ORIGINAL ARTICLE

Effect of radiation on endothelial functions in workers exposed to radiation

Asli Kurtar Mansiroglu[1]
Sincer Isa[1]
Gunes Yilmaz[1]

1. Abant Izzet Baysal University, Faculty of Medicine, Department of Cardiology, Bolu, Turkey

http://dx.doi.org/10.1590/1806-9282.66.7.992

SUMMARY

OBJECTIVE: *Our aim is to determine whether radiation affects the endothelial function of hospital staff working in the radiation unit for diagnostic and therapeutic purposes. We have evaluated endothelial function with vascular imaging parameters such as flow-mediated dilatation (FMD) and aortic stiffness index (ASI).*

METHODS: *A total of 75 employees, 35 of whom are exposed to radiation due to their profession and 40 as the control group, were included in our single-centered study. Demographic data, FMD, aortic stiffness, and echocardiographic findings of the two groups were compared.*

RESULTS: *There were no significant differences in demographic data. Median FMD values tended to be lower in the radiation exposure group [7.89 (2.17-21.88) vs. 11.69 (5.13-27.27) p=0.09]. The FMD value was significantly lower in the catheter laboratory group than in the radiation-exposed (p=0.034) and control (p=0.012) groups. However, there was no statistically significant difference between the non-catheter lab radiation exposed group and the control group (p=0.804). In addition, there was no statistically significant difference in the ASI value between the groups (p=0.201).*

CONCLUSION: *We have found that FMD is decreased among hospital staff working in radiation-associated areas. This may be an early marker for radiation-induced endothelial dysfunction.*

KEYWORDS: *Aortic Stiffness. Flow-Mediated Dilatation. Radiation. Endothelium, vascular. Occupational exposure. Radiation exposure.*

INTRODUCTION

Radiation is an important part of both diagnostic tests and treatment management of many diseases. When the literature was reviewed, increased cardiovascular events were noted in the follow-up of radiotherapy patients[1-3]. While many studies about radiotherapy patients have attracted attention, cardiovascular events in the employees who are exposed to ionizing radiation at work were not well defined.

It has been shown that thoracic radiotherapy in particular has accelerated the atherosclerotic process, increased frequencies of left-sided valve deterioration (most frequently aortic regurgitation), acute or chronic pericardial diseases and effusions, cardiomyopathies and conduction diseases even in patients with no cardiac risk factor[4].

There are several methods for evaluating

DATE OF SUBMISSION: 30-Dec-2019
DATE OF ACCEPTANCE: 19-Jan-2020
CORRESPONDING AUTHOR: Asli Kurtar Mansiroglu
Abant Izzet Baysal University Hospital, Department of Cardiology, Golkoy, 14280, Bolu, Turkey; Phone: +903742534656; Fax: +903742534615
E-mail: dr.asli.kurtar@gmail.com

endothelial dysfunction. Nowadays, ultrasonographic evaluation from the forearm of the flow-dependent vasodilatation is commonly used due to its simplicity, low cost, and lack of intervention. This method has proven to be quite reliable when compared to invasive methods[5]. Many blood vessels respond to shear stress by vasodilatation. This event is called flow-mediated dilatation. Radiotherapy has been shown to generate reactive oxygen species and activate the inflammatory process. Moreover, this event resulted in endothelial dysfunction in patients with Hodgkin lymphoma who received radiotherapy[4]. In addition, endothelial dysfunction is believed to be the earliest factor of many diseases[6].

Aortic elasticity is closely related to cardiovascular mortality[7]. Aortic distensibility (AD) and aortic strain (AS) are the elasticity indices of the aorta and reflect aortic stiffness[7]. It has been shown that non-invasive methods such as echocardiography and magnetic resonance were found to be as reliable as the invasive measurement with the use of a catheter with a micro manometer for the demonstration of the elastic properties of the aorta[8]. Many studies have shown that inflammation has a role in arterial stiffness probably due to endothelial dysfunction[9].

Here, we aimed to study FMD and aortic elasticity indices among radiation-exposed and unexposed hospital staff.

METHODS

This is a single-centered cross-sectional study conducted between August and November 2018 at the Bolu University Hospital. The study included 35 employees who have occupational radiation exposure (20 of them are interventional cardiologists and catheterization lab staff, 4 of them are orthopedists, 5 are interventional radiologists, and 6 urologists) and 40 employees who are away from radiation areas. The cath. lab. interventional cardiologist and lab. staff use Siemens Axiom Artis Cath/Anjio System and Siemens Axiom Artis Zee Floor Cath/Anjio System; interventional radiologists use Siemens Axiom Artis Cath/Anjio System and Siemens Artis Q Floor Cath/Anjio System; urologists and orthopedists use Siemens PowerMobile C-arms and GE OEC Brivo Prime C-arm 785 in the operating room.

