CASE REPORTS

Secondary Cancer Risk of Radiotherapy and Imaging Examination for Two Different Malignancies in One Patient

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Abstract

Purpose: Radiotherapy (RT), which is considered one of the critical treatments for cancer patients is also known as adjuvant therapy and palliative care, and can be attempted alone or concurrent with chemotherapy. Although RT reduces the risk of recurrence, the scattered dose may enhance the risk of secondary cancer induction; this is raising some challenges in clinical practice. To the best of our knowledge, few studies to date have assessed such effects of brain cancer adjuvant radiotherapy.

Materials and Methods: We estimated the RT-induced risk of secondary cancer for a 45-year-old patient who had undergone radiotherapy of the head and pelvis with a 6 MV photon beam in 15 and 10 sessions, respectively. The absorbed dose by the thyroid, breast, eye lenses, region overlying ovaries, and parotids was measured using Thermoluminescent Dosimeters (TLD). Since the patient was scanned before radiotherapy, it was decided to calculate their risk as well. To evaluate the cancer risk, radiobiological models for Excess Absolute Risk (EAR), as well as Excess Relative Risk (ERR) published by the Committee on the Biological Effects of Ionizing Radiation (BEIR) in report VII, were implemented. This study thus aimed to estimate the Risk of Exposure-Induced Death (REID) and assess the radiation dose delivered to patients from Computed Tomography (CT) scans and common diagnostic nuclear medicine examinations.

Results: The mean risk of secondary cancer for sensitive organs was calculated 3 years after radiotherapy. The highest estimated ERR was related to the region overlying right and left ovaries for pelvic radiotherapy (47.82) and (51.17), and the next highest EAR followed by right and left eye lenses for brain radiotherapy (18.09) and (15.43), respectively. In addition, other cancers arising from CT scans had the highest REID values for solid cancer (0.0015) and bone scans revealed the highest REID values for other cancers (0.00121).

Conclusion: Calculating the corresponding risks of RT is of great significance for the patients in procedural change. Choosing proper field sizes and adapted techniques to avoid excessive doses to healthy organs can thus be a great assistance in this regard.

Keywords: Radiotherapy; Cancer Risk; Thermoluminescent Dosimeters; Organ Dose.

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Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

There is credible scientific evidence for a 2-year latent period for potential late side effects of radiation therapy [1]. The survival rate following cancer can significantly increase so that improving methodology for ionizing radiation is regarded as an important component for curing cancer [2]. Therapeutic exposure may always expose the organs-at-risk to ionizing radiation even if they are located outside the collimated field [3]. The risk of secondary cancers associated with various image-acquisition techniques, including Computed Tomography (CT) scan and nuclear medicine has become increasingly important [4]. The Committee on Biological Effects of Ionizing Radiation (BEIR) VII has promoted more specific risk models based on exposure, organs, sex, and attained age to evaluate low-dose exposures of several organs. Since the doses absorbed by out-of-field organs are relatively low, the BEIR VII model seems reasonable for risk estimation [5]. The committee provides two parameters to present the risks: Excess Relative Risk (ERR) defined as the rate of disease in an exposed population divided by the rate of disease in an unexposed population minus 1.0, and Excess Absolute Risk (EAR) described as the rate of disease in an exposed population minus the rate of disease in an unexposed population [6].

Radiation risk after exposure is dominated by distance from high dose treatment volume. The relative risk of second cancer appears to be different for various organs. Several parameters like sex, genetics, lifestyle, organ, and exposure account for the risk of secondary cancer. Furthermore, it is recommended to substitute the effective dose for the Risk of Exposure-Induced Death (REID).

This study aimed to measure the scattered dose to out-of-field organs from the head and pelvic irradiations and to estimate the risk of developing second cancer of the eye lens, region overlying the ovaries, breasts, thyroid, and parotids for this patient. In this study, the risk of all stages that a patient is exposed to radiation, including CT scan, nuclear medicine, and radiotherapy was calculated. Since a cancerous patient is frequently exposed to radiation during the process of diagnosis and treatment, the risk of secondary cancer, which is one of the consequences was measured. Based on our knowledge, there is not any study that has been done in Iran or the world in which the risk of diagnosis and therapy is calculated together.

