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Out-Of-Field Dose Measurement and Second Cancer-Risk Estimation Following External Beam Radiotherapy and Brachytherapy for Cervical Cancer Treatment: A Phantom Study

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ABSTRACT

Introduction: The present study aimed to measure the scatter and leakage dose received by out-of-field organs while delivering Radiotherapy (RT) treatment of cervical cancer. Moreover, this study estimated the risk of second cancer (SC). The doses to out-of-field organs were measured using a lithium fluoride (TLD 100) dosimeter while delivering External Beam Radiotherapy (EBRT) by 6 MV photon beam with Brachytherapy Boost (BB) treatment in the humanoid phantom.

Material and Methods: The excess absolute risk of SC for the stomach, colon, liver, lung, breast, and kidney, as well as excess relative risk for the thyroid, were estimated based on Biological Effects of Ionizing Radiation VII report.

Results: The out-of-field organ doses varied with respect to distance between organs. The colon (3DCRT-282.13 cGy and IMRT-381.24 cGy in 25 fractions) and kidney (70.65 cGy in 3 fractions) received the highest doses with EBRT and BB, respectively. For most of the aforementioned organs, the calculated dose was 0.2 Gy/fraction according to the treatment planning system. With the age at exposure (i.e., 30 years) as a reference, the highest LARs were associated with the colon (0.74%) and breast (2.76%) in 3DCRT plus BB and IMRT plus BB, respectively. The lifetime attributable risk of SC was also shown to decrease with increasing the age at exposure for all the organs.

Conclusion: Although all the evaluated out-of-field organs in this study showed some levels of risk, the risk was more frequently reported for the colon, stomach, and breast with IMRT technique than that in 3DCRT.

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Introduction

Worldwide, cervical cancer is the fourth most common cancer in women and is estimated to account for 6.6% of all female cancers in 2018. Almost 80% of new cervical cancer occurs in developing countries and is considered the primary cause of mortality. It mostly affects middle-aged women with poor economic status who fail to carry out regular health check-ups [1]. In India, mortality due to cervical cancer accounts for 17% of all cancers among women within the age range of 30-69 years [2].

The standard care for locally advanced cervical cancer is external beam radiotherapy (EBRT) with brachytherapy boost (BB). A large number of patients undergo radiotherapy (RT), and the 10-year relative survival rate has been reported as 67.2% [3]. Conventional two-dimensional RT used in the treatment of cervical cancer in the last few decades is associated with the high frequency of acute and chronic late complications [4]. Therefore, this treatment method was highly replaced by three-dimensional conformal radiotherapy (3DCRT) that is relatively favorable in terms of delivered radiation dose and associated toxicity for non-targeted tissues [5].

On the basis of 3DCRT, a precise RT known as intensity-modulated radiotherapy (IMRT) has been developed that is used in EBRT as a curative and postoperative RT. An advantage of IMRT is that while minimizing the dose to adjacent noncancerous tissues, it can also deliver a relatively large radiation dose to tumor. As a result, greater locoregional control can be achieved through lower number of side effects. In the treatment of cervical cancer, IMRT is associated with lower gastrointestinal and hematological toxicities, compared to conventional RT; therefore, IMRT has been more widely used [6, 7].

The IMRT aims at better conformity that modulates the beam intensity within the tumor volume and for the normal structures, thereby reducing the volume of irradiated tissue. However, at

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a certain distance from the treatment field, the beam modulation leads to increased head leakage and requirement for a higher number of monitor units (MU) to deliver the same prescribed dose that result in a larger total body dose. Consequently, the downside of the IMRT is the potential to increase the radiation-induced second cancer (SC) in the out-of-field region [8].

Brachytherapy (BT) also plays a very important role in the treatment of locally advanced cervical cancer as a boost treatment. The BT allows delivering higher doses to the tumor while sparing the critical structures, persistently shown to reduce local recurrence and improve overall survival, compared to pelvic EBRT alone [9]. Using EBRT alone to deliver the tumoricidal dose would lead to delivering significant doses to the rectum, small bowel, and bladder that results in high acute and late toxicity. Therefore, it is very essential to deliver BB after EBRT [10].