All participants were informed about the study and were older than 18 years old. In the radiation-exposed group, the total working time with radiation ranged between 6 months and 26 years (6.3 ± 5.9 years). Demographic data and laboratory parameters of all employees were recorded. Presence of coronary artery disease, left ventricular heart failure (EF <50%), moderate and severe mitral and/or aortic valve disease, congenital heart disease, atrioventricular conduction abnormality, presence of pericardial effusion, moderate and severe kidney or liver disease, thyroid diseases, anemia, diabetes mellitus, dyslipidemia, hypertension, electrolyte imbalance, systemic inflammatory or infectious diseases or poor transthoracic echocardiography window were determined as the exclusion criteria. We received informed consent from each participant after approval of the study protocol by the Local Ethics Committee.

Echocardiographic evaluation

Echocardiographic procedures were performed with the 4-Mhz transducer of Vivid S6 (GE Vingmed, N-3191 Horten-Norway). All echocardiographic images were taken by a single-blind cardiologist within the left lateral position in the presence of continuous electrocardiography. And the mean of three consecutive cardiac cycles was used.

Left ventricular end-diastolic and end-systolic diameter, left ventricular septum thickness, left ventricular posterior wall thickness, and left atrium diameter were measured. Left ventricular ejection fraction was measured by modified Simpson's rule[10]. Two-dimensional and pulsed doppler measurements were taken according to the Criteria of the American Society of Echocardiography[10].

Aortic stiffness evaluation

Internal dimensions of the ascending aorta were measured in at least three consecutive cardiac cycles, at 3 cm from the origin of the aorta. The aortic systolic diameters (AoSD) and the diastolic diameters (AoDD) were taken, and then aortic strain, aortic distensibility, and aortic stiffness index were calculated according to the formulas[11]. While the systolic diameter was measured from the peak of the aorta, the diastolic diameter was measured from the R peak of the ECG.

1. Aortic diameter change (ADC): AoSD – AoDD
2. Aortic strain (AS) (%): ADC/AoDD
3. Aortic distensibility: 2x AS/PP
4. Aortic stiffness index: (SBP/DBP)/ [(ADC)/AoDD].

(SBP: systolic blood pressure, DBP: diastolic blood pressure, PP, pulse pressure: systolic blood pressure–diastolic blood pressure)

Ultrasonographic evaluation

After resting for at least 15 minutes in a quiet, dark, air-conditioned room (22–25 °C), the parameters were measured. Also, subjects were advised about going fasting for at least 8 hours and exercising, smoking, consuming alcohol or caffeine before taking the FMD measurements. The brachial artery diameter was measured in the antecubital fossa with a 7.5 MHz linear array transducer (GE Healthcare, M4S-RS, Tokyo, Hino-Shi, Japan).

The skin was marked with a pencil, so all evaluations were obtained from the same line.

TABLE 1. GENERAL CHARACTERISTICS OF THE STUDY GROUPS

Baseline characteristics	Radiation exposed group (n=35)	Control group (n=40)	P
	MEDIAN (Min-Max.)		
Age (years)	32 (22-51)	29 (20-52)	0.12
	MEAN		
Body mass index (kg/m2)	26 ±4	25± 5	0.33
Male/female	20/15	16/24	0.14
Hypertension (%)	3 (8%)	2 (5%)	0.54
Smoking (%)	12 (34%)	10 (25%)	0.38
Family history (%)	2 (6%)	7 (17%)	0.12

TABLE 2. ECHOCARDIOGRAPHIC DATA OF WORKING GROUPS

	Radiation exposed group (n=35)	Control group (n=40)	P
	MEDIAN (Min-Max.)		
EF (%)	62±5	63±4	0.23
LVDD	4.49±0.30	4.36±0.39	0.108
LVSD	2.68±0.27	2.75±0.29	0.361
LA	3.14±0.32	3.04±0.37	0.199
FMD	7.89 (2.17-21.88)	11.69 (5.13-27.27)	0.09
ASI	11.64 (3.70-76.57)	10.25 (5.63-54.06)	0.81
PW	0.92 (0.72-1.29)	0.90 (0.70-1.30)	0.11
IVS	0.89 (0.72-1.30)	0.90 (0.70-1.30)	0.17

EF: ejection fraction, LVDD: left ventricular end diastolic diameter, LVSD: left ventricular end systolic diameter, LA: left atrium, FMD: flow mediated dilatation, ASI: aortic stiffness index, PW: posterior wall, IVS: interventricular septum

TABLE 3. FMD VALUE OF WORKING GROUPS

	Radiation exposed-catheter lab group (n=22)	Non-catheter lab radiation exposed group(n=13)	Control group (n=40)	P
FMD %	5.96 (2.17-20.51)	11.90 (5.77-21.88)	11.69 (5.13-27.27)	0.025
ASI	13.9 (6.0-75.1)	9.8 (3.7-76.5)	10.2 (5.6-54.0)	0.201

FMD: flow mediated dilatation, ASI: aortic stiffness index

First, the basal diameter and flow rate of the brachial artery were taken. Then, the pressure was inflated up to 50 mmHg above the systolic blood pressure and waited for 5 minutes so the arm remained ischemic. The diameter and flow rate of the brachial artery were measured again 1 minute after the cuff pressure was lowered. FMD was calculated with the formula: FMD=100 x (maximum diameter after hyperemia-baseline diameter/baseline diameter)[11].

