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Measurement of Radiation Doses Adjacent to the Treated Volume in Radiotherapy for Carcinoma Cervix and Evaluation of Lifetime Attributable Risk

Measurement of Radiation Doses Adjacent to the Treated Volume and Evaluation of LAR

Mary Joan
Department of Radiological Physics
SMS Medical College and Hospitals
Jaipur, India

Sathiyan Saminathan
Department of Radiation Physics
Kidwai Memorial Institute of Oncology
Bangalore, India

Abstract:- Technological advances has improved the conformality of treatment and accuracy of dose delivery in radiotherapy. The radiation doses to organs at risk are also minimized. Radiotherapy is associated with second cancer risk as ionizing radiation is used for treatments. The normal tissues around the treated volume and the radiation doses received is of renewed concern as advanced modalities for diagnosis and treatment lead to early detection and long life expectancy of patients after treatment. The population of young patients is also on the rise. In this study, the radiation dose to these organs at risk from 3DCRT/ IMRT with brachytherapy is calculated using Eclipse and Brachyvision radiotherapy treatment planning system. An anthropomorphic heterogeneous female pelvis phantom was fabricated indigenously for physical dose measurements and verification. The radiation dose delivered to bladder, rectum and femoral heads from 3DCRT/ IMRT and Brachytherapy were measured and the lifetime attributable risk associated was evaluated. The treatment planning system accurately calculated the radiation doses to organs adjacent to the treated volume.

Keywords:- *Anthropomorphic Phantom; Lifetime Attributable Risk; Radiation Dosimetry; Second Cancer.*

I. INTRODUCTION

Technological advances improved the conformality of treatment and accuracy of dose delivery in radiotherapy. The radiation doses to organs at risk are also minimized [1]. Radiotherapy is associated with second cancer risk as ionizing radiation is used for treatments. The normal tissues around the treated volume and the radiation doses received is of renewed concern as advanced modalities for diagnosis and treatment lead to early detection and long life expectancy of patients after treatment. The population of young patients is also on the rise [2].

Cervical cancer, ranks fourth among women cancers across the globe affecting 5,28,000 women every year. With 2, 66,000 deaths in 2012, it also ranks fourth cancer death cause globally among women [3]. More than 20 percent of newly diagnosed cervical cancers are from India. Cervical cancer is the leading cancer constituting 26% of all female malignancies in our institute.

Radical radiotherapy is the standard of care of advanced carcinoma cervix. A combination of teletherapy and brachytherapy is the conventional practice. The most important factor leading to the success of radiotherapy of cervical cancer is the optimization of radiation doses to tumor and normal tissues. This is achieved by careful balance between external beam radiotherapy and brachytherapy. The overall duration of treatment also plays a significant role. 5 year survival rates reported for radiotherapy treatment alone for stage IIB is of 65% to 75%, stage IIIB is of 35% to 50% and stage IV is of 15% to 20% [4, 5]. A 10 year relative survival rate reported is 67.2% [6].

Advanced external beam radiation therapy (EBRT) treatment modalities like; 3-Dimensional Conformal Radiation Therapy (3DCRT) and Intensity Modulated Radiation Therapy (IMRT) provide accuracy in the dose delivery and dose escalation to the target volume [7]. Brachytherapy (BT) is a vital part of radiotherapy for locally advanced cervical cancer. High radiation dose delivery to the tumor sparing the critical structures is achieved through brachytherapy, reducing local recurrence and improved overall survival compared to pelvic EBRT alone [8]. The tumoricidal dose delivery either through 3DCRT or IMRT alone would lead to significant dose to rectum and bladder resulting in higher acute and late toxicity [9]. Several studies have been reported induction of second cancer following radiotherapy for treatment of cervix cancer. The risk of all second cancers and cancers of rectum/anus, urinary bladder and bone are especially higher as irradiated heavily [7, 10-12].

