radiation damages both normal cells as well as cancer cells, the goal of radiation therapy is to maximize the radiation dose to abnormal cancer cells while minimizing exposure to normal cells, which is adjacent to cancer cells or in the path of radiation. Normal cells usually can repair themselves at a faster rate and retain its normal function status than the cancer cells. Cancer cells in general are not as efficient as normal cells in repairing the damage caused by radiation treatment resulting in differential cancer cell killing (Begg A.C et al., 2011). Radiation can be given with the intent of cure as well as being used as a very effective modality of palliative treatment to relieve patients from symptoms caused by the cancer.

II. MATERIALS AND METHODS

This retrospective study is made up of a random selection of fifty cervical cancer patients treated with external beam radiation therapy between March 2012 and November 2013. Planning Computed tomography (CT) images with slice thickness of 2mm was attained for all patients while they were treated with a linear accelerator (LINAC) in supine form. The LINAC is a dual modality machine manufactured by Elekta which makes use of both electrons and photons (x-rays). The machine has multiple energies between the range of 6 and 15MeV for photons and 2 – 18MeV for electrons. All patients had a portal imaging pre-treatment verification film on the treatment machine. Patient's characteristics are summarized in table 1.The treatment couch digital readout of this verified patient position was taken as the intended or planned setup position in the study. Using LANTIS^{TM}, the digital daily treatment couch absolute positions of each patient in terms of the X, Y, and Z positions were recorded. These corresponded to the medio-lateral, supero-inferio and anterior-posterior position of the patient respectively. We generated dose values which were used to treat the cervical tumor from the treatment planning system and the values for the volumes were obtained

from the beam set up parameter of the individual patient.

III. NTCP CALCULATION

The Normal tissue complication probability equation is given as

$$NTCP = \exp[-N_o v^{-k} \exp\{-\alpha \tau D\}] \quad (1)$$

Where $\tau = \left[1 + {}^{d}/_{(\alpha/\beta)}\right]$, α is the coefficient of lethal damage, β is the coefficient of sub lethal damage, N is tissue/organ, non-negative adjustable parameter, D is the normal tissue dose, v is the uniformly irradiated partial volume of the organ i.e. v = V/Vref where V is the uniformly irradiated organ and Vref is the reference volume, k is the tissue/organ, non-negative adjustable parameter. From equation (1), N_0 and k are allowed to change depending on the type of the tissue / organ under consideration. It is important to note that the parameter k should be greater than zero, i.e. k > 0, if the best fit of normal tissue tolerance doses is to be obtained and as the volume of the irradiated tissue / organ increases, the NTCP of the tissue must also increase. Using equation (1), the values of the constants given in Table 2, the volume of irradiated organ given in Table 3 and the values of the doses given to the organs in Table 4, the NTCP values for the organs considered in this study (bladder, rectum and gastro-intestine) were calculated and presented in Table 3. The values of the Normal Tissue Complication Probability for the organs were found to be in the range of 0 and 1 except in the case of the Gastro-intestine (GIT) where extremely small values were found in some patients.

Table 1: Patient characteristics

Patients	50
Sex (females)	50
Median age (Range,yrs)	43(70,89)
Dose range	20-89(Gy)
Fractionation range	1.5-2

Table 2: Values of the fitted parameters for this study and that of Emami. The symbol E stands for error.

Organ	This study					Emami's work (1991)		
	k	αG	N	Δk(E)	ΔαG(E)	k	αG	N
Bladder	2.9652	0.1107	7007.99	2.807	0.0631	0.1582	0.0476	7007.99
Rectum	0.8041	0.0502	80.68	0.8041	0.023	0	0.0732	80.68
GIT	0.7348	0.1141	302.9	0.0269	0.0015	0.7617	0.1126	302.92

Table 3: Volume (cm^3) of irradiated Organs and values of NTCP for the different Organs

	NTCP values for the Organs at Risk for this study		
Volume of irradiated tissue	Bladder	Rectum	GIT
1000.00	0.2128	0.0866	2.0741e-20
1320.00	0.1415	0.0588	2.5878e-18
1300.00	0.3366	0.0766	9.3522e-23
0893.04	0.9006	0.1474	0.1772
2116.80	0.6526	0.1762	0.0883
0000.00	0.0000	0.0000	0.0000
1453.20	0.7134	0.1915	0.0883
1664.00	0.6189	0.2917	0.0883
2216.76	0.9365	0.1474	0.6700
1920.00	0.6841	0.5888	2.8476e-13
2520.00	0.3796	0.0866	0.0025
2470.00	0.6189	0.1915	0.0333
2210.00	0.6189	0.1339	0.1144

Table 4: Doses (Gy) for the various Organs of interest

Bladder Dose	Rectal dose	Gastro-intestine (GIT)
17	21	2
15	18	3
20	20	1
40	26	31
28	28	28
28	36	28
28	29	28
27	35	28
30	26	44
27	18	6
44	21	20
29	21	25
21	25	29

IV. FITTING PARAMETERS

Clinical dose data were used to calculate the NTCP values using equation (1) in order to estimate the values of k and αG. The least square fitting was done using the equation given as

$$f(x) = \exp[-\alpha * \exp\{-bx\}] \quad (2)$$

Where α and b are the fitting parameters. Comparing equation (2) with equation (1) k was calculated from the fitting equation as;

$$\alpha = NV^{-K} \quad (3)$$

$$K = \frac{LnN - ln\alpha}{lnV} \quad (4)$$

Where α is the fitting parameter.