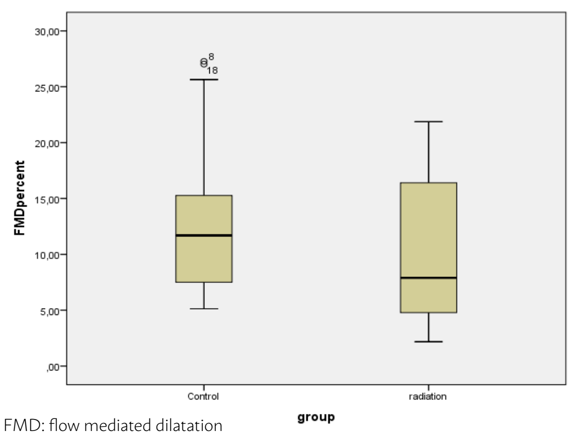
Statistical analysis

Quantitative variables were stated as mean± standard deviation (SD) and qualitative variables were expressed in numbers and percentages. The differences among independent groups were analyzed by the Student t-test in the case of normal distribution. The Mann-Whitney U test was used to compare variables without normal distribution. The Chi-Square test was used for the qualitative variables. To compare high-radiation exposed catheter lab medical staff with other medical staff and the control group, the Kruskal-Wallis test was used. A p-value < 0.05 was considered significant. Statistical analysis was carried out using SPSS v.18.0 software (IBM).

RESULTS

No significant difference was observed between the two groups in terms of demographic data (Table 1). Transthoracic echocardiography, FMD, and ASI parameters of the participants are shown in Table 2. Albeit not significant, the FMD of the radiation-exposed group tended to be lower than that of the control group [7.89 (2.17-21.88) vs. 11.69 (5.13-27.27], p=0.09 (Figure 1).

FIGURE 1. FMD COMPARISON OF CONTROL AND RADIATION GROUPS



FMD: flow mediated dilatation

The Kruskal-Wallis test revealed that the FMD value was significantly lower in the catheter laboratory group than in other radiation-exposed (p=0.034) and control (p=0.012) groups. However, there was no statistically significant difference between the non-catheter lab radiation exposed group and the control group (p=0.804). Also, there was no statistically significant difference in the ASI value between the three groups (p=0.201) (Table 3).

In Pearson's Correlation Test, the FMD value (-r=0.36, p=0.015) was significantly and negatively correlated with the presence of mean exposure time.

DISCUSSION

In our study, we found that the median FMD value tended to be lower in radiation-exposed workers.

The acute effects of radiation on the cardiovascular system may be undetected since this phase is usually asymptomatic. Therefore the rate of involvement is not clear. Endothelial damage, lipid, and inflammatory cell infiltration and lysosomal activation have been defined in this silent acute phase[12]. The use of FMD as an indirect marker of inflammation to determine this asymptomatic period is therefore important and constitutes the main purpose of our study. Reactive oxygen radicals and pro-inflammatory cytokines have been accused of radiation-mediated endothelial dysfunction. This is demonstrated by the rise of IL-6, CRP, TNF-α, and INF-ϒ-like pro-inflammatory cytokine in survivors of atomic bombs. It was also shown that the dose-dependent increase of markers that reflect systematic inflammation such as erythrocyte sedimentation rate (ESR) and IgG, IgA, and total immunoglobulins were increased[13]. Leukocyte aggregation is observed as a result of ICAM-1 and PECAM-1 activation in radiation-exposed endothelial cells[13]. With the release of thrombomodulin and PAI-1-like cytokines, endothelial cells become pre-thrombotic and atherogenic, and the pro-fibrotic process begins[14]. Increased levels of TGF-β through radiation result in collagen synthesis and fibrosis, leading to changes in the extracellular matrix[15].

In a study performed in patients with breast cancer, the endothelium-dependent vasodilatation of the axillary artery on the irradiated side was significantly reduced compared to the opposite side[16]. In another study, impaired NO-mediated relaxation in irradiated cervical arteries was related to a lack of expression of endothelial NO synthetase[17]. While carotid intima-media thickness of Hodgkin lymphoma patients increased compared with the control group in a 3-year follow-up, flow-mediated dilatation decreased in a persistent manner[18].