There is an increasing concern regarding SC following RT due to the early screening of patients at young age and increased survival rate. A study was performed by Chaturvedi et al. on following cancer registry data from Denmark, Finland, Norway, Sweden, and the United States for a cohort of 104,760 patients with cervical cancer. It was observed that 52,613 subjects received radiation in the form of EBRT or intracavitary BT or both. In a median follow-up of these patients for 12.2 years, a 12% increase was noticed in the incidence of SC in the colon, bladder, ovary, rectum, sinus, and genital sites, compared to that in patients who did not undergo RT [3].

Several studies reported the induction of SC following RT in subjects with cervical cancer; however, these studies mainly focused on SC risk evaluation of the bladder, colorectal leukemia, and Non-Hodgkin's lymphoma. In addition to population-based study Surveillance Epidemiological and End Results (SEER) program conducted by National Cancer Institute resulted a significantly increased risk of SC in esophageal, stomach, lung and bronchial cancer following cervical cancer treatment. The research cohort included women diagnosed with invasive cervical cancer identified in Denmark's population based cancer registries from 1943-1998. Follow-up for advanced second primary cancers began 1 year after the diagnosis of cervical cancer and finished at the earliest onset of second cancer diagnosis, death or completion of study period. [11]. From this perspective, the risk evaluation should be carried out for cancer patients undergoing RT. The present phantom study mainly focused on the measurement of doses delivered to organs in the out-of-field regions and analysis of SC risk. An out-of-field region is defined as the area outside the treatment field not considered and not even imaged for treatment planning purposes [12].

To estimate the rates of cancer incidence and mortality, several risk models have been developed by radiation protection bodies, such as the International Commission on Radiation Protection (ICRP), Biological Effects of Ionizing Radiation (BEIR), and United Nations Scientific Committee on the Effects of Atomic Radiation. The BEIR VII report was adopted for SC risk estimation and provides model parameters specific to patient gender, type of organ, age at exposure, and attained age for the estimation of SC risk.

The BEIR VII committee relied heavily on the analysis of the data of the atomic bomb survivors undertaken by the Radiation Effects Research Foundation for the development of sufficient risk models and variables to be applied in cancer risk estimation. Two contrasting risk models, namely excess relative risk (ERR) and excess absolute risk (EAR), were developed by the panel. It is possible to calculate the ERR by comparing the disease rate in an exposed population to the disease rate in an unexposed population. The EAR is the difference between the exposed population and unexposed population..

The third model adopted by the BEIR VII committee is the lifetime attributable risk (LAR). For the measurement of the lifespan, the LAR is nothing more than an EAR or ERR summation calculated for each year after the exposure to an expected lifespan of 80 years. The LAR also provides a lag time from exposure to the first cancer risk (i.e., 5 years for solid cancers) and dose and dose-rate effectiveness factor (DDREF) depending on the age of exposure and gender of the specimen. The DDREF factor is responsible for the reduction of low dose and medium dosage ionizing radiation effects, compared to high and heavy doses. This factor helps to combine the medium with high-dose epidemiological data and low-dose animal epidemiological data for which the BEIR VII committee proposes a DDREF factor 1.5 for all solid tumors [13].

The present study aimed to estimate the LAR of radiation-induced SC in the out-of-field organs, such as the liver, stomach, colon, thyroid, lung, and breast, as a consequence of 3DCRT plus BB or IMRT plus BB by the measurement of the scatter and leakage radiation through a phantom RT plan for cervical cancer.