In this study, the radiation dose to these organs at risk from 3DCRT/ IMRT with brachytherapy is calculated using Eclipse and Brachyvision radiotherapy treatment planning system (TPS). An anthropomorphic heterogeneous female pelvis phantom was fabricated indigenously for physical dose measurements and verification [13, 14]. The radiation dose delivered to bladder, rectum and femoral heads from 3DCRT/ IMRT and Brachytherapy were measured and the lifetime attributable risk associated was estimated.

II. MATERIALS AND METHODS

A. Fabrication of anthropomorphic heterogeneous female pelvic phantom

An anthropomorphic female pelvis phantom with tissue heterogeneities to achieve realistic radiation dose measurements was designed and fabricated. Computed tomography (CT) images were acquired in treatment setup for a median sized patient. The external body contour, target tumor volume, both left and right femur, bladder volume and rectum were contoured in the Eclipse planning system. The organ and bone structures were smoothed in shapes in each individual slice and milled on Pinnacle machine (EXCEL, England). The external contours of the organs delineated were used for creating moulds. CT number matched wax compound was used for the organs. Du Pont Delrin acetal homopolymer resin was used for the bone. Provisions to use different dosimeters and brachytherapy applicators were incorporated in the phantom. Thermo-luminescent dosimeters (TLD) were used for the measurements. The assembled phantom is shown in figure 1.

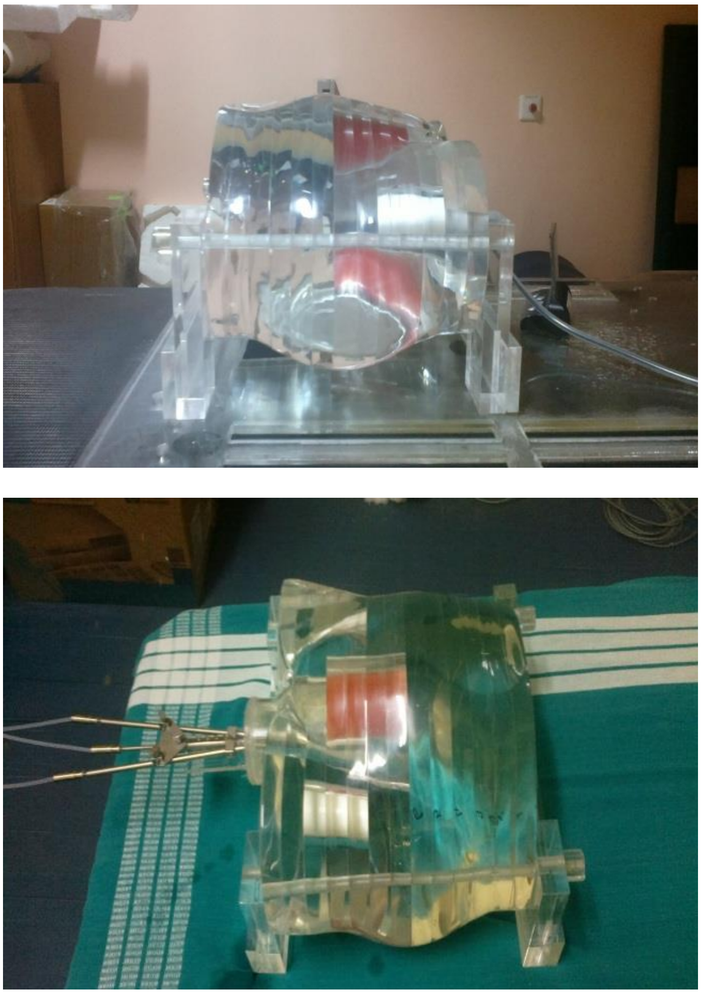

Fig 1:- The Indigenously Fabricated Female Pelvis Phantom in Treatment Position for EBRT and Brachytherapy