1.1. Case Presentation

A 45-year-old female with chief complaints of a small lump behind her head, as well as seizure, vertigo, dizziness, and pain in the pelvic area was referred to Ramezanzade radiotherapy center, Yazd in November 2021. On December 21st, 2021, following more investigations by nuclear medicine imaging, CT scan, and MRI, the patient was diagnosed with two lesions in both pelvic and brain regions.

Tumors of the pelvis may induce pain and significant loss of function and weight-bearing capacity.

Not using any contrast medium, the MRI revealed the presence of an extra-axial epidural mass lesion of 25 * 10 mm in size, located at the left frontal lobe and associated with signal changes due to underlying bone and diffuse abnormal bone marrow at pelvic bone and bilateral femur. The result of a whole-body bone scan through intravenous injection of 20 mCi Technetium 99m-methyl diphosphonate (^{99m}Tc-MDP) in anterior and posterior projections exhibited multiple high metabolic bone lesions in the skull, ribs, spine, left humerus, left iliac and left femur (Figure 1). As determined by pathology of breast, the exact origin of the disease was shown to be the high grade triple negative ductal carcioma with inconspicuous tubule formation and marked nuclear pleomorphism (Figure 2).

No surgical modality was used, the patient started to receive radiotherapy for a total dose of 30 Gray in 10 fractions individually in pelvis and 37.5 Gray in 15 fractions in head regions by Linear Accelerator Medical (COMPACT) with 6 MV photon beam in Ramezanzadeh

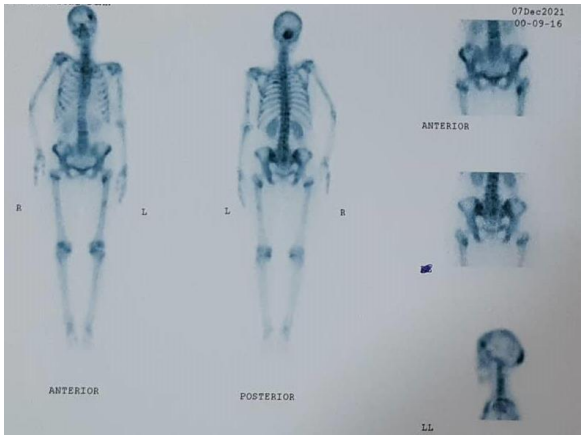

Figure 1. Image of whole body bone scan with 20mCi ^{99m}Tc-MDP in nuclear medicine. Images exhibited multiple high metabolic bone lesions in the skull, ribs, spine, left humerus, left iliac, and left femur

radiotherapy center, Yazd. Typical treatments delivered an average dose to the tumor of 15 Gy for pelvic from AP and PA field with the patient's position being supine, as well as 18.75 Gy for head from right lateral and left lateral field alone (Figure 3). The patient was irradiated through a 15 × 22 cm^2 radiation field with an Source-to-Surface Distance (SSD) of 92.9 cm for whole brain treatment and 15 × 30.6 cm^2 radiation field using an SSD of 91.9 cm for pelvic treatment. The per-fraction tumor doses during the whole brain and pelvic radiotherapy were 250 cGy and 300 cGy, respectively.

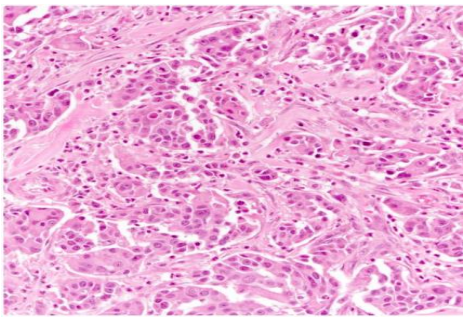

Figure 2. Pathologic images of breast. Microscopy showed high-grade triple negative ductal carcinoma (20 × magnifications).

(a)

(b)

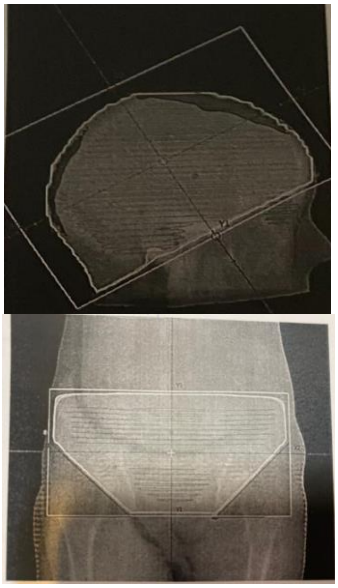

Figure 3. Field arrangement of RT. a) Field design of the brain. b) Field design of the pelvis