The calculated values of k and αG are listed in table 2 along with those of Emami and coworkers. Due to the unavailability of adequate data, no attempt was made to correlate the NTCP with a reference volume. To solve this problem and to simplify the calculation, the organs were assumed to have the same reference volume. A C++ program code was written to help in the plotting computation and the Gnuplot plotting software was used for both the plots and fitting.

V. RESULTS AND DISCUSSION

The analyzed relations of the NTCP equations of the organs (bladder, rectum and gastro intestine) were then plotted against the various organ doses Fig 1-3 show graphical representations of the curves of NTCP plotted between the organ doses (bladder, rectum and gastro-intestine) while keeping the whole volume of the irradiated organ constant. This was done to demonstrate the applicability of the linear quadratic model of the NTCP equation. Each figure has three curves which shows 3/3 partial volume, whole volume and 1/3 partial volume of irradiated organ whose labelling have been properly differentiated with the colored lines. The whole volume curve gives the line for the plotted data obtained from this research. For each figure, it can be seen that as the dose increases for these organs, the probability of complication gets larger. From the plot of the ordinary equation of the linear quadratic model, the expected shape of the curve is supposed to be an S-shape curve or a sigmoid curve. But In this study, Fig 2 – 3, does not clearly exhibit the S-curve behavior. This may probably be due to the fact that doses as high as 125Gy were not administered to the organs (rectum and gastro-intestine) as shown in these figures. From previous works Rubin and Cassarett (1968), Emami (1991) and Khewar (2005) where patients were given doses as high as 125Gy, the graph clearly exhibits this sigmoid shape and from these works, it is seen that the higher the doses, the more likely that the S-curve shape is obtained. The fitting equations have been incorporated into all the graphs along with the values of the fitting parameters (α and b) as shown in Figures 1 – 3. It should be noted that the value b is the same as αG (comparing Equation 1 with 2) and the value a is gotten in order to obtain the value of k which explains the volume effect on the curve. Fig 4.1 shows a curve of NTCP against bladder dose. In this curve, it is observed that the values of NTCP do not appreciate until a threshold dose is applied. The shape of the curve is sigmoid and it is seen from this graph that the curve for the whole volume and 1/3 partial volume begins to rise when a dose of about 5Gy and 15Gy was administered respectively.

For the 3/3 partial volume, the threshold dose is obviously negative. This difference in threshold value simply means that when we have 1/3 of the whole volume of the organ irradiated at a particular dose say 15Gy, there is no probability of complication (about 0%) as compared to a higher probability of complication (15%) when the whole volume of the organ is irradiated. Tripling the whole volume of the bladder by three is not reasonable as seen in the figure as doses less than zero cannot be administered to the patients. This study therefore demonstrates that the NTCP in bladder is highly volume dependent. The fitting equation and the value of the fitting parameter have been incorporated into the plot (Fig 1). The value of the fitting parameters α and b (αG) have been calculated to be approximately 10.3413 and 0.1101 respectively.

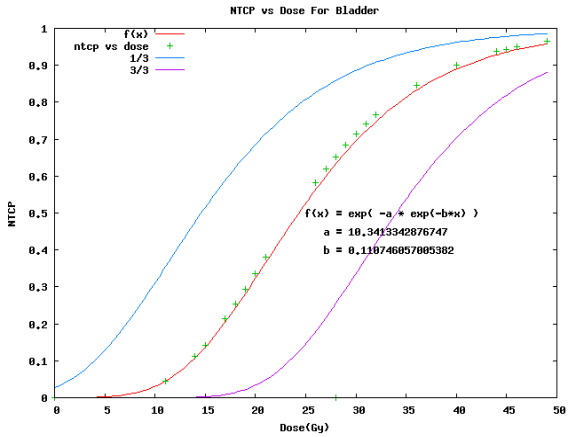


Fig 1: Curve of NTCP against Bladder dose

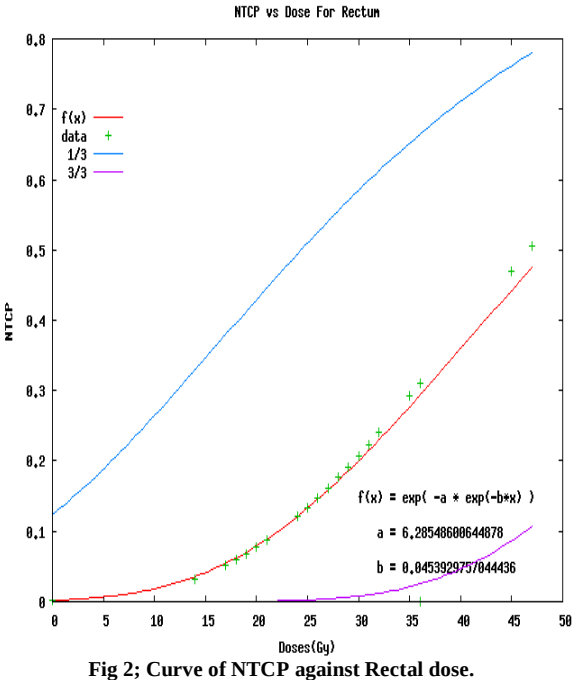


Fig 2; Curve of NTCP against Rectal dose.