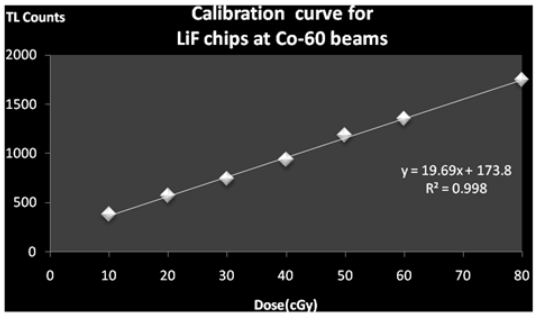
Materials and Methods

Planning for standard three-dimensional conformal radiotherapy box field and intensity-modulated radiotherapy with brachytherapy boost:

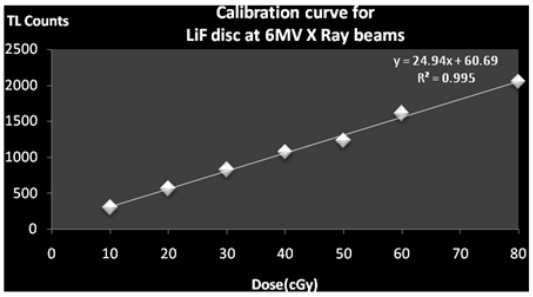
The out-of-field doses to organs were measured using a TLD 100 thermoluminescent dosimeter (TLD chips). These chips are with the size of 4.5 mm diameter and 0.9 mm thickness and used for calculations in both EBRT by 6MV photon beam and BB by Co-60 gamma radiation. For this purpose, the dosimeters were

calibrated for the known dose of Co-60 gamma rays of 1.25 MeV mean energy in a telecobalt machine (Theratron 780-E, Best Theratronics, Ottawa, Canada). Moreover, the dosimeters were irradiated for the same dose of 6MV photon beam in the linear accelerator (Varian Medical Systems, Clinac 2300 CD, Palo Alto, CA, USA) to obtain energy correction factor [14].

To correct inter-chip variation in a batch, the individual calibration factor was established by the irradiation of the TLD chips to known doses in the out-of-field dose range of 10-100 cGy in the steps of 10 cGy. Only TLD chips with sensitivity ranging within 5% were selected for the measurements. The calibration curves for the Co-60 beam and 6MV X-ray beam are shown in figures 1a and 1b, respectively. In addition, the linearity behavior of chips was verified before using for organ dose measurement.



(a)

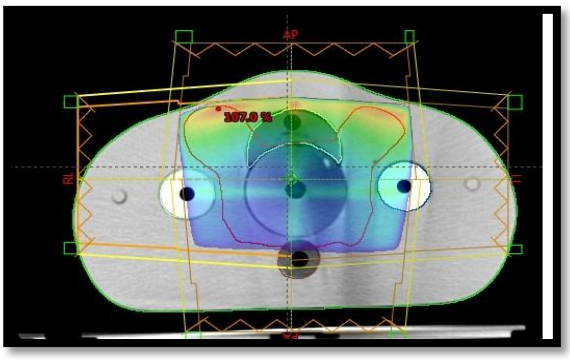


(b)

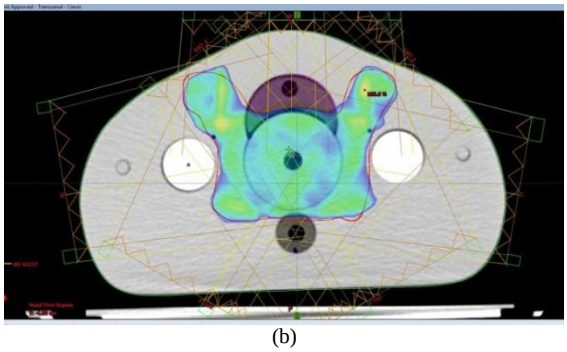
Figure 1. a) Calibration curve at Co-60 beam, b) Calibration curve at 6 MV X-ray beam

For out of field dose measurement in this study **,**the humanoid phantom consists of water equivalent Poly Methyl Metha Acrylate (PMMA) slabs which were integrated to form a body shape was used. Each slab has thickness of 2 cm and provision to hold TLD chips at various organs . The phantom was simulated in a computed tomography (CT) simulator (Wipro GE health care, Chicago, US) for planning transverse CT images. For BB planning, the additional plug to hold the applicator was inserted and simulated in the pelvic part of the phantom. Planning CT images (without BB applicator) of phantom was transferred to the treatment planning system (TPS) (Eclipse V 13.7, Varian Medical Systems, Palo Alto, CA, USA) for delineating tumor volume and other normal tissues. Following that, a 3DCRT plan with four fields (i.e., box field technique) was created, and a dose was calculated for 6 MV photon beam by anisotropic analytical algorithm (Figure 1a).