2. Materials and Methods

2.1. Measurement

This is a 45-year-old Iranian female patient. She started to notice a small lump behind her head then she proceeded to have a CT scan, Magnetic Resonance Imaging (MRI), and nuclear medicine which confirmed a suspicious abnormality. This report was about infiltrative carcinoma metastasis in brain and bone sites. She was treated with radiotherapy for a total dose of 30 Gray in 10 fractions in pelvis and 37.5 Gray in 15 fractions in the head region. In this study, Lithium fluoride Thermoluminescent Dosimeters (TLD) (GR-200) with a diameter of 1.8 mm and a thickness of 9.3 mm were used for organ dose measurements. GR-200 is lithium fluoride with magnesium, copper, and phosphorus impurities (LiF: Mg, Cu, P) [7]. It benefits from a very low detection threshold and the equivalence to tissue.

The TLs were read by a TLD reader (TLD 7103 reader, Iran), and the operating conditions for reading this dosimeter. The heat rate was 6~20 ˚C /sec, preheating 135˚C for 5~15 sec, the readout from 135 ˚C to 240 ˚C and annealing at 240 ˚C for 10 to 20 seconds.

To calibrate the TLs, a farmer ionizing chamber (FC65-G, Scanditronix, Sweden) was deployed. The 16 Slab phantoms, each with 1 mm in thickness, were placed in the chamber to satisfy the electronic equilibrium and the absorbed dose was measured through the approach proposed by IAEA TRS 398. Next, the farmer chamber was replaced by TLs and the calibration factors were derived [8] (Equation 1):

$$Dose = (TL_i).ECC_i \,.\, C_F.\frac{RL_0}{RL_i} \qquad (1)$$

In this regard, TL denotes the number of readings read by the device, C_F, the calibration coefficient of the reader, ECC correction factor was for each TLD crystal. RL_i is the Reference light of the device during the first reading of TLD and RL_0 is the average reference light of the device for all readings.

Five organs including the thyroid, the region overlying the ovary, parotid, breast, and eye lens were chosen for direct dose measurement using TLD. In this regard, three TLDs were placed in individual thin-walled plastic bags and taped in pairs to the eye lenses, thyroid, parotid, breast, and regions overlying the ovary.

2.2. Second Cancer Risk Estimation for MV (Megavoltage)

In this study, we estimated the risk of thyroid, eye lens, parotid, and breast secondary cancer-induced RT from the proposed method in the BEIR VII report. For estimating the risk, a dose of the ovary is equated to the regions

overlying the ovary. Reported values, according to the relationship, are functions of age at the time of treatment, dose, gender, and attained age of risk (Equation 2).

$$ERR\ or\ EAR\ (D.s.e.a) = D.\beta s.exp(\gamma e*).(\frac{a}{60})^{\eta} \quad (2)$$

In the above formula, D stands for dose in terms of Sv, e for age at the time of treatment, e* for e < 30 equal to (e - 30) / 10 and zero for e > 30, the parameters η and γ quantify the dependence of the ERR or EAR on e and a, η and β_s specified for each organ.

The committee's preferred ERR and EAR models for site-specific cancer incidence and mortality are set out in Table 1.

Table 1. Committee's Preferred ERR and EAR Models for Estimating Site-Specific Solid Cancer Incidence and Mortality

Cancer Site	ERR Models			EAR Models		
	B_f	γ	η	B_f	γ	η
Breast	0.52	0	-2	9.4	-0.51	3.5
Ovary	0.38	-0.3	-1.4	0.7	-0.41	2.8
Thyroid	1.05	-0.83	0	-	-	-
Other solid cancer	0.45	-0.3	-2.8	4.8	-0.41	6

2.3. Second Cancer Risk Estimation for KV (Kilovoltage)

Since we used CT scan and gamma camera to diagnose the disease, their risk calculation was also on the agenda. International Commission on Radiological Protection (ICRP) in publication 128 [9, 10] presented conversion coefficients for estimating individual organ doses and effective doses based on ICRP 60 tissue weighting factors due to the administration of radiopharmaceuticals [11, 12]. Effective doses were measured according to organ doses and weighting factors recommended in ICRP 103. The CT/SPECT scan effective dose and risk were calculated through Impact Dose software (v.2.2, CT Imaging GmbH, Erlangen, Germany) and the personal computer-based Monte Carlo (PCXMC) software (v. 2, STUK, Helsinki, Finland).

