Original Article *Iran J Ped Hematol Oncol. 2023, Vol 13, No 4, 225-232*

Estimation of Secondary Cancer Risk of Radiosensitive Organs for Leukemia from Head Radiotherapy in Pediatric Patients

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Received: 18 July 2023 **Accepted:** 04 October 2023

Abstract

Background: The scattered radiation from the treatment volume might be more significant for children than for adults because of life expectancy. The present study used biological effects of ionizing radiation (BEIR) VII models to estimate radiation-induced secondary cancer risks in irradiated organs following three-dimensional conformal radiation therapy (3D-CRT) of Acute Lymphocytic Leukemia (ALL) in children. Both excess absolute risk (EAR) and excess relative risk (ERR) models were used to estimate the secondary cancer risks of eye lenses, thyroid, parotid, breast, and region overlying ovaries.

Materials and Methods: In this expository cross-sectional study, from 45 patients who were examined, 16 patients age under 18 years (mean age of 9.6) met the criteria for entering the study in Shahid Ramezanzadeh Hospital in Yazd underwent whole brain radiotherapy (WBRT) using COMPACT accelerator. Measurement was performed using thermoluminescent dosimeters (TLD). After radiation therapy, the secondary cancer risk in these organs was calculated.

Results: The organ dose mean values in female patients were 1.8±0.1, 1.65±0.61, 1.47±0.04, 0.1±0.03, and 1.58±0.52 cGy in the eye lenses, parotid, thyroid, breast, and region overlying ovaries, respectively and 2.7±0.6, 0.76±0.17, 0.6±0.05, and 0.005±0.002 cGy for eye lens, parotid, thyroid, breast, and testis of male patient, respectively. The ERR and EAR were estimated after 3, 5, 10, 15 and 20 years for eye lens, parotid breast, and ovary/testis for female/male.

Conclusion: Higher risk values were found for eye lenses and thyroid. The scattered rays decreased by increasing the organ distance from the treatment radiation field.

Keywords: Dosimetry, Neoplasms, Pediatrics, Radiation, Radiotherapy, Risk

Introduction

Radiotherapy is used in the treatment of various types of cancer using external radiation. Received rays in radiotherapy should be adjusted, so that despite the complete tumor coverage during therapy, the possibility of reaching the healthy tissues and organs, especially organs with higher risk, should be less (1). One of the most common malignant pediatric diseases is acute lymphocytic leukemia (ALL) (2, 3). However, even if the organs at risk (OARs) are located outside the collimated field, they might be exposed to ionizing radiation by therapeutic external irradiation (4).

Scattered radiation can develop second cancer, which is very important in pediatric patients (5, 6).Estimating the dose of out-of-field organ and reduction the amount of them is important to prevent secondary cancers (7). Risk models for estimating the risk were developed by the committee on Biological Effects of Ionizing Radiation (BEIR) VII. For both genders and the age at the risk assessment time, parameters for specific organs are provided by these models according to the Japanese atomic-bomb survivor data (8). In the study by Rijkee et al., the types of radiotherapy methods for minimizing the

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[DOI: 10.18502/ijpho.v13i4.13768]

possibility of inducing secondary cancers were examined (9). Tubiana (10) found that pediatric radiotherapy at doses as low as 10 cGy can cause thyroid and breast malignancies. Due to recent developments in radiotherapy modalities, it is essential to re-evaluate the dose because it is a vital aspect of justifying their use and children is considered important because of life expectancy. The present study aims to estimate the risk of developing second cancer in out-of-field organs for leukemia in children aged 18 years.

Materials and Methods

This study included 15 patients aged from 1 to 18 years referred to Ramazanzade Hospital (Yazd-Iran). The study aims to measure out-of-field organ dose leukemia treated as a whole brain. Patients were treated using 6-*MV* photon beams of a COMPACT linear accelerator.

