ORIGINAL ARTICLE

Estimation of Radiation-Induced Secondary Cancer Risk in Lung Cancer Patients Following Three-Dimensional Conformal Radiotherapy

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Abstract

Purpose: Lung cancer treatment often involves radiotherapy, which can lead to an increased risk of secondary cancers in sensitive organs and Organs At Risk (OARs). Understanding this risk is crucial for optimizing treatment strategies and minimizing long-term adverse effects. The objective of this study is to estimate the Secondary Cancer Risks (SCRs) in sensitive organs and OARs using radiation-induced cancer risk prediction models, specifically the Biological Effects of Ionizing Radiation (BEIR) VII model and the International Commission on Radiological Protection (ICRP) model.

Materials and Methods: The radiotherapy dosimetric data of 30 lung cancer patients were collected all of whom underwent Computed Tomography (CT) scans. The PCRT-3D Treatment Planning System (TPS) was used for the treatment planning process. The risks were calculated based on the dose distribution in the target volume. The models for Excess Absolute Risk (EAR) and Excess Relative Risk (ERR) values (per 100,000 person-year) were utilized to estimate SCRs in planning target volume, OARs, and sensitive organs.

Results: The results indicate that, according to the BEIR VII model, the estimated EAR of cancer per 100,000 person-years was 38.39 in the heart, 35.83 in the esophagus, 5.49 in the contralateral lung, 2.17 in the liver, and 3.41 in the pancreas. Conversely, using the ICRP model, the EAR was calculated to be 58.73 in the heart, 38.78 in the esophagus, 20.48 in the contralateral lung, 3.49 in the liver, and 5.44 in the pancreas. These findings suggest that lung cancer patients treated with 3DCRT exhibit relatively high SCRs in the heart, esophagus, and contralateral lung organs in both models.

Conclusion: In this study, SCRs in a range of organs in lung cancer patients treated with 3DCRT were quantified. Our findings revealed that there were comparatively high SCRs in the heart in 3DCRT of lung cancer patients. Based on the findings of the current investigation, the ICRP model SCRs are greater in comparison to the BEIR VII model. These findings underscore the importance of considering SCRs in treatment planning and highlight the need for further research to optimize radiation therapy strategies and minimize long-term risks for lung cancer patients.

Keywords: Biological Effects of Ionizing Radiation VII; International Commission on Radiological Protection; Lung Cancer; Radiotherapy; Secondary Cancer Risk; Treatment Planning.

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1. Introduction

Cancer remains a significant global health challenge, claiming around 10 million lives annually and ranking as the leading cause of death [1, 2]. In 2020, lung cancer ranked as the second most commonly diagnosed cancer, with 1.8 million fatalities and 2.2 million new cases reported, accounting for 11.4% of all cancer instances. Notably, it also stood as the leading cause of cancer-related deaths globally, contributing to 18% of all such deaths [3].

Pathological diagnosis of lung cancer is a multi-step procedure that starts with morphologic diagnosis and proceeds through proteome profiling, the study of tumor gene expression, and the identification of somatic mutations [4].

For nearly a century, radiotherapy has served as a cornerstone in the treatment of malignant tumors. However, it is widely recognized that radiation exposure carries an inherent risk of cancer development. Consequently, a growing number of long-term cancer survivors face the potential of therapy-induced cancers, commonly referred to as second malignant neoplasms, owing to increased life expectancy and the efficacy of radiation therapy. This realization necessitates a heightened awareness among healthcare professionals regarding the risk of radiation-induced cancers [5]. Over the past 20 years, as a complementary treatment for early cancer, postoperative radiation has become increasingly popular. Additionally, studies have shown that it is successful in lowering rates of overall survival and locoregional recurrence [6-10]. Radiotherapy plays a pivotal role in managing lung cancer across all stages [11].

It is crucial to remember that patients who receive radiotherapy may experience significant radiation doses in certain tissue volumes. Among all the radiation adverse effects that could occur, the elevated secondary cancer risk (SCR) due to scattered radiation from the primary malignancy treatment is of particular concern [12-17]. These concerns have been substantiated by numerous radiation epidemiology studies conducted through extensive follow-up of long-term cancer survivors [18-23].

The conventional treatment approach for stage I peripheral Non-Small-Cell Lung Cancer (NSCLC) involves lobectomy, which accounts for the majority of lung cancer cases. However, lobectomies are major surgical interventions often resulting in clinically significant declines in lung function [24]. Furthermore, the treatment of lung cancer has seen extensive utilization of three-Dimensional Conformal Radiation Therapy (3DCRT) to accommodate the mobility of respiratory tumors. The broader irradiation field necessitated by this mobility often results in excessive exposure of normal lung tissue. Consequently, 3DCRT, with its improved volume coverage, has emerged as a preferred approach, especially considering the limitations of conventional radiation therapy in terms of locoregional control and survival outcomes [25].

Several authoritative bodies, including the International Commission on Radiological Protection (ICRP) [26], the National Council on Radiation Protection and Measurement (NCRP) [27], and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [28] have provided the information that is currently available regarding SCRs following radiotherapy. From 1956 through 2007, assessments on the potential for secondary cancer were provided by the National Academy of Sciences (NAS) Committee on Biological Effects of Ionizing Radiation (BEIR) (ADD this reference here as well). In one of the findings of the committee, models for Excess Absolute Risk (EAR) and Excess Relative Risk (ERR), alongside reporting procedures, were devised. Radiation dose and the age of the patient receiving radiation were linked to the risk of subsequent cancer. In the BEIR VII report, the most updated and comprehensive estimation for cancer and other health effects from low-level ionizing radiation exposure was presented. It is considered the first reports which include detailed estimations for cancer incidence and cancer mortality [29].