For the same tumor volume, inverse IMRT plan with seven fields was created, and inverse optimization was performed by photon optimizer algorithm (Figure 1b) to achieve the conformal dose distribution. Similarly, the 3D intracavitary BB plan was developed for CT images in high dose rate (HDR) plus TPS (Eckert & Zeigler Bebig, Germany) for Cobalt-60 gamma rays of 1.25 MeV mean energy (Figure 1c). The total prescription dose for EBRT was 50 Gy delivered as 2 Gy per fraction, and the prescribed dose for BB was 22.5 Gy delivered as 7.5 Gy per fraction. The out-of-field doses were measured for 3DCRT plus BB and IMRT plus BB.



(a)



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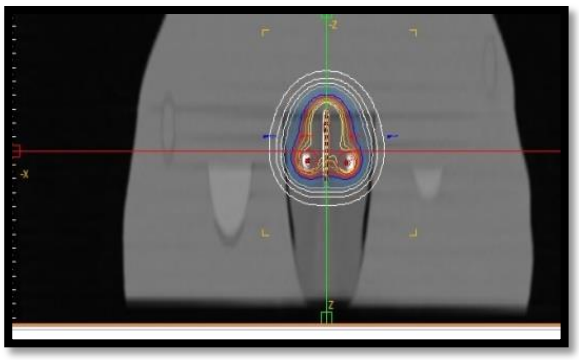

(c)

Figure 2. a) Three-dimensional conformal radiotherapy plan with dose distribution, b) Intensity-modulated radiotherapy plan with dose distribution, c) Brachytherapy boost plan with dose distribution

Measurement of out-of-field organ doses using a lithium fluoride (TLD 100) thermoluminescent dosimeter in a humanoid phantom

The phantom was firstly positioned at the initial reference marks and then shifted to the treatment isocenter using the TPS calculated shifts in the linear accelerator. Following that, treatment isocenter was marked for further irradiation. The TLD chips were uniformly placed within the position of delineated organs (i.e., the breast, lung, thyroid, liver, colon, stomach, and kidney) outside the planned field. Furthermore, each TLD was uniquely identified, and the absorbed dose was calculated using the calibration factor. The TLDs were read out using TLD reader and pre-annealed by keeping TLD chips in an oven to 400^{o}C for an h followed by free cooling to the air temperature. Five fractions of each planning technique were delivered in the measurement session. The EBRT plans were delivered in a linear accelerator (Clinac 2300 CD, Varian Medical Systems, Palo Alto, CA, USA) with 6MV X-ray photon beam, and BB plans were delivered in HDR-BT machine (Multisource, Eckert & Ziegler BEBIG, Germany) with mean photon energy of 1.25 MeV gamma rays.

Lifetime attributable risk estimation of radiation-induced second cancer

The ERR or EAR can be calculated using the following equation:

$$\text{ERR (D, s, e, a) and EAR (D, s, e, a)} = \beta_s d \exp(\gamma e^*)\left(\frac{a}{60}\right)^{\eta} \quad (1)$$

The biological parameters used in this equation were obtained from the studies performed based on the Hiroshima and Chernobyl incidents. Here D-Dose measured; e-age at exposure; a-attained age. The EAR and ERR specific parameters are β_S, γ and η given for various organs for each sex by BEIR VII report.