Organ dose measurements

Lithium fluoride thermoluminescent dosimeters (TLDs) (TLD-200 SDDML,China) was used to measure the radiation dose with a thickness of 9.3 mm and a diameter of 1.8 mm (13). Readouts were recorded over the 5~15-sec interval from 135˚C to 240˚ (TLD reader CTLD 7103 Reader, Imen Gostar Raman Kish, Iran). GR-200 TL detector set to a heating rate of 6~20 *˚C/sec* (11). A 6 MV photon beam was used to calibrate TLDs on the same element correction coefficient (ECC) factor. Dosimeter sensitivity was compared to the mean sensitivity of the population through ECC factor. In the second step, TLDs were divided into 7 groups exposed for 1, 2, 4, 8, 16, 32, and 64 *cGy*, respectively, and one group was for control. After determining the sensitivity factor of each TLD crystal, the TLDs were grouped into 10 batches consisting of three TLDs with similar sensitivity. The crystals were placed at the surface eye lens, thyroid, parotid, breast, and region overlying ovary. One batch was considered to measure the background dose. Doses were estimated based on Equation 1:

(1)

$$\text{Dose} = (TLi) \cdot ECCi \cdot CF$$

In which, TL is the amount of readings read by the device (*nC*), Calibration Factor (C_F) determines the calibration coefficient of the reader, and the ECC show correction factor for each TLD crystal that has no unit (12). The mean value of the three TLD readings and by applying TLDs coefficients absorbed-dose of the organ was considered in *cGy*.

Second cancer risk Model

During head radiotherapy, the total dose was 1800 *cGy* in 10 fractions. In children undergoing brain radiation therapy, the risk of inducing second cancer was evaluated using organ dose measurements. The excess absolute risk (EAR) and the excess relative risk (ERR) of eye lens, parotid, thyroid, breast, and ovary cancer of children were indicated by risk coefficients. The equivalent organ doses per fraction were multiplied by risk factors to estimate the secondary cancer risk to individual organs (13). For both ERR and EAR, *Equation 2* represents the BEIR IIV committee recommended model.

(2)

$$\text{ERR (D.s.e.a) and EAR}$$

$$\text{(D.s.e.a)} = D \cdot \beta s \cdot \exp(\gamma e^{*}) \cdot \left(\frac{a}{60}\right)^{\eta}$$

In this equation, *D* is the equivalent organ dose, (in *Sv*); *e* is the age at exposure time; β_S, γ, and η are model parameters; $e^{*} = ((e - 30))\gamma 10$ for $e < 30$ and 0 for $e > 30$ years; and *a* is the obtained age.

The parameters values, set based on the body organs and gender of patients, are shown in Table I.

The present study aimed to estimate the cancer risk in patients aged 1 to 18 years with ALL cancer. TLDs were located on target region consisted of 3 TLDs in the badge, including right and left eye lenses, parotids, breasts, gonads, and thyroid in every two treatment fields (left lateral, and right lateral) on every patient.

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Statistical Analysis

The measured scattered dose values resulting from radiotherapy were compared between sexes using Mann-Whitney tests. Kolmogorov-Smirnov test was used to check the normality of data distributions before the comparison tests. The statistical analysis was performed with SPSS software (version 16, SPSS Inc, Chicago, IL, USA). P-values lower than 0.05 were considered as a significant difference between the assessed groups.

Results

In 16 patients undergoing 3D-CRT, the absorbed dose in different OARs was measured for ALL cancer that received 18 *Gy* in 10 fractions. Table II reveals the absorbed dose mean values as *cGy* of the radiation dose delivered to the tumor site. For ALL children under 18 years, doses varied from 11.8 to 0.005 depending on the sex and primary cancer site. The highest amount of scattered radiation was absorbed by eye lens during head irradiation. However, the lowest amount of scattered radiation was received by organs below the diaphragm, so gonad received the lowest radiation dose for whole brain irradiation except ovary that received extra dose due to the sensitivity of this organ and the young age of female patients in this study.

