Original

Out-of-Field Dose Measurement by TLD Dosimetry and Estimation of Radiation-Induced Secondary Cancer Risk of Thyroid and Breast from Head Radiotherapy

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ABSTRACT

Background: Radiation therapy, the most common form of cancer treatment, can result in late complications, such as secondary breast and thyroid cancers.

Objective: This study aimed to evaluate the risk of secondary cancers using two radiobiological models of Excess Absolute Risk (EAR) and Excess Relative Risk (ERR) in patients with brain cancer undergoing radiotherapy for improved survival rates of cancer patients.

Material and Methods: In this expository cross-sectional study, 45 patients under the age of 40 years underwent Whole Brain Radiotherapy (WBRT) using a compact accelerator in Shahid Ramezanzadeh Hospital, Yazd, Iran. Out-of-field organ dose measurement was performed using a Thermoluminescent Dosimeter (TLD) to determine the dose to thyroid and breast tissues. The risk of secondary cancers in these organs was calculated 3, 5, 10, 15, and 20 years after radiation therapy.

Results: The mean values of thyroid cancer risk in men and women were 0.418±0.509 and 0.274±0.306, respectively. ERR values of breast cancer in 3-, 5-, 10-, 15-, and 20-year women undergoing radiation therapy were 1.084±2.938, 0.594±1.407, 0.248±0.497, 0.138±0.248, and 0.091±0.148, respectively. EAR values of breast cancer in 3-, 5-, 10-, 15-, and 20-year women following radiation therapy were 0.064±0.060, 0.077±0.071, 0.119±0.100, 0.178±0.248, and 0.259±0.178, respectively.

Conclusion: After irradiation, the risk of secondary cancer is affected by factors, such as the patient's age and gender. The secondary thyroid cancer is higher than that of other organs, such as the breast, in the patients undergoing WBRT.

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Keywords
Second Cancer Risk; Out-of-Field Dose; Dosimetry; Radiotherapy; Breast; Thyroid

Introduction

Secondary-cancer risk of radiation is considered a late impact of primary cancer radiotherapy [1-3] since radiation treatment can be also a carcinogens [4, 5]. Childhood cancer treatment has recently improved, leading to the survival of nearly 75 percent of childhood cancer patients in the United States of America (USA) [6].

Survivors of pediatric malignancies, who received radiation therapy to the head, are at expanded risk of subsequent primary thyroid and subsequent breast cancer due to dose scatter from radiation therapy into the patient's head to field organs [7].

The chance of auxiliary cancer in illuminated tissue can be estimated using absorbed dosimetry results [8]. Out-of-field photon risks are associated with organs distal to the target volume. The Committee on the Biological Effects of Ionizing Radiation (BEIR) VII developed a risk model to estimate the risk as a function of exposure, age, sex, and organs based on information from Japanese nuclear bomb survivors [9]. Excess Relative Risk (ERR) and Excess Absolute Risk (EAR) are expressed as a value relative to background risk and the difference in absolute risk between exposed and control populations, respectively [10, 11].

Out-of-field doses are measured in tissue equivalent humanoid phantoms using open square fields at a gantry angle of 0°, which cannot simulate the real conditions of head and neck radiotherapy [12] due to the grading of the scattered radiation dosage to field organs, such as the thyroid and breast due to head illumination. The current study aimed to assess the risk of creating auxiliary cancers in male and female leukemia and brain tumor patients, aged 1 to 40 years. Accordingly, the dose was measured out-of-field by placing a Thermoluminescence Dosimeter (TLD) in the tissue.