In 2003, Hall and Wuu documented the occurrence of radiation-induced second cancers. They expressed concern that transitioning from 3DCRT to Intensity-Modulated Radiotherapy (IMRT), which employs more fields and monitor units to enhance exposure, may elevate the risk of secondary cancers. This heightened risk is attributed to the increased volume of normal tissue exposed to low doses and total body exposure caused by leakage radiation. According to their findings, IMRT is associated with nearly twice the incidence of second malignancies compared to 3DCRT [30]. Comparable to what was performed in this study, Chao *et al.* [31] assessed the SCRs caused by Stereotactic Body Radiation (SBRT) for patients with lung cancer. In the study, the Organ

Equivalent Dose (OED) idea and the Schneider model were used to estimate SCRs [13]. They have shown that younger patients exhibit higher SCRs. Kim *et al.* compared the SCRs from scattered and leakage doses following IMRT, Volumetric Arc Therapy (VMAT), tomotherapy, and proton beam therapy in patients with lung cancer [32, 33].

To our knowledge, no study has systematically compared or evaluated secondary cancer risks in lung cancer patients undergoing 3DCRT radiotherapy using multiple radiation-induced cancer risk prediction models. Therefore, the present study aims to assess the SCRs in the Planning Target Volume (PTV), Organs At Risk (OARs), and radiation-sensitive organs following radiotherapy in lung cancer patients, employing both the BEIR VII model and the radiobiological model from the ICRP.

2. Materials and Methods

This study involved 30 patients (15 males and 15 females) with lung cancer who received 3DCRT. The patients ranged in age from 37 to 67, with two patients beyond 70 years of age. On average, the patients in this study were 53 years old. This is thought to be the youngest age group for both males and females to develop this disease. An expert physicist performed the treatment planning process for each patient using his/her CT scan. Plans with doses depending on CT estimates were designed using Técnicas Radiofsicas, Zaragoza, Spain, PCRT-3D (v6.0.2) TPS. A Shinva linear accelerator (Shinva-Compact 6 MV, China) with a 6-MV photon beam was used for all dose delivery to the patients, as part of their treatment. After obtaining the Dose-Volume Histograms (DVHs) for the PTV and OARs for all patients, the mean organ doses in Gy were calculated and incorporated into various mathematical formulas from the BEIR VII [29] and ICRP [26] models to estimate SCRs. The SCRs results were computed and compared, with further comparison between male and female patients.

2.1. Characteristics of Patients

The lung cancer patients were treated at Vail Asr Radiation Oncology Center (Qom, Iran). Table 1 lists the patient characteristics, including the total number of patients, the prescribed dose (Gy), PTV volume (cc), volumes of organs (cc), and the patients' ages at the exposure time (year).

Table 1. Characteristics of patients in lung cancer in the present study

Characteristics	Number
Total number at patients (15 males, 15 females)	30
Age, range in years	37-71
Prescribed dose (Gy)	61.00
PTV (cc)	834.68 ± 352.23
Liver volume (cc)	1301.38 ± 466.59
Pancreas volume (cc)	176.26 ± 92.68
Gallbladder volume (cc)	37.33 ± 16.26

2.2. Treatment Planning

For the purpose of radiotherapy planning, a CT simulation scan was performed on each patient, with a slice thickness of 5 mm. Every patient was placed with their arms above their heads while resting supine. PTV was identified using Digital Imaging and Communications in Medicine (DICOM)-formatted CT scans, OARs, and sensitive organs. A radiation oncologist contoured the PTV and OARs, including the heart, spinal cord, esophagus, and contralateral lung; in addition to the sensitive organs, including the liver, pancreas, and gallbladder. Using a superposition algorithm, PCRT-3D TPS was used to execute the planning and compute dose estimates based on CT. Patients were treated one time per day and five times a week with a prescribed dose of 61 Gy in total 33 fractions. For the first phase of the treatment, a specified overall dose of 45 Gy as 1.8 Gy per fraction was delivered, within the second phase a total dose of 16 Gy as 2 Gy per fraction, was administered as the boost phase. The treatment plan consisted of using 2, 3, or 4 fields (parallel opposed or oblique technique). The Clinical Target-Volume (CTV), Gross Tumor-Volume (GTV), and PTV were determined by the oncologist for radiotherapy. The plan was performed to increase the isodose level of PTV to 95% of the recommended dose, while the maximum dose remaining at 107% of the recommended dose PTV was produced on a 3D virtual simulation workstation by extending the margin for CTV by 10 mm. The margin provided to the CTV takes into account treatment execution variances and uncertainties, such

as patient movement and setup displacements, organ movement, and changes in the size and form of the CTV. Figure 1 provides sample images of 3DCRT treatment plans for one lung cancer patient, illustrating Digital Reconstructed Radiographs (DRR) and different image views. In this figure parts (a), (b), (c), and (d) are related to DRR, axial, coronal, and sagittal views, respectively.

The DVH curves of all the patients for the PTV, OARs, and sensitive organs were collected. Figure 2 shows a sample for one patient that includes DVH curves for PTV, OARs, and some sensitive organs. The data for D_{mean} (Gy), D_{max} (Gy), and D_{min} (Gy) were collected by TPS from DVHs following the plan designation. The values of absorbed dose obtained from DVH analysis of a sample patient are quantitatively summarized in Table 2.

Table 2. The differential dose-volume histograms reveal D_{max}, D_{mean}, D_{min} in cGy to the PTV, OARs and sensitive organs DVHs for a sample patient

Organ	D_{max} (cGy)	D_{mean} (cGy)	D_{min} (cGy)
PTV	6702.20	6159.73	3821.57
Heart	6550.12	1698.86	243.33
Spinal cord	2613.91	308.72	34.12
Esophagus	5435.58	1180.51	223.78
Contralateral lung	6403.62	347.17	188.49
Liver	2504.14	311.02	82.65
Pancreas	248.43	194.27	81.60
Gallbladder	229.33	182.87	243.26

2.3. Calculating the Secondary Cancer Risk

The BEIR VII [29] and ICRP [26] risk models based on the linear no-threshold (LNT) model, which primarily uses cancer incidence rates observed in survivors of the Japanese nuclear bombings, were employed to estimate the Secondary Cancer Risks (SCRs) following radiation therapy. Consequently, 3DCRT was used to treat patients with lung cancer, and the mathematical formulas for these models were applied to calculate the Excess Relative Risk (ERR) and Excess Absolute Risk (EAR) values for all patients.