Table III shows means of secondary cancer risk of eye lens, parotid, breast, ovary, and testis 3, 5, 10, 15, and 20 years after head irradiation. The three-year ERR of female were 840.31±88.35, 1234.6±82.21, 5.39±0.5, and 437.91±79.02, and the EAR were 0.07±0.005, 0.053±0.005, 0.001±0.0001, and 0.007±0.0007 for eye lens, parotid, breast, and ovary, respectively. The ERR of male for eye lens, parotid and testis were 91.49±9.71, 22.67±8.43, 0.17±0.04, and the EAR after 3 years were 0.49±0.05, 0.15±0.09 and 0.001±0.0009, respectively. In general, for thyroid only mean of ERR could be calculated that its value was 0.66 and 1.47 for males and females, respectively. The absorbed dose for ALL patients is presented in *Figure 1*. For leukemia children under the age of 16 years, peripheral doses varied depending on the field irradiation. During head radiotherapy, the highest amount of scattered radiation was absorbed by eye lens.

Table I: ERR and EAR models for estimating site-specific solid cancer risk and mortality (TABLE 12-2 BEIR VII page 272) (23)

Cancer site	ERR models				EAR models			
	β_M	β_F	ɤ	η	β_M	β_f	ɤ	η
Breast	-	0.51	0	-2	-	9.4	-0.51	3.5
Thyroid	0.53	1.05	-0.83	0	-	-	-	-
Ovary	-	0.38	-0.3	-1.4	-	1.2	-0.41	2.8
Prostate	0.12	-	-0.30	-1.4	0.11	-	-0.41	2.8
Other solid cancer	0.27	0.45	-0.3	-2.8	6.2	4.8	-0.41	2.8

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Table II: The mean values of absorbed dose are given as cGy of the radiation dose delivered to the tumor site according to the age and sex of the patients

Sex	Mean Age	Mean absorbed dose for eye lens	Mean absorbed dose for parotid	Mean absorbed dose for thyroid	Mean absorbed dose for breast	Mean absorbed dose for gonad
Female	4.4	1.8	1.65	1.47	0.1	1.58
SD	±0.3	±0.1	±0.61	±0.04	±0.03	±0.52
Male	11.8	2.7	0.76	0.6	-	0.005
SD	**±0.1**	**±0.6**	**±0.17**	**±0.05**	**-**	**±0.002**

Table III: Mean values of ERR and EAR for eye lens female/male, parotid, breast, prostate, and region overlying ovary

Risk / Organ	ERR 3 years	ERR 5 years	ERR 10 years	ERR 15 years	ERR 20 years	EAR 3 years	EAR 5 years	EAR 10 years	EAR 15 years	EAR 20 years
Eye lens Female/male	840.31±88.35/91.49±9.71	368.02±41.71/56.68±6.25	99.91±6.21/ 25.18±6.68	41.98±8.25/ 13.46±4.2	21.76±1.75 /8.08±0.48	0.07±0.005/ 0.49±0.05	0.14±0.09/ 0.73±0.07	0.45±0.02/ 1.65±0.07	1.06±0.06/ 3.08±0.29	2.04±0.26/ 5.29±0.37
Parotid Female/male	1234.6±82.21/22.67±8.43	454.46±91.10/14.42±1.11	109.7±8.21/ 6.39±0.3	43.97±2.85/ 3.42±0.1	22.23±1.63 /9.66±1.30	0.053±0.005/0.15±0.09	0.1±0.01/ 0.22±0.01	0.36±0.03/ 0.48±0.04	0.86±0.08/ 0.87±0.07	1.7±0.6/ 1.61±0.8
Breast Female	5.39±0.5	2.86±0.2	1.11±0.6	0.58±0.02	0.35±0.01	0.001±0.0001	0.004±0.002	0.023±0.009	0.06±0.002	0.14±0.05
Ovary	437.91±79.02	35.68±9.65	15.27±4.08	9.04±0.16	6.18±0.03	0.007±0.0007	0.03±0.008	0.2±0.04	0.6±0.03	1.61±0.01
Testis	0.17±0.04	0.11±0.08	0.04±0.003	0.02±0.001	0.01±0.001	0.001±0.0009	0.001±0.0001	0.003±0.0001	0.006±0.0001	0.01±0.001