Material and Methods

This expository cross-sectional study included 45 patients, aged 1 to 40 years referred to Ramazanzade Clinic (Yazd-Iran). These patients were exposed to a 6-MV photon from a COMPACT straight quickening agent (Elekta Quickening agent, compact demonstrate, made in China beneath UK permit) in three groups, including under 16 years with an average fractionated dose of 1.8 Gy for a total treatment dose of 18 Gy, 16-30 years, and over 30 years of age by a total dose of 30 Gy in 10 fractions. The second primary cancers were classified as breast and thyroid cancers. A total of 60 lithium fluoride TLDs (TLD-200) were utilized for organ dose measurements utilizing LiF, Mg, Cu, and P (GR-200) with a 1.8-millimeter diameter and a 9.3-millimeter thickness [13]. Readouts were recorded over the 5~15-second interim from 135˚C to 240˚C. GR-200 TL locator set to a warming rate of 6~20 ˚C/sec. The TLD was calibrated using a 6-MV photon pillar with the same basic adjustment components. Dosimeter sensitivity was compared with the mean sensitivity of the population through the ECC factor. In the second step, TLDs were divided into 7 groups (with 3 TLDs in the badge), exposed for 1, 2, 4, 8, 16, 32, and 64 cGy, respectively, and one group as a control. The crystals were placed at the surface thyroid and breast. Doses were estimated based on Equation 1, as follows:

$$Dose = (TL_i) \, . \, ECC_i \, . \, C_F \qquad \text{(Eq.1)}$$

where TL is the number of readings read by the device (nC), CF shows the calibration coefficient of the reader, and the ECC indicates the correction factor for each TLD crystal [14].

Secondary cancer risk estimation

Different models were utilized to measure the hazard of auxiliary cancers in radiotherapy [15]. Tumor dosage for headlight is 18 and 30 Gy in children and adults, respectively. Organ doses per division were duplicated by particular chance components to measure risk in each section [16]. The National Institutes Committee (NIC) on BEIR VII has provided sex, age, and organ-specific risk components to survey the EAR and ERR of radiation-induced cancer.

$$\text{ERR (D.s.e.a)} = \text{D. } \beta\text{s.exp}(\gamma\text{e*}). \left(\frac{a}{60}\right)^{\eta} \qquad \text{(Eq.2)}$$

$$\text{EAR (D.s.e.a)} = \text{D. } \beta\text{s.exp}(\gamma\text{e*}). \left(\frac{a}{60}\right)^{\eta} \qquad \text{(Eq.3)}$$

where D is the dose in Sv. βs, γ, and η are organ-specific parameters, which are based on patients' gender. a and e are the attained age (years) and exposure age (years). e* is 30 e [9]. The panel recommended ERR and EAR models for site-specific cancer incidence, and Table 1 showed mortality.

Table 1: Committee's preferred Excess Relative Risk (ERR) and Excess Absolute Risk (EAR) models for estimating site-specific solid cancer incidence and mortality

Cancer site	ERR models				EAR models			
	β_M	β_F	ɣ	η	β_M	β_F	ɣ	η
Breast	-	0.051	0	-2	-	9.4	-0.51	3.5
Thyroid	0.53	1.05	-0.083	0	-	-	-	-

β_M, β_F, γ, and η are particular parameters for distinctive organs for each sex
EAR: Excess Absolute Risk, ERR: Excess Relative Risk
ERR and EAR per 104 PY-Sv for exposure at age 30+ and attained age 60

Results

Radiation-induced extra-field organ doses were calculated for 45 patients, who underwent Whole Brain Radiotherapy (WBRT) for children and adults. Tables 2 and 3 show the risk of thyroid and breast secondary cancer for 3, 5, 10, 15, and 20 years after treatment. The patients under the age of 16 years, received a total of 18 Gy in 10 fractions, and the patients over the age of 16 years were divided into two groups, including 16-30 years and 30-40 years, who received 30 Gy in 10 fractions and divided into two groups according to the coefficient (e*) in calculating the risk of cancer. Thyroid measurements were significantly different by sex in each age group (P-value≥0.001). This rate for females was 1.5 times higher than for males due to the sensitivity of the thyroid, showing female children are more at risk of radiation. According to Tables 2 and 3, the mean risk of secondary thyroid cancer after treatment was calculated 0.418 and 0.274 for females and males, respectively (P-values<0.05 were considered significant).