Additionally, these models provided details on the specific organs associated with sex as well as data on how incidence varied with exposure age and attained age by parameters. To calculate D_{mean}, D_{max}, and D_{min} to sensitive organs and OARs in Gy, the DVHs of

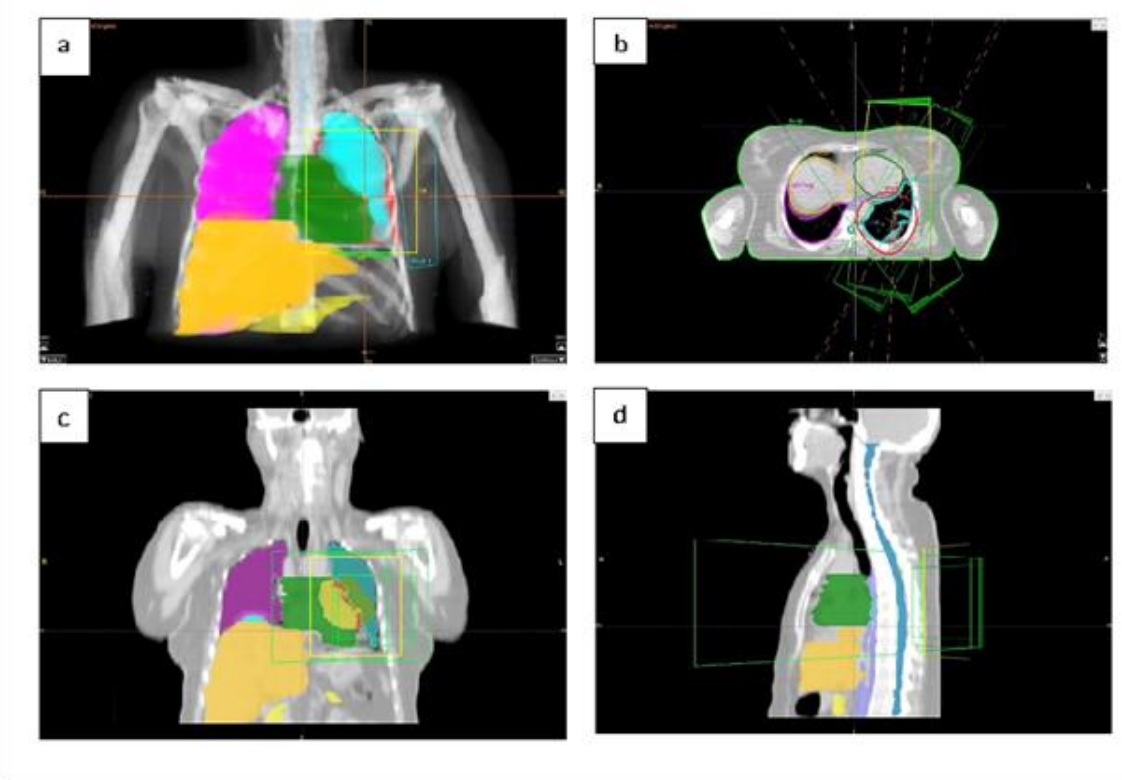

Figure 1. Sample images of 3DCRT treatment plans for one lung cancer patient: digital reconstructed radiograph (DRR) (a), axial (b), coronal (c), and sagittal (d) views

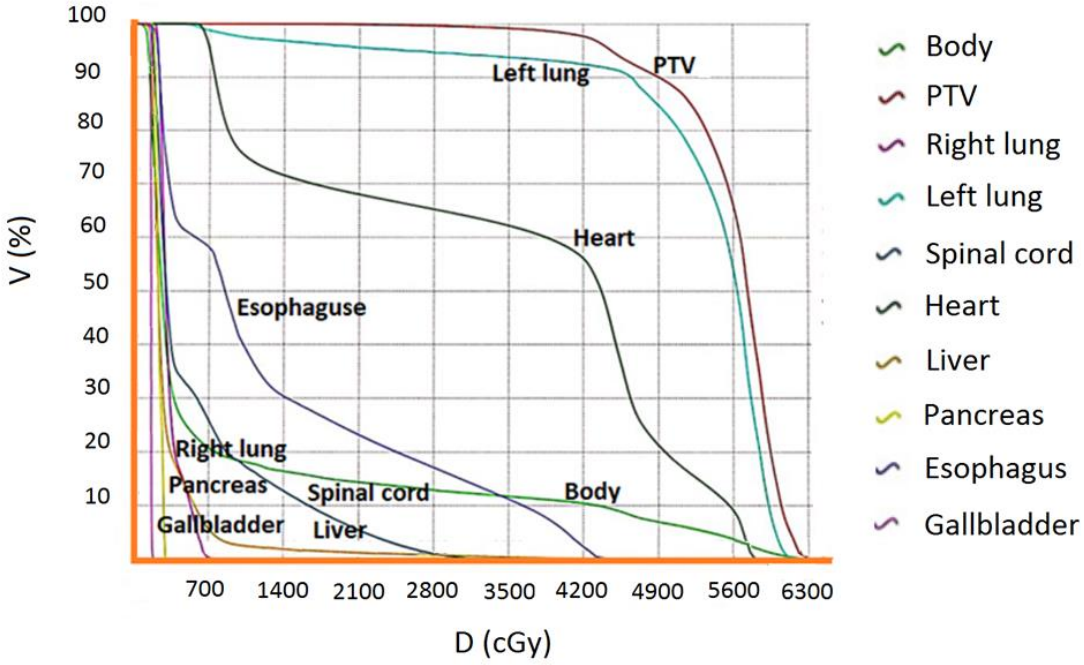

Figure 2. Sample DVH curves for PTV, OARs and some sensitive organs for a patient with lung cancer in the present study

organs were used. The parameters of the models depend on the patient's age at the time of radiation exposure (exposure age), the patient's gender, and the attained age.