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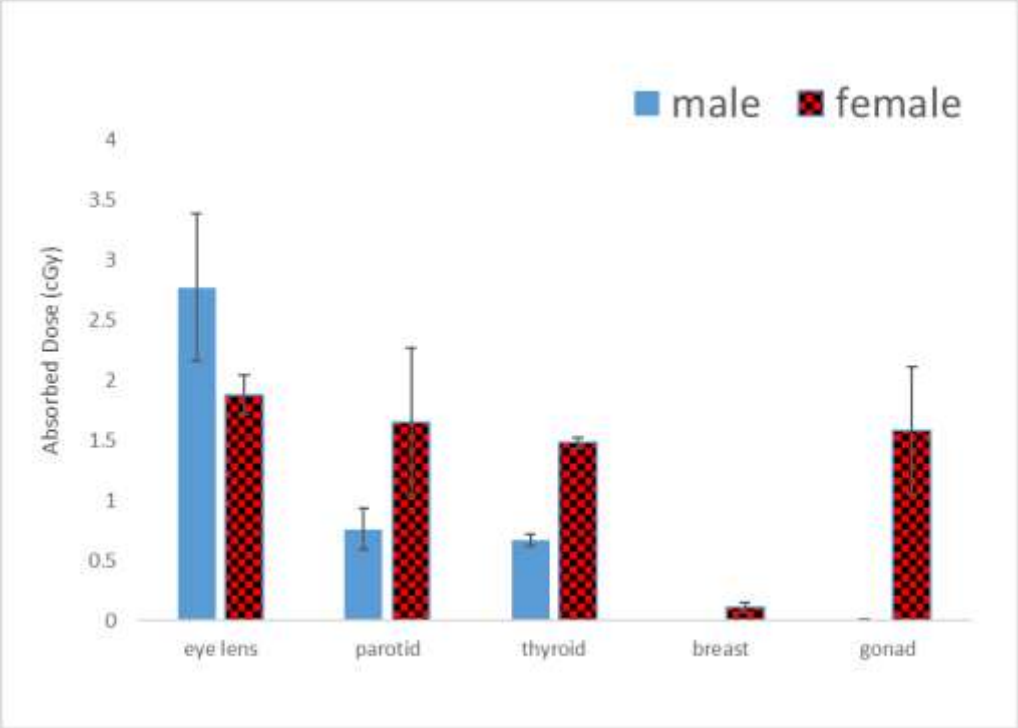

Figure 1. Absorbance dose for organs of leukemia patients from head radiotherapy

Discussion

During brain radiotherapy, this study measured sensitive organ dose in children with leukemia in Shahid Ramzanzadeh radiation therapy center in Yazd province. By increasing the distance of the irradiated field area, the scattered dose to out-of-field organ decreased. A dose of 18 Gy is given to pediatric patients during brain radiotherapy for a typical cancer. Thyroid dose was found to be 0.2-0.34 cGy based on the field size used and the distance between the field edge and thyroid gland. In the study by Mazonakis et al., thyroid doses of 8.0-194.0 cGy were estimated for pediatric patients irradiated with 50 Gy to the tumor. Due to the increased total dose, brain radiotherapy might lead to higher thyroid does. Kourinou et al. (14) conducted a study on a phantom, and the risk of thyroid cancer in women was reported to be 5.5 times higher than that of men. In this study, the amount of thyroid risk in females was 2.2 times higher than males.