For organs other than the breast, lung, and thyroid, the BEIR VII report recommends the calculation of LAR as obtained by the following equation [15]:

$$\text{LAR}=\left(\sum_a^{90} ERR(D,e,a) \times \lambda_1^C \times \frac{S(a)}{S(e)da}\right)^{0.7} \times \left(\sum_a^{90} EAR(D,e,a) \times \frac{S(a)}{S(e)da}\right)^{0.3} \quad (2)$$

Where *EAR* and *ERR* are calculated using equation 1, and λ_1^C is the baseline cancer risk data taken from ICRP-103 [16]. The ratio $\frac{S(a)}{S(e)}$ is the probability of a person surviving to the attained age (i.e., a) following exposure at age (i.e., e), which was calculated from lifespan tables for Indian population. The cumulative LAR was calculated by the summation of LAR up to 70 years of attained age. For most organs, weights 0.7 and 0.3 are recommended by BEIR VII report. In this regard, the weights are reversed for the lung. As recommended by BEIR VII, only EAR is used for calculating the LAR of the breast. Similarly, only ERR is recommended for the thyroid. For the kidney, there is no specific parameter recommended by BEIR VII; therefore, the kidney is not included in the LAR risk calculation [15].

Results

Measured organ doses

Table 1 shows the mean dose per organ from 3DCRT, IMRT, and BB deliveries with one sigma uncertainty. The uncertainty range and mean uncertainty were reported as 0.03-3.57 and 0.8, which were within acceptable limits, respectively [11]. Pattern of dose distribution was as expected in this study. The equivalent dose with BT resulted in a higher dose to nearby organs than those with 3DCRT and IMRT. With teletherapy, IMRT resulted in higher out-of-field doses for out-of-field organs due to greater leakage radiation associated with IMRT for all the organs.

The colon (3DCRT-282.13 cGy and IMRT-381.24 cGy in 25 fractions) and kidney (70.65 cGy in 3 fractions) received the highest doses with EBRT and BB, respectively. The distant organs, such as the liver, lung, and breast, received lower doses than nearby organs in BB; however, the distant organs received 20-fold lower doses than nearby organs in 3DCRT. Nevertheless, this difference was only 3-4 times with IMRT treatment.

Table 1. Measured doses to out-of-field organs

Out-of-field organ	Absorbed dose (cGy)		
	3DCRT (25 fractions)	IMRT(25 fractions)	Brachytherapy (3 fractions)
Liver	9±0.09	128±1.28	1.9±0.3
Lung	12±0.03	91±0.52	1.5±0.14
Breast	14.3±0.17	87.5±0.84	1.44±0.17
Thyroid	123.95±0.24	152±1.3	10.43±2.4
Colon	282.125±0.55	381.24±1.38	69.39±0.03
Kidney	217.375±3.57	291±1.97	70.65±0.5
Stomach	53.7±0.48	157.5±0.51	17.12±0.4

3DCRT: Three-dimensional conformal radiotherapy
IMRT: Intensity-modulated radiotherapy

Lifetime attributable risk

In this study, the LAR was estimated for two different dose categories, such as 3DCRT plus BB and IMRT plus BB. Three fractions of BB did not result in significant doses to out-of-field organs due to rapid fall-off dose distribution; therefore, the LAR was calculated for cumulative treatment dose. With the age at exposure (i.e., 30 years) as a reference, the highest LAR was associated with the colon (0.74%) and breast (2.76%) in 3DCRT and IMRT, respectively.

The LARs were reported as the lowest values for the liver (3DCRT: 0.005% and IMRT: 0.1% with the age at exposure) in both treatment techniques.