2.4. BEIR VII Model

Equations 1 and 2 include EAR and ERR formulas based on all solid cancers:

$$EAR = \beta_s D\, Exp\,(\gamma e^*)(^{a}/_{60})^{\eta} \quad (1)$$

$$ERR = \beta_s D\, Exp\,(\gamma e^*)(^{a}/_{60})^{\eta} \quad (2)$$

where D is the average organ dose in Gy, e is the years of exposure, a is attained age in years, L is a latent phase without risk equal to five years for solid tumors, $a = (e + L)$. Additionally, if the patient is under the age of 30 (e<30), e^* is ((e-30)/10) while e^* is 0 for patients who are older (e≥30). Depending on the quantity type (EAR and ERR) used, the values for these parameters which depend on the type of model (β_s, γ with η) are presented in Table 3 [3].

2.5. ICRP Model

The ICRP risk assessments for the majority of cancer types are based on a methodology with different variables and mathematical models compared to the BEIR VII model, as mentioned below:

$$EAR = g_s D \times e^{-g_e \cdot (e-30) + g_a \cdot ln\left(\frac{a}{70}\right)} \quad (3)$$

$$ERR = g_s D \times e^{-g_e \cdot (e-30) + g_a \cdot ln\left(\frac{a}{70}\right)} \quad (4)$$

Table 3. Parameters in risk incidence model based on BEIR VII report [3]

Organ	EAR				ERR			
	$\beta_{M.}$	$\beta_{F.}$	γ	η	$\beta_{M.}$	$\beta_{F.}$	γ	η
Liver	2.20	1.00	-0.41	4.10	0.32	0.32	-0.30	-1.40
Lung	2.30	3.40	-0.41	5.20	0.32	1.40	-0.30	-1.40
Other tumors	6.20	4.80	-0.41	2.80	0.27	0.45	-0.30	-2.80

β_M, β_F, γ and η parameters depending on the gender, organ and type quantity of BEIR VII model.

Where D is the dose to organ g_s, g_e, g_a parameters for the ICRP model, g_s risk per Gy at age 70 for exposure at age 30, g_e age at exposure % change in ERR or EAR per decade increase, g_a power of attained age by which the ERR or EAR varies. Table 4 [1] shows the coefficients: g_s, g_a, and g_e.

2.6. Analytical Statistics

The Statistical Package for the Social Sciences (SPSS) application (version 26, SPSS Inc., Chicago, USA) was used to conduct the statistical analysis. The dose data distribution was examined for normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. A significance level of <0.05 was used to interpret the p-value from these tests. If the p-value is less than or equal to 0.05, the null hypothesis is rejected, indicating that the data does not follow a normal distribution [5]. A separate two-tailed t-test was used to compare parameters between models with a normal distribution. For parameters with non-normal data distributions, a non-parametric Mann-Whitney-Wilcoxon test was employed. The p-value was calculated with a significance level of <0.05 to interpret the results. A p-value less than 0.05 indicates a significant difference between the two models.

3. Results

3.1. Organ Doses

The estimated absorbed dose (D_{max}, D_{mean}, and D_{min}) to PTV, and OARs (such as heart, esophagus, spinal cord, contralateral lung, liver, pancreas, and gallbladder) were calculated for each patient. Table 5 shows the comparison between the D_{max}, D_{mean}, and D_{min} in OARs and sensitive organs, based on the study by Emami *et al.* and the tolerance dose for normal tissues [35]. In Table 6, we have shown the values of the dosimetric average of D_{max}, D_{mean}, and D_{min} for all patients of lung cancer with radiotherapy compared to a prescribed dose in treatment planning.

3.2. Results of the BEIR VII and ICRP Models for Secondary Cancer Risk

According to the BEIR VII model, the values of the statistical results of EAR and ERR in the above OARs, and various sensitive organs for each patient are presented in Table 7. In this table, the values of mean, and range, including maximum and minimum, are reported as descriptive statistics.

The second model in this study, the ICRP model, uses different mathematical equations and parameters from the prior model but is otherwise quite similar to the approach of the first model for risk calculation. In Table 8, the values of the mean for EAR, ERR, and range-included maximum and minimum are reported as descriptive statistics. Statistical analysis of OARs and sensitive organs for all patients using EAR and ERR, obtained from BEIR VII and ICRP models are reported as the descriptive statistics are present in Table 8. Both Figures 3 and 4 are related to BEIR VII and ICRP models, respectively.

3.3. Comparison of Cancer Risk in Male and Female

To investigate the disparity between the two genders, a p-value comparison between the males and females was used for each model. And the mean ERR and EAR values in each model were obtained from BEIR VII and ICRP risk calculation models. Tables

Table 4. Parameters in risk incidence model based on ICRP report [1]

Cancer type	Gender	EAR			ERR		
		g_s	g_e	g_a	g_s	g_e	g_a
Liver	Male	4.180	0.024	2.380	0.250	0.017	-1.650
	Female	1.300	0.024	2.380	0.400	0.017	-1.650
Lung	Male	6.470	-0.001	4.250	0.290	-0.017	-1.650
	Female	8.970	-0.001	4.250	1.360	-0.017	-1.650
Esophagus	Male	0.480	-0.064	1.380	0.400	0.017	-1.650
	Female	0.660	-0.064	1.380	0.650	0.017	-1.650
Another tumor	Male	7.450	0.024	2.380	0.220	0.017	-1.650
	Female	10.450	0.024	2.380	0.170	0.017	-1.650

g_s, g_e, g_a parameters depending on the gender, organ and type quantity of ICRP model.