This is due to the fact that the coefficient β in Equation 2 defined as the gender coefficient βF, was 1.05 for females and 0.53 for males. The reason for the higher coefficient value is that radiation sensitivity of the thyroid is higher in females than in males. The risk of breast cancer for women after WBRT was calculated, and measurements were made on phantoms equivalent to 5- and 10-year-old humans. In the primary radiation field, most of the second neoplasms are observed. In the study by Svahn-Tapper et al. (15), they stated that a modest increase in cancer risk might be caused by organ doses below 1 Gy . Within 5 cm of the treatment fields 22% of subsequent neoplasms were reported in the study by Diallo et al. (16). Regarding the estimation of secondary cancer risk, the results of previous studies had been quite variable

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depending on the assumed target localization, dose distribution and secondary cancer model (for reviews, see (17, 18)). Our calculated absorbed dose are 1.4 and 0.6 cGy for female and male thyroid in 3DCRT, this is in good agreement with Ahmadi et al. (19). The findings show that although there is a small risk of inducing secondary cancer at locations far from the irradiated area, it is not insignificant. A study by Haddad (20) found that the mean scrotal radiation dose, measured by TLD, for 33 patients was 3.77 Gy, or 7.5% of the total dose, which is higher than the dose measured in the present study for the testis. It can be explained by the fact that in the Haddad study, the total dose received was higher (50 Gy) than in the present study (18 Gy). According to limited studies of pediatrics radiotherapy, a comparison had been done with adults. In our previous and related research on out-of-field dose measurement and estimation of radiation induced secondary cancer risk of thyroid and breast from head radiotherapy the mean values of thyroid cancer risk in men and women were 0.418±0.509 and 0.274±0.306, respectively. In the current study the higher mean dose was noticed 0.6±0.05 and 1.47±0.04 for men and women. The higher mean dose values presented in our study were found for sensitivity of children's organs compared to adults (21). Guibout C et al. (22) measured the relative risk of breast cancer after childhood Hodgkin's disease treatment. Their estimation of the excess relative risk of breast was 7.0. Our results cannot be compared with these reports because of the different irradiation position but both studies clearly reveal that the risk of secondary cancer induction may be due not only to a higher radiation dose to the nearest organs, but also to a specific susceptibility.

At small distances from the field edge, higher cancer risk values were reported. Parotid, ovary, and eye lens had the highest second cancer risk in the present study, respectively. Parotid and eye lens were the most probable determinants due to their proximity to the field and ovary was at high risk due to the low mean age of the girls in this study and the sensitivity of this organ.

According to calculated data, the secondary cancer risk is associated to sex, age, and distance from field edge.

Conclusion

In the current study, the scattered dose and the second cancer risk to the eye lens, parotid, thyroid, breast, and gonad from the treatment of leukemia were measured. The eye lens, parotid, thyroid, and breast increased the risk of inducing secondary cancer as a result of close distance to the treatment fields. Ovary is a sensitive organ against irradiation and age of patient is an important factor. The interpretation and values of EAR and ERR parameters are different although they explain the same thing, and generally, ERR decreases with increasing age after irradiation, while EAR increases significantly for both sexes after being exposed to radiation.

For survivors of childhood leukemia, conducting a long term follow-up about the second cancer development might be of vital importance.

Ethical considerations

The national ethics committee confirmed the study with the ethical code of "IR.SSU.MEDICINE.REC.1400.315". We did not perform any intervention in normal diagnostic or therapeutic procedures, and we just used the exposure parameters and images of the patients in this study. Therefore, gathering the consent forms was waived due to the prospective nature of this study.

Funding Source

This work was supported by Shahid Sadoughi University of Medical Sciences

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[DOI: 10.18502/ijpho.v13i4.13768]

and Health Services, under grant No. 14282. The funding source had no role in the design of the study and would not have also any role during its execution, analyses, interpretation of the data, or decision to submit the results.

Conflict of interest

The authors declare no competing interest.

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