Figure 1 reveals the mean dose received by the thyroid gland based on gender in the age group of adults and children. The highest number of readings (nc) and entrance dose level (cGy) was observed for females. Figure 2 compares the mean breast dose received by children aged under 16 years, females 16-30 years, and females over 30 years. Female children aged under 16 years of age received a higher dose. According to the higher dose received, the risk of secondary breast cancer is higher at young ages.

Figure 3 compares thyroid ERR in females and males based on patient age after irradiation. Table 2 shows women are at the highest risk of secondary thyroid cancer, due to the greater susceptibility of this organ in women. Figure 4 shows the ERR for breast, and the ERR decreased by increasing age after radiation exposure.

Figure 5 shows increasing EAR by incremental age after radiation. The received dose of thyroid is significantly different in females and males, and the mean received dose in the breast of females aged under 30 years and over 30 years (P-values<0.001).

Discussion

In the current study, the estimation of the risk of secondary cancer in two organs is an important result. In addition, this study provides the first-ever estimation of cancer risk using the BEIR VII model and extracts two types of risk metrics, ERR and EAR, for two distinct age groups: children and adults. In 2017, Ahmadi et al. [17] reported the mean absorbed dose of thyroid due to WBRT in women and men

Table 2: Risk of thyroid and breast cancer for females

Number	Age	ERR of thyroid	ERR 3 years of breast	ERR 5 years of breast	ERR 10 years of breast	ERR 15 years of breast	ERR 20 years of breast	EAR 3 years of breast	EAR 5 years of breast	EAR 10 years of breast	EAR 15 years of breast	EAR 20 years of breast
1	1	1.849	13.823	6.143	1.827	0.863	0.501	0.0003	0.0011	0.0113	0.0441	0.1143
2	4	1.505	5.523	3.341	1.601	0.835	0.511	0.0013	0.0055	0.0304	0.887	0.2009
3	4	1.339	4.116	2.490	1.028	0.558	0.350	0.0010	0.0041	0.0227	0.0661	0.1497
4	6	1.276	2.664	1.784	0.843	0.489	0.319	0.0044	0.0088	0.0353	0.0928	0.1967
5	7	1.103	0.840	0.583	0.290	0.173	0.115	0.0025	0.0047	0.0163	0.0408	0.0835
MEAN	4.4	1.414	5.393	2.868	1.118	0.584	0.359	0.002	0.004	0.023	0.066	0.149
STD	±2.3	±0.282	±5.021	±2.091	±0.613	±0.282	±0.161	±0.001	±0.002	±0.009	±0.024	±0.051
6	23	0.169	0.084	0.073	0.052	0.039	0.030	0.0149	0.0196	0.0349	0.0575	0.0886
7	28	0.092	0.063	0.056	0.042	0.033	0.026	0.0084	0.0106	0.0175	0.020	0.0395
8	28	0.097	0.059	0.052	0.039	0.030	0.024	0.0071	0.0098	0.0163	0.0251	0.0366
9	29	0.092	0.043	0.038	0.028	0.022	0.018	0.0029	0.0038	0.0063	0.0097	0.0142
MEAN	27	0.113	0.062	0.054	0.040	0.031	0.025	0.008	0.011	0.018	0.029	0.044
STD	±2.34	0.032	±0.014	±0.012	±0.008	±0.006	±0.004	±0.004	±0.005	±0.010	±0.017	±0.027
10	32	0.233	0.054	0.048	0.037	0.030	0.024	0.0516	0.0629	0.0978	0.1454	0.2073
11	32	0.215	0.060	0.053	0.041	0.033	0.027	0.0570	0.0694	0.1079	0.1604	0.2288
12	33	0.219	0.065	0.059	0.046	0.037	0.030	0.0731	0.0885	0.1363	0.2003	0.2835
13	33	0.215	0.056	0.050	0.039	0.031	0.025	0.0624	0.0755	0.1163	0.1709	0.2420
14	33	0.256	0.055	0.049	0.038	0.031	0.025	0.0614	0.0743	0.1144	0.1681	0.2380
15	34	0.216	0.032	0.028	0.022	0.018	0.015	0.0416	0.0500	0.0763	0.1114	0.1564
16	34	0.199	0.062	0.056	0.044	0.035	0.029	0.0807	0.0970	0.1479	0.2160	0.3034
17	34	0.194	0.085	0.077	0.060	0.048	0.040	0.1108	0.1331	0.2030	0.2964	0.4163
18	34	0.194	0.088	0.080	0.062	0.050	0.041	0.1150	0.1381	0.2107	0.3076	0.4320
19	34	0.171	0.066	0.059	0.046	0.037	0.031	0.0858	0.1031	0.1572	0.2295	0.3224
20	35	0.185	0.033	0.030	0.023	0.019	0.016	0.0503	0.0600	0.0909	0.1315	0.1835
21	36	0.184	0.043	0.039	0.031	0.025	0.020	0.0742	0.0884	0.1324	0.1902	0.2639
22	38	0.194	0.044	0.040	0.032	0.026	0.022	0.1008	0.1192	0.1751	0.2480	0.3404
23	38	0.144	0.055	0.050	0.040	0.033	0.027	0.1260	0.1490	0.2190	0.3101	0.4256
24	38	0.165	0.060	0.055	0.044	0.036	0.030	0.1380	0.1632	0.2398	0.3395	0.4660
25	38	0.194	0.063	0.057	0.046	0.038	0.031	0.1446	0.1710	0.2513	0.3559	0.4884
26	40	0.172	0.054	0.050	0.040	0.033	0.028	0.2574	0.3021	0.4371	0.6101	0.8278
MEAN	35.05	0.197	0.057	0.052	0.041	0.033	0.028	0.095	0.114	0.171	0.246	0.342
STD	±2.46	±0.027	±0.015	±0.013	±0.010	±0.008	±0.007	±0.052	±0.061	±0.087	±0.120	±0.161