PCXMC software was also used to estimate the REID on the BEIR VII report. PCXMC measures the risks based on patient age and gender [13].

3. Results

The absorbed dose of several organs was estimated in a 45-year-old patient following the radiotherapy of the brain and pelvic cancer. Estimating the risk of such cancers is examined in the BEIR VII report. Secondary cancer risk due to radiotherapy for patients with various cancers differs with age, location of primary cancer, and dose of radiation received by the organs. Tables 2 and 3 reveal the risk of second cancer from out-of-field photons for the thyroid, parotid, breast, and ovary. As is shown, the scattered doses decreased by the distance from the field edge. The ERR and EAR for 3 years after radiotherapy are presented in Figure 4 for the brain and pelvic radiotherapy, respectively.

Table 2. Estimates of excess relative risk and excess absolute risk of second cancer for brain radiotherapy

Organ at Risk	ERR for 3 years	EAR for 3 years
Right eye lens	10.95	18.09
Left eye lens	13.95	15.43
Right parotid	5.52	9.11
Left parotid	8.28	15.70
Thyroid	2.58	-
Right breast	0.87	2.58
Left breast	1.11	3.28
Right ovary	0.021	0.009
Left ovary	0.027	0.012

Table 3. Estimates of excess relative risk and excess absolute risk of second cancer for pelvic radiotherapy

Organ at Risk	ERR for 3 years	EAR for 3 years
Right eye lens	0.34	0.56
Left eye lens	0.35	0.59
Right parotid	0.42	0.69
Left parotid	0.31	0.52
Thyroid	0.51	-
Right breast	0.48	1.41
Left breast	0.61	1.8
Right ovary	47.82	21.7
Left ovary	51.17	23.26

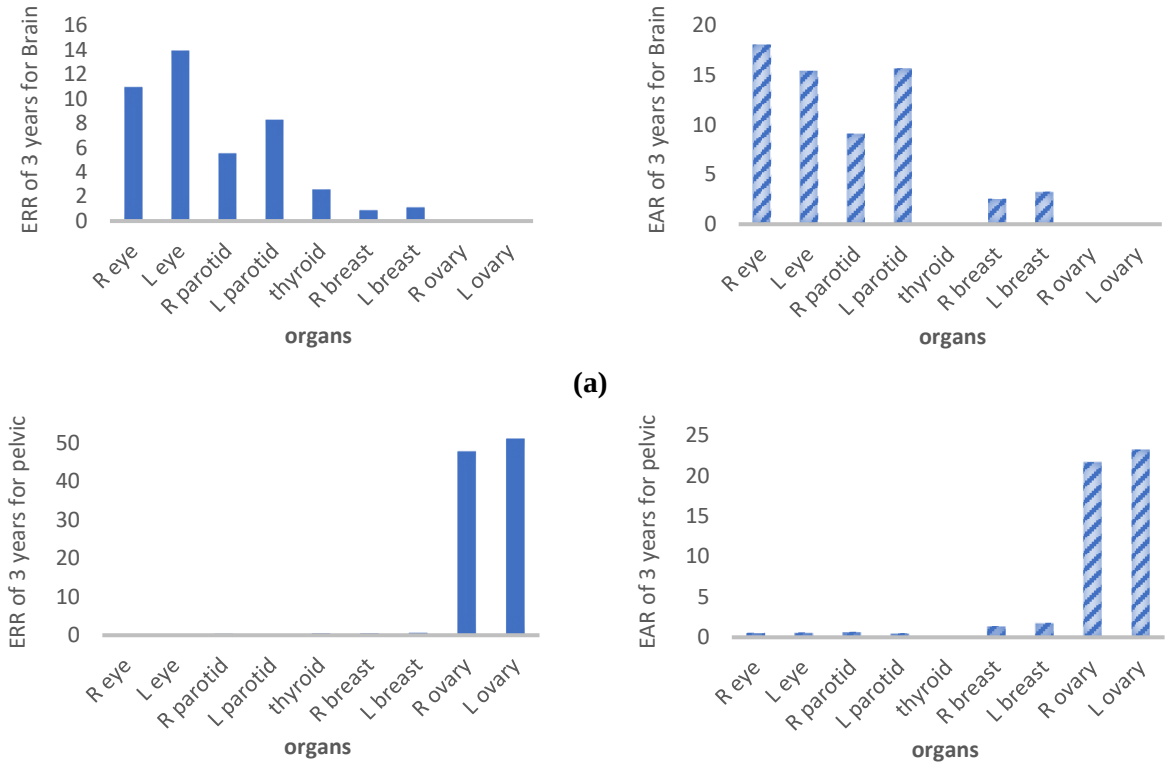

Figure 4. Excess Relative Risk (ERR) and Excess Relative Risk (EAR) per fraction for out-of-field organs of a 3-year-old patient from radiotherapy for (a) brain radiotherapy, (b) pelvic radiotherapy