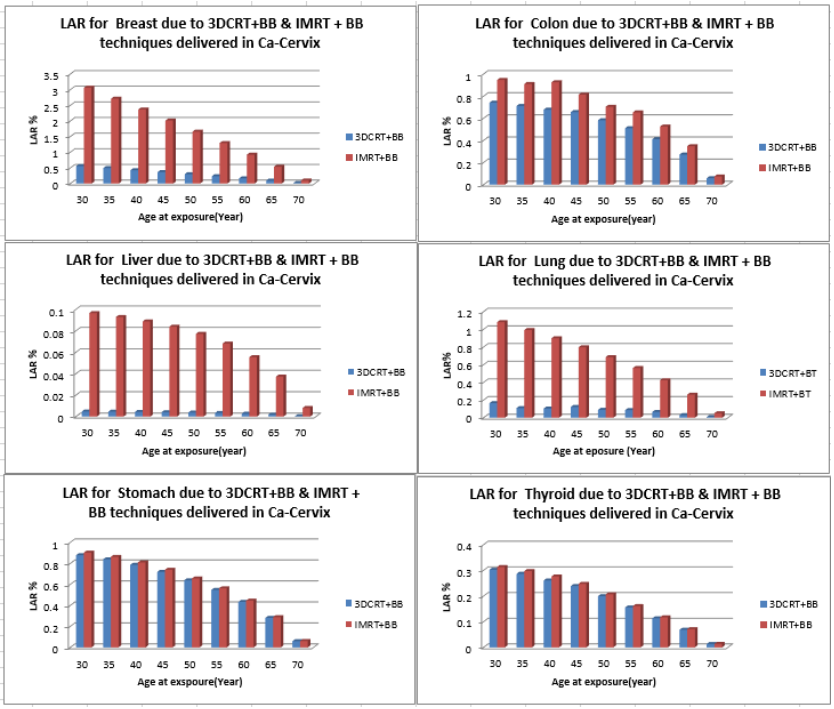

Figure 3. Calculated lifetime attributable risks of second cancer in organs resulting from three-dimensional conformal radiotherapy plus brachytherapy boost (blue bar) and intensity-modulated radiotherapy plus brachytherapy boost (red bar) as a function of age at exposure

As shown in Figure 2, the LAR associated with the breast and lung results in higher than 1% with IMRT and lower than 1% in 3DCRT. Other out-of-field organs, such as the colon, liver, and stomach, were reported with lower than 1% LAR with both treatment methods. The thyroid was reported with lower than 0.5% LAR for both treatment techniques.

The uncertainties associated with model parameters given in the BEIR VII report were considerable for the estimation of LAR. The uncertainty was mainly dominated by the uncertainty in the estimated value of the model parameter β in the models of ERR and EAR.

Discussion

As a tertiary cancer center(Acharya Tulsi Regional Cancer Treatment and Research Centre, Bikaner) in the northwestern part of India, we treat patients from different parts of northern region. Total number of patients with cervical cancer registered in 2018 was 522. Average age of the subjects suffering from cervical cancer has been reported as 54 years. In addition, nearly 40-50% of the patients are below the age of 50 years. Increasing trend of young subjects with cervical cancer leads to performing studies on the dose received by critical organs and associated cancer risk.

As the organs present in the infield volume, such as the bladder, rectum, bowel bag, and femoral head, are considered and included in the simulation CT, the doses received by organs present in the infield volume are accurately calculated by the TPS.The accurate dose calculations in this region assist the planner and oncologist to optimize the doses received by these organs. However, the doses received by organs in the out-of-field regions are not accurately calculated by most commercial TPS, since the TPS is not commissioned for out-of-field dose calculations [17, 18].

According to a study performed by Huang et al. on the accuracy of out-of-field dose calculation by TPS, it was concluded that the pinnacle TPS used for dose calculation underestimated the out-of-field dose by an average of 50%. Even the location nearby the treatment field shows 30% calculation errors [14]. Similarly, the TPS used for the present study was calculated as 0.4% of the prescribed dose for all the out-of-field organs irrespective of the distance from the treatment field. Therefore, it is essential to use the *in vivo* dosimetry protocol for dose measurement in this region.

The LAR for out-of-field organs showed a strong dependency on age at exposure for all the evaluated organs. The risk decreased with an increase in the age at exposure as given in BEIR report. It represented that the younger patients were at greater risk than older patients due to increased radiosensitivity. With teletherapy, the risk comparison between the planning techniques showed that IMRT plus BB resulted in greater risk than 3DCRT plus BB treatment for the out-of-field organs. With 3DCRT technique, the colon, stomach, breast, and thyroid demonstrated a greater risk than the liver and lung. With IMRT technique, the breast, lung, colon, and stomach were observed with a greater risk than the liver and thyroid.