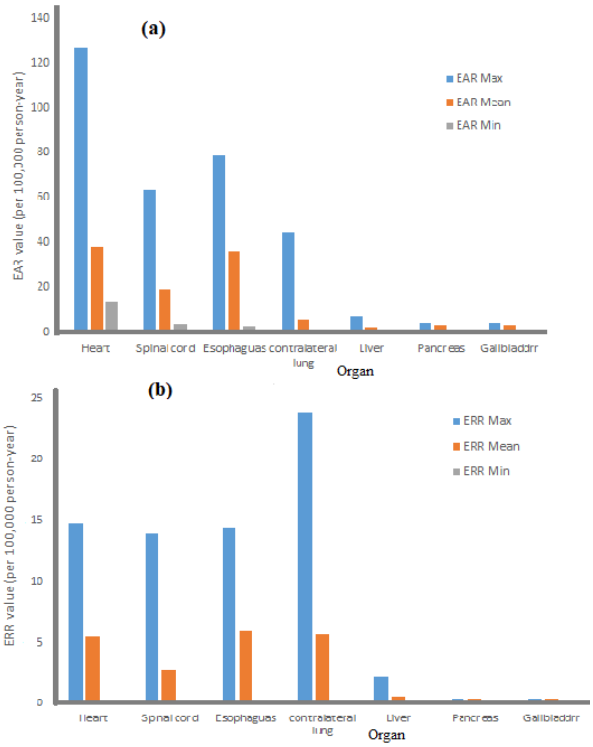

Figure 3. The (max, mean, min) EAR (a) and ERR (b) (per 100,000 person-year) values in OARs and three sensitive organs as average for 30 patients treated with radiotherapy for lung cancer using the BEIR VII model

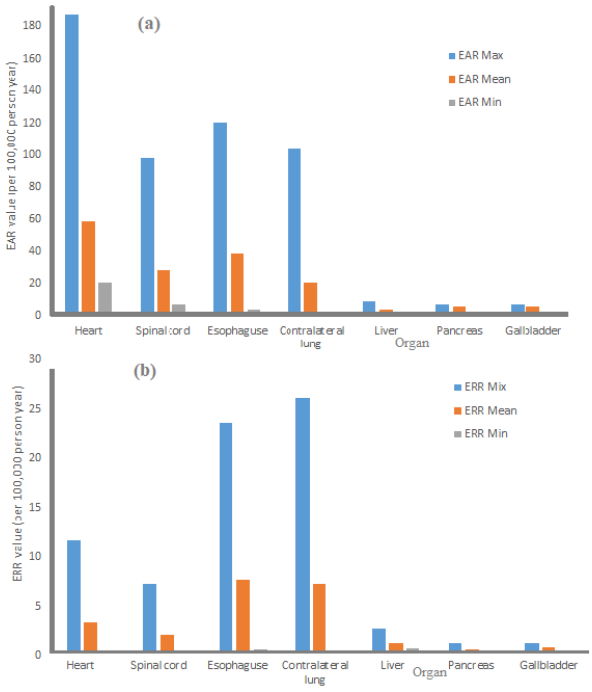

Figure 4. The (max, mean, min) EAR (a) and ERR (b) (per 100,000 person-year) values in OARs and three sensitive organs as average for 30 patients treated with radiotherapy for lung cancer using the ICRP model

Table 5. Comparison of the (D_{max}, D_{mean}, D_{min}) in OARs and sensitive organs for 30 lung cancer patients with after radiotherapy, with the tolerance dose based on the study by Emami *et al.* [4]

Organ	D_{max} (Gy)	D_{mean} (Gy)	D_{min} (Gy)	Tolerance does (Gy)
Heart	56.24	19.34	4.24	40.00
Spinal cord	35.18	10.55	2.58	47.00
Esophagus	47.45	18.18	3.05	55.00
Contralateral lung	44.42	6.33	2.70	17.50
Liver	7.554	4.43	1.81	30.00
Pancreas	3.10	2.64	2.01	-
Gallbladder	2.96	2.63	2.27	-

Table 6. Comparison of (D_{max}, D_{mean}, D_{min}) (Gy) with prescribed dose (Gy) for all 30 patients who underwent radiation therapy of lung cancer

Organ	D_{max} (Gy)	D_{mean} (Gy)	D_{min} (Gy)	Prescribed dose (Gy)
Target	65.98±10.03	55.05±5.53	34.94±3.15	61.00

9 and 10 display the mean EAR and ERR values for male and female patients from both models. In Figure 5, EAR from BEIR VII model (part (a)), ERR from BEIR VII model (part (b)), EAR from ICRP model (part (c)), and ERR from ICRP model (part (d)) are presented.

4. Discussion

In this investigation, SCRs in OARs and radiation-sensitive organs was estimated for 3DCRT lung cancer patients based on EAR and ERR quantities: from both

Table 7. Statistical results the (max, mean, min) EAR and ERR values (per 100,000 person-year) in OAR and sensitive organs obtained from BIER VII model [2]

Organ	EAR Max (per 100,000 person-year)	EAR Mean (per 100,000 person-year)	EAR Min (per 100,000 person-year)	ERR Max (per 100,000 person-year)	ERR Mean (per 100,000 person-year)	ERR Min (per 100,000 person-year)
Heart	126.76±105.40	38.39±26.61	13.41±10.22	14.78±12.01	5.52±4.05	0.32±0.28
Spinal cord	63.29±35.2	19.18±14.33	3.61±1.3	13.92±12.10	2.78±1.62	0.24±0.10
Esophagus	78.76±40.44	35.83±25.72	3.05±2.90	14.44±12.25	5.91±4.01	0.26±0.09
Contralateral lung	44.92±36.20	5.49±4.71	1.38±0.86	23.79±21.16	5.90±3.86	0.28±0.14
Liver	7.24±5.19	2.17±2.08	0.24±0.12	2.19±1.77	0.66±0.60	0.11±0.03
Pancreas	4.25±2.48	3.41±1.92	0	0.48±0.32	0.38±0.36	0
Gallbladder	4.05±2.36	3.48±1.99	0	0.46±0.29	0.38±0.35	0