EAR: Excess Absolute Risk, ERR: Excess Relative Risk, STD: Standard Deviation

Table 3: Risk of thyroid cancer for males

Number	Age	ERR of thyroid
1	8	0.932
2	10	0.821
3	10	0.794
4	12	0.654
5	15	0.450
6	16	0.364
7	16	0.340
MEAN	12.42	0.622
STD	±3.25	±0.238
8	32	0.100
9	37	0.099
10	37	0.088
11	37	0.079
12	38	0.107
13	38	0.060
14	39	0.080
15	39	0.052
16	39	0.052
17	39	0.050
18	39	0.047
19	40	0.041
MEAN	37.83	0.071
STD	±2.08	±0.023

ERR: Excess Relative Risk, STD: Standard Deviation

as 1.976±0.611 cGy and 2.213±1.041 cGy, respectively, in Isfahan, Iran, which is almost ten times more than Yazd city.

In Inskip (2001)' study on the risk of thyroid cancer after radiation therapy in children, thyroid cancer is two to three times more common in females than in males [18]. Oglivy-Stuart et al. showed that 29.6% of patients developed secondary thyroid cancer between 2.6 and 5.1 years after WBRT [19]. Increasing age after WBRT leads to a decrease in the risk of secondary cancer in patients.

The women's risk of thyroid cancer is 5.5 times higher than that of men [7], and the risk of breast cancer was observed in women after WBRT, in which measurements were taken in phantoms corresponding to humans aged 5 and 10 years. In a study by Zabihzadeh et al. (2015) on phantom, the secondary thyroid risk for secondary thyroid cancer was 1.87 in women and 1.72 in men [20]. In this study, thyroid risk was 1.52 times higher in women than in men because factor β, defined as the sex factor βF in Equations 2 and 3, was 1.05 for females and 0.53 for males. This higher coefficient of thyroid radiosensitivity can be due to higher radiation sensitivity of the thyroid in females than in men. Kourinou's study, conducted on brain tumors, leukemia, and cervical Hodgkin tumors in 5- and 10-year-old phantoms, estimated extra-field doses to the