B. Treatment Planning for 3DCRT/ IMRT with Brachytherapy

The phantom CT scan was acquired on Philips MX16. 2 mm thick slice helical scans were taken. The machine parameters were set to 120kVp tube voltage and 230mA current. Four-field 3-dimentional conformal and IMRT treatment planning were done. (Varian Eclipse 3D planning system (AAA algorithm)). The dose prescription/fraction was 2Gy. The 3DCRT/ IMRT plans were generated for a total dose of 50Gy. The tumor target volumes and the normal structures bladder, rectum and femoral heads were contoured for radiotherapy treatment planning. The radiation dose to bladder, rectum and femoral heads were assessed using TLDs between the treatment fractions. The treatment delivery and measurements were performed on a Varian Clinac 2100C DHX accelerator (Varian Medical Systems, Inc., Palo Alto, USA). The brachytherapy plan for intra-cavitary brachytherapy (ICBT) application of tandem and ovoids was planned on Brachyvision treatment planning system from Varian for brachytherapy planning. The brachytherapy treatment was delivered on the high dose rate machine Gammamed plus. The radiation doses to multiple points on the normal structures were measured using TLDs.

C. Measurement and Evaluation of Organ doses Adjacent to the Treated Volume

The organs at risk which receive considerable radiation dose during radiotherapy for carcinoma cervix are bladder and rectum. The brachytherapy dose prescription is modified to reduce the bladder and rectum doses. Multiple organ reference dose points were marked on the treatment plan. The measurements were repeated four times for each measurement point.

TLD 100 (LiF:Mg,Ti) thermo-luminescent dosimeter rods were used for measurements. The exposed TLDs were read on the TLD reader system Harshaw 2000. The TL responses to dose linearity of the selected TLD rods were studied by exposing them to different radiation doses in 1.25 MeV γ-rays from a telecobalt machine (Theretron 780C). High energy photon beam calibration is performed with 6MV photons from a linear accelerator (Varian Clinac 2100 DHX). The TLDs gave a linear response up to 10Gy.

D. Evaluation of Lifetime Attributable Risk (LAR)

While ensuring the maximum dose delivery to the target structure, it is unavoidable that the nearby structures also receive a significant dose. Hence, the risk associated with the normal structure doses are mainly focused on doses to organs far away from the target tumor volume [15]. The probability of second cancer occurrence is greater with higher doses and the data of second cancer incidence are based on second cancers near the treated target tumor volume. Dorr and Herrmann (2002) [16] found that within 5 cm of the boarders of the target volume occurs up to 90% of second cancers. Boice et al (1985) [17] observed about half of the second tumors were adjacent to the treatment field border. Considering the improved radiation dose conformity by advanced radiotherapy treatment techniques this is especially significant.

The radiation dose corresponding to second cancers varies significantly for normal tissues adjacent to the treated volume and away from the treated volume as the adjacent tissues gets irradiated by the primary radiation beams. The Linear Non- Threshold (LNT) model for the low-dose region over estimates the risk of second cancer to the tissues adjacent to the treated volume. Cell killing takes place at higher doses and hence the smaller risk of second cancer. [16-18]. Schneider (2006) [19] pointed out that several papers [20, 21], ignored the primary radiation beam endowment to the incidence of second cancer as they have evaluated secondary radiation exposures to the organs distant from the treated volume. For normal tissues adjacent to the treated volume which receives a higher radiation dose Sachs and Brenner (2005) [22] proposed a biological model with minimal dependency to parameters incorporating carcinogenic effects, cell killing and proliferation/ repopulation effects. These were in congruence with the second cancer incidence clinical data for high dose regions.

The BEIR VII report [23] recommends calculating LAR as given in the below equation.

$$LAR= \left(\sum_a^{90} ERR(D,e,a) \times \lambda_1^C \times \frac{S(a)}{S(e)da}\right)^{0.7} \times \left(\sum_a^{90} EAR(D,e,a) \times \frac{S(a)}{S(e)da}\right)^{0.3}$$

This equation is not suitable for estimation of risk to thyroid, breast and lung.