*: $p< 0.05$ means a significant difference

Table 8. Statistical results the (max, mean, min) EAR and ERR values (per 100,000 person-year) in OAR and sensitive organs obtained from ICRP model [26]

Organ	EAR Max (per 100,000 person-year)	EAR Mean (per 100,000 person-year)	EAR Min (per 100,000 person-year)	ERR Max (per 100,000 person-year)	ERR Mean (per100,000 person-year)	ERR Min (per100,000 person-year)
Heart	187.22±73.06	58.73±32.47	20.5±17.22	12.09±5.56	3.56±2.90	0.19±0.03
Spinal cord	98.43±49.62	28.64±21.69	7.18±6.88	7.33±5.68	2.15±2.24	0.03±0
Esophagus	120.41±102.80	38.78±36.65	3.4±1.43	27.39±15.09	8.80±6.83	0.28±0.1
Contralateral lung	103.77±91.45	20.48±16.93	2.43±1.04	30.02±69.21	8.81±6.78	0.30±0.09
Liver	8.99±6.47	3.49±3.33	0.38±0.12	3.21±2.28	1.11±1.10	0.04±0
Pancreas	6.54±4.37	5.44±3.36	0	1.40±0.30	0.31±0.25	0
Gallbladder	6.44±5.93	5.68±3.4	0	1.48±0.27	0.55±0.50	0

*: $p< 0.05$ means a significant difference

Table 9. Mean EAR, ERR (per 100,000 person-year) and p-value averaged for 30 lung cancer patients for comparison for a male and female based on the BEIR VII report [2]

Organ	BIER VII (EAR)			BIER VII (ERR)		
	Male	Female	*p*-value	Male	Female	*p*-value
Heart	46.24	30.52	0.07	4.38	6.66	0.39
Spinal cord	24.46	13.30	0.03*	2.51	3.06	>0.99
Esophagus	46.72	24.93	0.01*	6.43	7.80	0.83
Contralateral lung	5.35	5.62	0.14	0.93	1.74	<0.00*
Liver	2.87	1.48	0.01*	0.73	0.60	>0.99
Pancreas	4.34	2.62	0.00*	0.84	0.40	0.82
Gallbladder	4.34	2.61	0.00*	0.84	0.40	0.82

*: $p< 0.05$ mean a significant difference

Table 10. Mean EAR, ERR (per 100,000 person-year) and p-value averaged for 30 lung cancer patients for comparison for a male and female based on the ICRP model [1]

Organ	ICRP (EAR)			ICRP (ERR)		
	Male	Female	*p*-value	Male	Female	*p*-value
Heart	46.85	70.66	0.02*	4.62	2.77	0.08
Spinal cord	26.92	30.44	0.83	2.84	1.39	0.01*
Esophagus	32.74	44.80	0.59	7.69	9.94	0.48
Contralateral lung	18.71	22.24	0.14	2.82	33.42	<0.00*
Liver	5.02	1.97	<0.00*	1.06	1.17	0.23
Pancreas	4.43	6.23	0.21	0.41	0.20	0.01*
Gallbladder	4.48	6.23	0.26	0.88	0.21	0.01*

*: $p< 0.05$ mean a significant difference

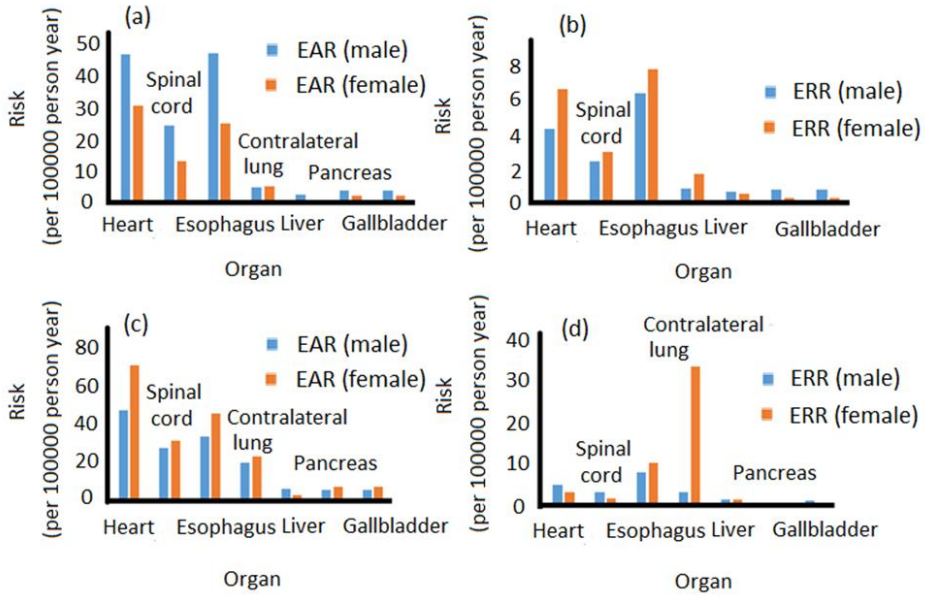

Figure 5. The mean EAR and ERR (per 100,000 person-year) values in OARs and three sensitive organs as average for male and female patients treated for radiotherapy with lung cancer as EAR from BEIR VII model (a); ERR from BEIR VII model (b); EAR from ICRP model (c); ERR from ICRP model (d)