Acquisition parameters include Kilovoltage peak (KVp), Milliampere-seconds (mAs), and scan length associated with an effective dose to a CT scan and administered activity as well as the corresponding effective dose.

Tables 4, 5 Present risk of exposure-induced death per million scans values for diagnostic nuclear medicine and CT scan examinations.

Table 4. Estimating risk of exposure for nuclear medicine

Organ at risk (NM)	REID(%)
breast	0.000052
Ovary	0.000117
Other cancer	0.00121

Table 5. Estimating risk of exposure for computed tomography scan

Organ at risk (CT)	REID (%)
Breast	0.000391
Ovary	0.00018
Other cancer	0.00158

4. Discussion

In radiation therapy, the estimation of the out-of-field dose is illustrated by Kalliopi M. Kourinou. In this study, scattered doses of radiosensitive organs and the risk of cancer due to radiation therapy for head and neck cancer in children were evaluated. Radiation therapy for brain tumors, leukemia, and Hodgkin's neck was performed on 5- and 10-year-old phantoms with 6 mV photons [14]. And doses of the thyroid, breast, lung, and several other organs were measured to evaluate dispersed doses outside the field. It was shown that the thyroid, lungs, and breasts are at higher risk because they are close to the radiation field. In the present study, thyroid and other organ dose measurements were performed on a real patient. The out-of-field doses and risk of secondary cancer varied considerably depending upon the location of the organ-at-risk relative to the primary cancer site. As expected, eyes were located at the lowest distant positions from the head region so the eyes received the most amount of radiation, which is compatible with the same study [15]. Several other studies have focused on the second cancer risk after radiotherapy.

The associated second cancer risk was dependent on the age at the time of treatment, gender, and organ dose. The thyroid dose is much lower than the value of 2500 cGy which may be associated with thyroid dysfunction [16]. Although, Shore [17] has reported that thyroid doses as low as 10 cGy can cause secondary malignancies. Svahn-Tapper *et al.* [18] reported that organ doses below 1 Gy may lead to a modest increase in cancer risk. Gold *et al.* [19] reported that 14% of secondary cancers occur far from the irradiated area. Diallo *et al.* [20] showed that 22% of subsequent neoplasms occur 5 cm away from the treatment fields. These reports clearly show that the risk of secondary cancer induction at distant locations from the irradiated area may be relatively small but not trivial. The higher cancer risk values presented in our study were found for organs located at small distances from the field edge.

Many risk factors are triggered by cancer accumulation [21]. In the present case, the highest risk of secondary cancer risk from head radiotherapy was related to the eyes, and for pelvic the maximum risk involved gonads.

In this study, it was found that the amount of scattered radiation to different organs during radiotherapy pertains to distance.

Critical organs were found to be eyes and gonads in this patient treatment. Miah *et al.* also reported that scattered radiation dose to different organs differs with the patients' height [22]. In general, to reduce scattered radiation to some vital organs of the body, care should be taken to choose the field size without compromising the tumor volume.

5. Conclusion

The out-of-field dose is the result of scattering and leakage. Much as RT bears a critical role in the management of many malignant tumors, out-of-field doses and the risk of second cancer contribute to the cancer of various organs. The presented dosimetric results show that the risk of developing subsequent neoplasms in abdominopelvic organs is low or even negligible. The thyroid gland, eye, parotid, and breast have increased risk for second cancer induction due to the close proximity to the applied treatment fields Several considerations could function as simple methods to reduce out-of-field dose to other organs. The technicians must also be extremely careful in the patient setup. The late effect of RT and imaging should be informed to the patients as well. The out-of-field dose and risk of secondary cancer decrease with increasing distance from the target. A few recommendations such as adapting to specific organs, managing image dose, and decreasing the target volumes could be suggested to reduce the risk of secondary cancer after radiotherapy.

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