Excess Absolute Risk (EAR) and Excess Relative Risk (ERR) calculated using equation

$$ERR(D,s,e,a) \text{ and } EAR(D,s,e,a)= \beta_s d \exp(\gamma e^*)\left(\frac{a}{60}\right)^{\eta}$$

λ_1^C is the baseline cancer risk data and taken from ICRP-103 [24]. The ratio $\frac{S(a)}{S(e)}$ $\frac{S(a)}{S(e)da}$ is probable survival to attained age ‘a’ from exposed age ‘e’, calculated from life span tables for Indian population. D, dose measured; EAR, ERR, β_S, γ and η parameters specific to various organs and both sex. $e^* = \frac{(e-30)}{10}$ for e<30 and 0 for e>30 years based on time since exposure is calculated by t=a-e from BEIR VII report for solid cancer incidence.

III. RESULTS AND DISCUSSION

A. Measurement and Evaluation of Organ doses Adjacent to the Treated Volume

The mean measured doses to normal tissues adjacent to the treated volume of cervix cancer radiotherapy for a fraction of 3DCRT/ IMRT and brachytherapy is tabulated in Table 1, 2, 3.

Organ	**Dose/ # (Gy)**	
	3DCRT	
	Measured Dose + SD	***Calculated Dose***
Bladder	1.99+0.012	2.00
Rectum	2.03+0.015	1.99
L Femoral Head	1.45+0.006	1.46
R Femoral Head	1.35+0.014	1.35

Table 1:- Mean Measured Dose + Standard Deviation with Respect to TPS Calculated dose for the Critical Organs for a Fraction of 3DCRT

Organ	**Dose/ # (Gy)**	
	IMRT	
	Measured Dose + SD	***Calculated Dose***
Bladder	1.99+0.016	1.99
Rectum	1.99+0.036	2.00
L Femoral Head	1.03+0.016	1.01
R Femoral Head	1.06+0.021	1.08

Table 2:- Mean Measured Dose + Standard Deviation with Respect to TPS Calculated Dose for the Critical Organs for a Fraction of IMRT

Organ	**Dose/ # (Gy)**	
	ICBT	
	Measured Dose + SD	***Calculated Dose***
Bladder	2.25+0.015	2.29
Rectum	2.16+0.031	2.16
L Femoral Head	0.522+0.037	0.699
R Femoral Head	0.633+0.024	0.644

Table 3:- Mean Measured Dose + Standard Deviation with Respect to TPS Calculated Dose for the Critical Organs for a Fraction of ICBT

High doses optimization is the major focus of the radiotherapy treatment planning. Intermediate doses also optimized but with lower priority. Low doses optimizations are not generally addressed during treatment planning [1]. The bladder and rectum receives high doses in the external beam radiotherapy of carcinoma cervix. The femoral head also receives intermediate doses. The present study confirms the adequacy of treatment planning system in accurately optimizing these doses. The high doses received by the organs adjacent to the treated volume in the external beam radiotherapy of cervix cancer are unavoidable. The radiation doses to these organs adjacent to the treated volume are calculated accurately with the treatment planning system. The organ tolerance doses are achieved by incorporation of brachytherapy and judicious optimization. Brachytherapy enables steep dose fall gradients reducing the dose to the organs adjacent to the treated volume. The dose distributions of 3DCRT, IMRT and brachytherapy are shown in figure 4, 5, 6.