Table 11. Mean EAR and ERR (per 100,000 person-year) and p-value averaged for all lung cancer patients for comparison of cancer risk from BEIR VII (2) and ICRP (1) models

Organ	EAR (per 100,000 person-year)			ERR (per 100,000 person-year)		
	BEIR VII model	ICRP model	*p*-value	BEIR VII model	ICRP model	*p*-value
Heart	38.39±26.61	58.73±32.47	0.00*	5.52±4.05	3.56±2.90	0.27
Spinal cord	19.18±14.33	28.64±21.69	0.04*	2.78±1.62	2.15±2.24	0.69
Esophagus	35.83±25.72	38.78±36.65	0.64	5.91±4.01	8.80±6.83	0.00*
Contralateral lung	5.49±4.71	20.48±16.93	<0.00*	5.90±3.86	8.81±6.78	<0.00*
Liver	2.17±2.08	3.49±3.33	0.07	0.66±0.60	1.11±1.10	0.04*
Pancreas	3.41±1.92	5.44±3.36	0.00*	0.38±0.36	0.31±0.25	0.77
Gallbladder	3.48±1.99	5.68±3.4	0.01*	0.38±0.35	0.55±0.50	0.95

BEIR VII and ICRP models. By calculating (D_{max}, D_{mean}, and D_{min}) in Gy, data about the dose distribution in the PTV and OARs was obtained from DVHs in OARs and sensitive organs during lung cancer radiotherapy.

The absorbed dose (D_{max}, D_{mean}, and D_{min}) in Gy to OAR and sensitive organs are reported in Table 5. It was found that the average (D_{max}, D_{mean}, and D_{min}) (Gy) in the heart and esophagus had the highest values among the other organs. For example, the average Dmean in the heart is 19.34 Gy, and the average D_{mean} in the esophagus is 18.18 Gy. The average dose in other organs such as spinal cord, contralateral lung, liver, are equal to: 10.55, 6.33, 4.43 Gy respectively. The pancreas and gallbladder have the lowest D_{mean} of 2.64 and 2.63 Gy, respectively.

It is observed that the D_{mean} (Gy) in heart, spinal cord, esophagus, contralateral lung and liver was lower than the tolerance dose (Gy) in normal tissues for 3DCRT based on the study Emami *et al.* [31] (Table 5). This is attributed to the skill of the radiotherapy physicist in designing the treatment plan with the prescribed dose. In Table 6, D_{mean} was less than the prescribed dose (Gy) for all 30 patients. This is a good point attributed to the accuracy of the treatment plan design, dividing the dose into phases and fractions during treatment planning.

As demonstrated in Table 7, the SCRs from the BEIR VII model for all patients are presented in OARs and sensitive organs. The heart and oesophagus have much higher average EAR and ERR values than the other organs, measuring (38.39, 35.83) and (5.52, 5.91) per 100,000 person-year, respectively. As opposed to that, average EAR and ERR values in the pancreas are 3.41 and 0.38 per 100,000 person-year, respectively, indicating a lesser risk. Whereas the value of βM, βF for EAR in OARs as heart, oesophagus, and spinal cord and

sensitive organs as the liver, pancreas, and gallbladder are high, equal to 6.20, 4.80, respectively [29]. According to the (Table 3: Parameters in the liver, lung and other tumors in risk incidence model based on BEIR VII report), where β the cases cancer per Gy at the age of exposure 30 and attained age 60, β differs depending on the patient's gender. But the heart and oesophagushave the highest dose values among all organs and these organs are closest to the target and are affected by the radiation field. On the other hand, the liver has low Mean EAR value compared then the others of the organs. Also, the lower risk ERR is in pancreas and gallbladder. These organs are located at a distance somewhat from the target and it have low dose among the organs.

Relying on Table 8 for the ICRP model, the average EAR values in the heart and oesophagushave a higher value compared to the other organs average EAR with values 58.73, and 38.78 per 100,000 person-year, respectively. And higher risk in average ERR to the contralateral lung, oesophagus and heart of values equal to 8.81, 8.80, and 3.56 per 100,000 person-year, respectively. Where the heart and oesophagus have the highest dose values among all organs. While the liver is the lowest-value organ for average EAR among all organs and pancreas has low value of average ERR value were 3.49 and 0.31 per 100,000 person-year, respectively. Figure 4 (panel (a)) demonstrates that the mean risk values for EAR from the ICRP model with ERR are higher in organs that are located in the therapeutic field or nearby (heart, oesophagus, spinal cord, and contralateral lung). Also, the value of gs (for males and females) for EAR in OARs as heart, and spinal cord and sensitive organs as the pancreas and gallbladder are high, equal to 7.45 and 10.45, respectively. In Table 4, parameters in risk incidence model based on ICRP report, for liver, lung, oesophagus and other tumors [26] are presented, where gs is the types cancer per Gy at the age of exposure 30 and attained-age 60, gs differs depending on the patient's gender and its similar β parameter in BEIR VII model. Where the heart and oesophagus have the highest dose values among all organs and these organs are closet to the target and are affected by the radiation field.

Table 10 displays the findings of the statistical analysis of OARs and sensitive organs for all patients using the independent t-test and Mann-Whitney test for comparison of EAR and ERR, which are derived using the BEIR VII and ICRP models. it was found that there is a noticeable distinction in p-value among the BEIR VII and ICRP radiobiology models for EAR values in pancreas, gallbladder, heart, spinal cord, and ipsilateral lung ($p < 0.05$). Additionally, there is no discernible change in p-value of risk values for the EAR in liver and esophagus between both models ($p> 0.05$). A comparison among BEIR VII and ICRP models in the liver, esophagus, and contralateral lung shows that the differences in ERR values for the two models are significant ($p < 0.05$). While the EER risk values in the heart, spinal cord, liver, pancreas, and gallbladder do not show a significant difference in ($p > 0.05$).