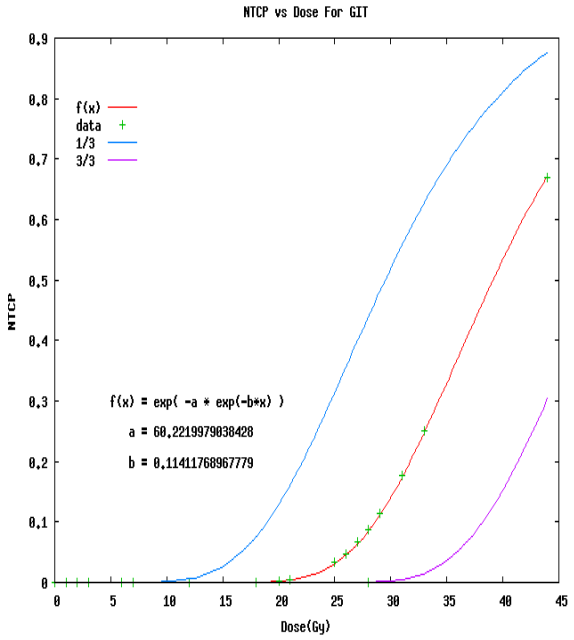


Fig 3: Curve of NTCP against GIT dose

Fig 2 is a curve of NTCP against rectal dose. This curve does not show the sigmoid shape within the range of values and simply reduces the exponential shape as in the case of fig 3. It will be observed that Fig 2 is the steepest of all the curves and this is due to the fact that the value of αG is lowest for the rectum. This confirms the explanation that the lower the value of αG the steeper the slope. The NTCP value for whole volume and 1/3 partial volume begins to appreciate at a dose of about 6Gy and 27Gy respectively. For 3/3 partial volume, the NTCP appreciates at a region within the negative portion of the curve. At a dose of say 30Gy, it will be observed that the probability of complication for 3/3 partial volume, whole volume and 1/3 partial volumes are 45%, 11% and less than 1% respectively. This study therefore shows that for rectum, it is safer to administer doses not greater than 30 Gy to 1/3 of the whole volume. This is because at 30Gy for 1/3 partial volume, the rectum experiences little or no complication whereas in the case of the whole volume of the irradiated organ, the probability of complication is at about 0.11. The fitting parameters a and b (aG) were calculated to be 6.2854 and 0.0453 respectively.

Fig 3 shows a curve of NTCP against Gastro-Intestinal dose. In this curve, it is observed that as the doses to the GIT increases, the probability of complication also increases. The threshold values for 3/3 partial volume, whole organ volume and 1/3 partial volume of the intestine are at about 12Gy, 21Gy and 32Gy respectively. It is observed that at a certain dose say 20Gy for the whole volume and 1/3 partial volume, no complication occurs but for the 3/3 volume the complication probability rises to 0.1(10%). At 10Gy for 3/3 partial volume, the probability of complication is 0%. This implies that at a dose of 20Gy, no portion of the GIT becomes complicated or damaged for whole volume and 1/3 partial volume. But for the 3/3 volume, 10% of the GIT becomes damaged at 20Gy with no complication at a dose of 10Gy.This study therefore shows that it is safer to administer doses as high as 20Gy to the GIT for whole volume and 1/3 partial volume but not for 3/3 partial volume. The value of the fitting parameters a and b (aG) have been calculated to be approximately 60.3413 and 0.1141 respectively.

CONCLUSION

From the various graphs, it is seen that a fairly good result have been found between the curves. For each figure, it was generally observed that a good relationship exists between the N.T.C.P value and the organ (bladder, rectum and Gastro-Intestine) doses given. As the doses increases for all the organs, the probability of complication gets larger for these ranges (0%-100%). This observed result is in agreement with what other researchers have done.

Rubin and Cassarett (1968), (Emami et al., 1991) and Khewar (2005). For all the organs, it was observed that the smaller the volume of the organ, the lesser the complication to these organs (bladder, rectum and gastro-intestine). Also, as the value of αG for all the organs decreases (Table 2), the curves becomes steeper. The value of αG determines how sharp the dose increases in these organs.

The fitted values of k and αG obtained in this work shows significant discrepancies when compared with the work done by (Emami et al., 1991). This may be due to the fact that in the work done by Emami et al, the conventional 2D-Traetment planning system was used unlike the 3D-treatment planning system which was used for this research work. Secondly, unlike in the case of Emami et al doses as high as 125Gy were not administered to the patients included in this study. Values of k for the various organs considered in this work indicate that organs which have high values of $k>1$, have a higher volume dependency than organs which have lower values of $k<1$.

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