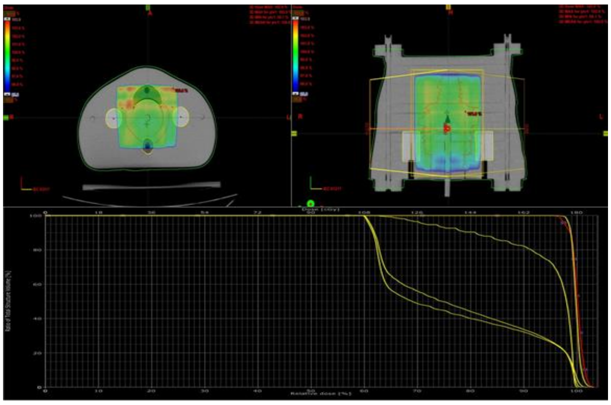

Fig 4:- 3DCRT Treatment Plan

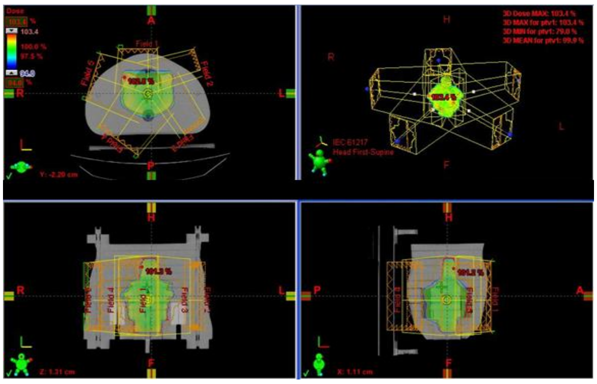

Fig 5:- IMRT Treatment Plan

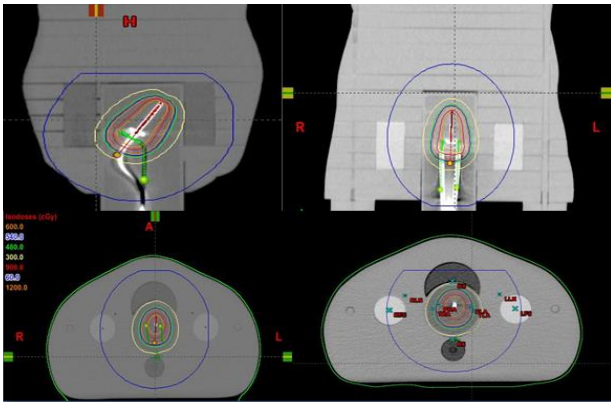

Fig 6:- HDR ICBT Treatment Plan

B. Evaluation of Lifetime Attributable Risk (LAR)

Several risk assessment and evaluation models have been developed by various international commissions for radiation protection and safety such as International commission on Radiation Protection (ICRP), Biological Effects of Ionizing radiation (BEIR) committee of the United Nations Scientific Committee on the Effects of Atomic Radiation Effects of ionizing radiation (UNSCEAR) to estimate the probability of incidence of cancer and mortality due to cancer. The BEIR VII [23] model for second cancer risk estimation was adopted in this study as this report provides model parameter specific to patient sex, type of organ, age at exposure and attained age for estimating the risk of second cancer.

The lifetime attributable risk for the critical organs adjacent to the treated volume during 3DCRT/IMRT along with ICBT was evaluated. The uncertainties associated with model parameters given in BEIR VII report for the estimation of LAR are high. The uncertainty is mainly dominated by the uncertainty in the estimated value of the model parameter β in the models of ERR and EAR.

The organs adjacent to the treated volume receives higher doses in the radiotherapy treatment of carcinoma cervix such as bladder, rectum and femoral head are included in the CT simulation for radiotherapy treatment planning. The radiation dose received by organs outside but adjacent to the treated volume are calculated accurately by the treatment planning system and enables the optimization of dose delivered. As per the data available from epidemiological studies, majority of the second cancer incidences (up to 80 %) are in the intermediate to high dose regions [6, 25-26]. Though unacceptable this unavoidable radiation dose to the normal tissues adjacent the treated volume leads to substantial radiation risk. The lifetime attributable risk is related to age at exposure and it decreases as the age at exposure increases [23, 27-28]. Though the volume of critical organs adjacent to the treated volume receiving higher doses with IMRT is lower, the more number of monitor units (MU) to deliver same dose results in higher integral dose to the normal tissues and is of concern [29-31]. Regular screening, early detection and advanced treatment modalities considerably improved the life expectancy of the patients treated for carcinoma cervix with radiation. This emphasizes the necessity of long-term post treatment follow-up. Also, it is crucial that the medical physicists and radiation oncologists understand the impact of the radiation doses adjacent and outside the treated volume and methods to manage them.

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