In this study, the highest LAR was obtained for the breast in IMRT. The risk associated with the breast was five times higher with IMRT than that with 3DCRT.

Although the breast received cumulative dose lower than those of the colon, stomach, thyroid, and liver, the EAR specific parameter β given by BEIR VII report was the highest for the breast (EAR of 9.9/10000PY Sv) that resulted in the highest risk.

The IMRT aims at better conformity that constricts the field edge, thereby reducing the volume of irradiated tissue. However, at a certain distance from the treatment field, the beam modulation leads to increased head leakage and results in higher doses [19]. In comparison to 3DCRT, the greater number of MUs associated with IMRT (Total MU with 3DCRT: 286 and Total MU with IMRT: 1305) also results in out-of-field doses due to increased head leakage and scatter radiation [20-22].

There were only few studies performed on the evaluation of risk of SC following pelvic irradiation [11, 23, 24]. Most of these studies focused on prostate irradiation, and very few studies were performed on the analysis of SC risk following EBRT and BT for the treatment of cervical cancer. One of the phantom studies performed by Lee et al. on the estimation of SC risk associated with EBRT and BT demonstrated higher doses with BT for nearby organs than those with EBRT for an equivalent dose.

In addition, in the aforementioned study, the risk of SC for all the organs in the out-of-field regions was shown to decrease with the increase in the age at exposure. The equivalent dose to nearby organs is higher for BB than that for EBRT. For the age at exposure (i.e., 30 years) as a reference, the higher LAR with EBRT was reported for the stomach, lung, and thyroid, and the highest LAR results with BB were obtained for the stomach [11].

In the present study, the results of LAR associated with 3DCRT plus BB techniques also are in line with those of the above-mentioned study. Results of the present study indicated that the high level of SC risk associated with the out-of-field radiation dose necessitates posttreatment follow-up. The high dose volumes received by critical organs nearby the target substantially reduced with IMRT. However, far from the treatment field, IMRT resulted in a significant low dose-volume, which increased the concern about the induction of SC. This problem can be mitigated by the reduction of the modulation factor; furthermore, head leakage can decrease by the effective lead shielding of head treatment [25].

A study performed by Senkus E et al. on squamous cell carcinoma following cervical cancer treatment confirmed that new tumors were located outside the irradiated field with different histology, which is attributed to low-dose leakage and scatter radiation [26]. An international collaboration among cancer registries following the treatment of cervical cancer was carried out by D. Boice et al. [27]. Results of the second primary cancer risk estimated per 10^6 PY-rad corroborated the highest incidence of the breast, acute nonlymphocytic leukemia, stomach, colon, and thyroid, compared to that of the liver and kidney.

In the sites far from the cervix, the above-mentioned study reviewed the highest second primary incidence of the lung, oesophagus, and breast. The present study also verified the probability of SC induction in the breast and lung associated with IMRT. Although the radiation-induced SC risk models and parameters are presented with uncertainties, these models made it possible to include the risk in the plan optimization in addition to deterministic effects.

Conclusion

In this study, scatter and leakage radiation dose to out-of-field organs during RT of cervical cancer with EBRT and BB was measured, and the risk of SC resulting from radiation exposure was estimated. The patients suffering from cervical cancer are expected to live long enough to develop SC due to early screening and treatment; therefore, this study was performed to estimate the radiation-induced SC risk following RT. However, all the evaluated out-of-field organs in this study showed some levels of risk, the risk was more frequently reported for the colon, stomach, and breast. This final result may be acceptable in older patients if local tumor control is achieved with reduced toxicity. According to the findings of this study, it can be concluded that there is a need for a follow-up study regarding the subjects with cervical cancer to establish a solid database on SC risks related to RT.

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