Based on the BEIR VII model, data in Table 10 imply that a significant difference exists in average EAR values between males and females in the spinal cord, esophagus, pancreas, and gallbladder ($p < 0.05$). But for average EAR values in the heart and contralateral lung, there is no significant difference between both models ($p > 0.05$). Additionally, there is a difference between the two genders for the average ERR value ($p < 0.05$) in the contralateral lung. while all other OARs and sensitive organs are not significant ($p > 0.05$) in both genders. It is observed the average EAR values in the esophagus and heart are the highest-risk organ in males and the liver is the lowest-risk in females' organ among all close organs in males and females. In addition, EAR values for males are higher compared to females. While the average ERR, values are higher for females compared to males, as presented in (Figure 4). Where the average ERR values in the heart and oesophagus in females higher than in males while lower value for ERR is the pancreas in males.

According to Table 11 in the ICRP model, the average EAR values in the heart and oesophagus in females higher than the average EAR values in males among other organs. But the lowest value for EAR in the pancreas for females, too. The EAR for males and females in the heart and liver is considerably different ($p < 0.05$). On the other hand, a significant difference is not determined for average EAR values in the spinal cord, esophagus, contralateral lung, pancreas, and gallbladder between the two genders of the ICRP model ($p > 0.05$). While there is no significant difference in the ERR between males and females in the liver, heart, and oesophagus ($p > 0.05$), there is a significant difference in the ERR value in the spinal cord, contralateral lung, pancreas, and gallbladder between the two genders ($p < 0.05$).

From (Figure 5 parts (c) and (d)), it is observed that, the ICRP model, average EAR values in the heart are higher for females compared to males. It is also noted that the contralateral lung has the highest mean values for ERR in females. And, according to the ICRP model, the lowest risk values of ERR in females in pancreas. In fact, it has been hypothesized that the increased radiosensitivity of females may be somewhat influenced by hormonal variations. When ionizing radiation exposure risks for males and females of all ages are averaged out, it is shown that females are at a slightly higher risk of developing major health effects, including cancer than males. However, when a specific individual is involved, one needs to be cautious when attempting to determine the significance of such a discrepancy. The EAR quantity based on the BEIR VII model in the heart, oesophagus, spinal cord, and gallbladder for males has a higher beta (βm) parameter compared to βF value in females. And gs parameter in female value higher than value in male.

Our results align with previous studies highlighting the importance of treatment planning in minimizing radiation-induced toxicity. Studies by Zhang *et al.* [36] and Bellière *et al.* [37] underscored the significance of dose optimization in reducing organ toxicity and improving treatment outcomes. Additionally, our findings are consistent with literature demonstrating the risk of secondary cancers in organs adjacent to the irradiated volume, as highlighted by Darby *et al.* [38] and Svahn-Tapper *et al.* [39]. In more detail, Zhang *et al.* [36] performed a study on the radiation-related SCRs in organs while receiving therapy using various irradiation treatments to treat breast cancer. In that research, the Organ Equivalent Dose (OED) and EAR were determined using Dose-Volume Histograms (DVHs). With the VMAT and IMRT plans compared to 3DCRT plans, PTV received significantly lower mean doses of OARs and OED.

Bellière *et al.* [37] has examined the viability of high-dose of 74 Gy from 3DCRT for treatment of non-small-cell lung-cancer-(NSCLC). They found that radioactive lung cancer in people with high lung V20Gy. Esophagitis in grade was among the acute effects. A review of radiation-related cardiac disease was published by Darby *et al.* [38]. They discovered that breast cancer patients undergoing chemotherapy had a substantially lower survival rate after ten years. A previous study by Shore [40], low thyroid dosages of up to 10 cGy can lead to secondary cancers. Because this tissue is so close to the treatment volume, during neck-region treatment, the breast received the highest distributed dose. The bulk of the neoplasms that develop later do so either in the main field of radiation or a place that borders volume of the treatment. According to Svahn-Tapper *et al.* [39], organ exposures under 1 Gy could marginally increase the risk of developing cancer. According to Diallo *et al.* [41], 22% of subsequent tumors are developed within 5 cm of the treatment field. These findings are consistent with the findings of the current investigation, which found that organs that are located adjacent to the irradiated volume have greater Dmean values, the findings of the present investigation demonstrate that the heart, oesophagus,and contralateral lung have the highest SCRs. These data unambiguously show that, while not insignificant, there may not be much of a risk of secondary cancer development in organs far from an irradiated region. 14% of secondary malignancies, according to Gold *et al.* [42], take place outside the exposed region.

As one limitation of this study, it can be mentioned that SCRs were not calculated for other radiotherapy modalities such as IMRT, VMAT, and tomotherapy. There are also other models for SCR calculation, and they were not evaluated in this study. Calculation of SCR for other radiotherapy modalities and using other models is suggested as subjects for future study in this field.

5. Conclusion

Both EAR and ERR in the BEIR VII and ICRP models are directly proportional to dose and parameters, as demonstrated by mathematical equations. Since the risk of secondary cancer rises with higher doses to the organs, the heart and esophagus have the highest average SCRs. The pancreas and gallbladder had the lowest SCR among the sensitive organs in the treatment field, due to their smaller doses. According to the results of the current study on the use of 3DCRT for lung cancer, the SCRs from the ICRP model are higher compared to the BEIRVII model. Female patients have higher SCRs based on the ICRP model compared to male patients.

Based on the results of the current study, it is recommended that strategies should be followed to decrease the dose to the heart and esophagus and also the dose to female patients in 3DCRT of lung cancer. By choosing the appropriate field size and methods to prevent excessive doses to OARs and sensitive organs,

the care given to lung cancer patients requires caution to be able to minimize the dose that is absorbed by the surrounding organs. This may reduce the possibility of causing secondary cancer in the future for lung cancer patients undergoing 3DCRT.

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