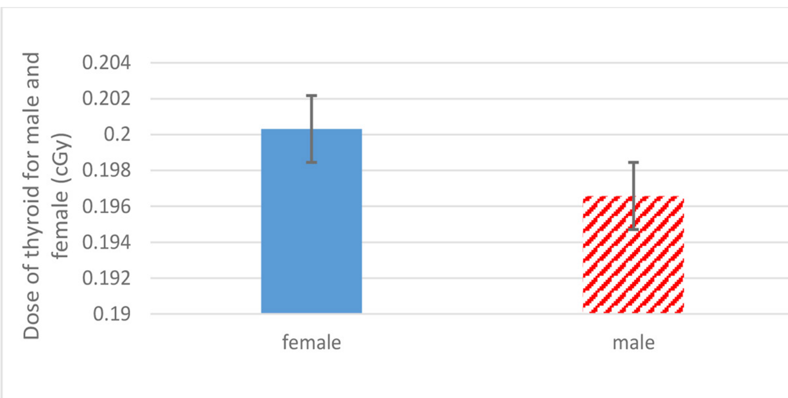

Figure 1: Out-of-field dose of thyroid for males (diagonal column) and females (solid column)

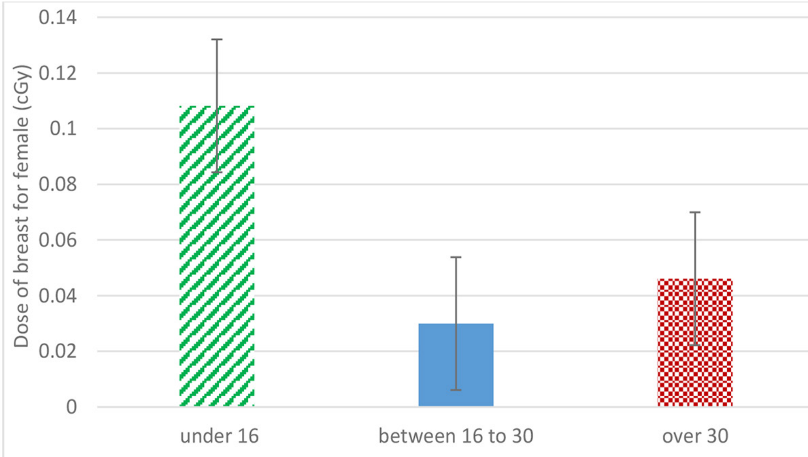

Figure 2: Out-of-field dose of breast for females aged under 16 years (diagonal column), between 16 to 30 years (solid column), and over 30 years (dotted column)

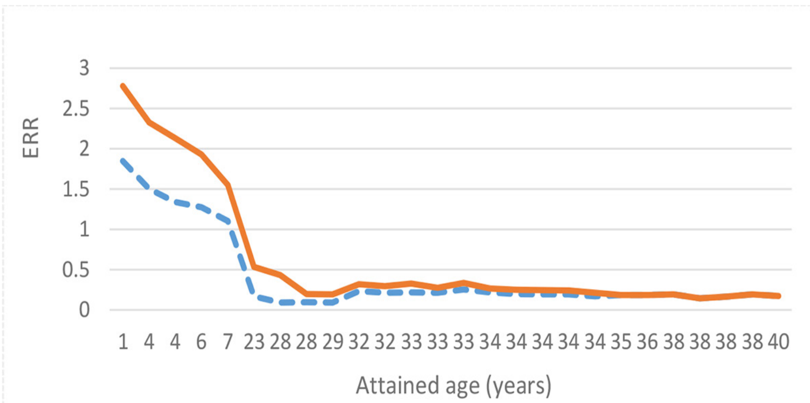

Figure 3: Excess Relative Risk (ERR) patterns in radiation induced risks of thyroid for males (dashed line) and females (solid line)

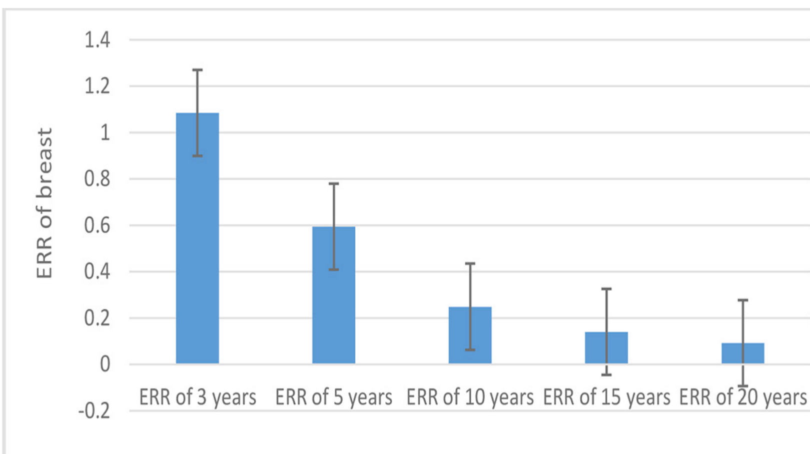

Figure 4: Excess Relative Risk (ERR) of breast for 3, 5, 10, 15, and 20 years after treatment

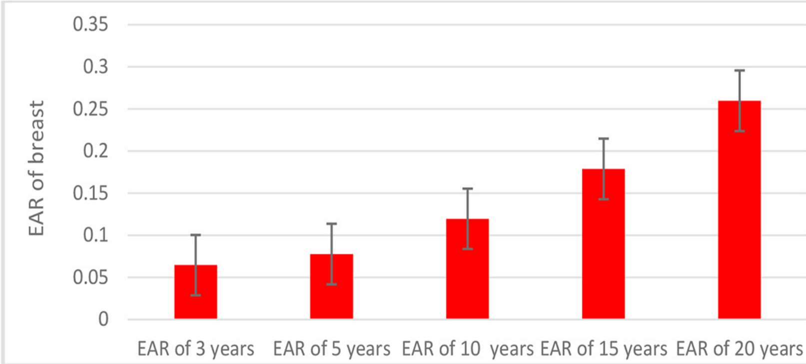

Figure 5: Excess Absolute Risk (EAR): Excess Absolute Risk of the breast for 3, 5, 10, 15, and 20 years after treatment

thyroid, lungs, breast, and several other organs. Further, organs closest to the treatment field presented the highest risk due to their proximity to the treatment field. According to this study, no comparable studies were in the area of measuring secondary breast cancer risk in WBRT.

Conclusion

In the present study, TLDs were employed to assess the dose received by the thyroid and breast in 45 patients treated with a compact accelerator. The dose reaching these organs is a result of scattered radiation generated within the patient's body, radiation leakage from the device head, and scattered radiation produced by the machine's collimator. The extent of stray radiation and leakage from the device head and collimator depends on the specific treatment device and collimator design. According to the results, the absorbed dose of secondary radiation in the thyroid and breast remains below the permissible thresholds for these organs during WBRT. Despite the same concept of ERR and EAR, there is a difference between values and interpretations of the associated parameters. ERR decreases with age following irradiation, while EAR increases significantly in both genders, and EAR increases with age at the time of treatment, whereas ERR decreases. Therefore, increasing the distance between the organs and the treatment radiation field led to a decrease in the level of scattered radiation.

Authors' Contribution

MH. Zare conceived the original idea. Sh. Rahbar Yazdi and MH. Zare carried out the experiment. Sh. Rahbar Yazdi wrote the manuscript and fabricated the sample. Sh. Rahbar Yazdi supervised the project, designed the model and the computational framework and analyzed the data. All the authors read, modified, and approved the final version of the manuscript.

Ethical Approval

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.

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Conflict of Interest

None

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