The known long latent period of radiation requires the follow-up of the patients after radiation exposure in a wide period of 10-15 years[19]. Radiation has effects on the pericardium, myocardium, valves, coronary arteries, and conduction system in the heart; pathology in the epicardial and endocardial coronary arteries may result from coronary obstruction; semilunar and atrioventricular valve pathology, stenosis or regurgitation are caused by valvular fibrosis; and pathology in the myocardium may result in cardiomyopathy[19]. Pericardial construction and inflammation, as well as pathologies in the transmission system and pericardium, may occur[19]. The most common cardiac effects are pericardial, while the lesser effects are in the conduction system[2]. The long latent period and the absence of specific symptoms in patients suggest that the number of patients known to be affected is very low. However, in these patient groups, the primary mechanism for death, 10 years after radiation exposure, was cardiac mortality[1]. Myocardial infarction was the most common cause of cardiac mortality[3]. Compared to the general population, 2.2-2.7 times more cardiac disease was observed in these patients[2].

Since patients with breast cancer and Hodgkin lymphoma have a relatively long cancer-specific survival and can be followed up for 10-15 years after receiving radiotherapy at a young age, cardiac effects of radiation have been examined in this patient group treated with thoracic radiotherapy (RT)[11]. Cardiac damage has been less reported in lung cancer patients treated with radiotherapy; the late-term effects of radiation could not be detected in these patients due to insufficient survival of this patient group[20]. In our study, the mean radiation exposure time is 6,3 years, and the amount of irradiation is quite lower than in patients treated by radiotherapy. Total radiation dose can reach >30-35 Gy in radiotherapy and this dose is a risk factor for radiation-induced cardio toxicity[4]. However, interventional cardiologists in high-volume centers have a radiation exposure of about 5 mSv/per year[21]. This exposure dose is higher than that of the medical staff that works at the catheter laboratory. Although we couldn't observe chronic effects that may be associated with radiation exposure, it is noteworthy that FMD value began to deteriorate even in the short term and with the low exposure dose among catheter laboratory medical staff that are relatively exposed to higher radiation dose than other radiation-exposed medical staff and control group.

It has been shown that there is a correlation between the presence of coronary artery disease (CAD) and the elastic parameters of the aorta[22]. In this hypothesis, it is suggested that vasa vasorum originating from the coronary arteries and feeding abnormalities in the arterial wall disrupt the elastic properties of the aorta in the presence of CAD[22]. It is also known that radiation-induced fibrosis may result in increased arterial stiffness and, consequently, may be a potential biomarker of radiation-induced atherosclerosis[23]. In our study, ASI parameters were not significant between the two groups. This may be explained by the process that requires 10-15 years for CAD in radiation exposure, and our study is insufficient to assess the process currently.

The most obvious effects of ionizing radiation among medical staff are on the skin and eye, especially due to direct unprotected exposure[24]. While erythema in the skin can be observed within a few hours, cataract may occur about 6 months after exposure[24]. In a meta-analysis in which cardiologists performing cardiac catheterization were compared with the control group, cataract cases were found to be significantly higher among cardiologists; the underlying biological mechanism has been interpreted as the accelerated proliferation of the endothelium and blood cells by radiation[25].

Our study is single-centered. Because there is a small number of employees in the catheter laboratory, in order to obtain the sufficient number of employees, those who received radiation as per their occupation such as orthopedy, interventional radiology, and urology, but whose exposure dose is not as high as those working in the catheter laboratory were also included. The statistical insignificance of FMD and ASI values may be due to that. Because of this, we compared three groups and showed that the FMD value was significantly lower in the catheter laboratory group. We aimed to overcome this limitation by planning a future multi-center study, with only catheter laboratory staff. In addition, the inclusion of employees from the different departments brought about the use of different brands and models of devices. Due to the irregular use of dosimeters, the exposed dose values were not included in our study. We designed our study with employees in units exposed to radiation for at least 6 months. This is one of the limitations of our study.

CONCLUSIONS

We have found that FMD may decrease among hospital staff that are exposed to radiation due to their profession. This may be an early marker for radiation-induced endothelial dysfunction and routine cardiovascular monitoring of radiation workers may prevent future cardiovascular events. Long-term follow-up and larger-scale studies should be considered for a better definition of possible cardiovascular effects among radiation-exposed medical staff.

Competing interests

The authors declare that they have no competing interests

RESUMO

OBJETIVO: *O nosso objetivo é determinar se a radiação afeta a função endotelial de funcionários do hospital que trabalham em unidades com exposição à radiação para fins diagnósticos e terapêuticos. Avaliamos a função endotelial com parâmetros de imagens vasculares, tais como dilatação fluxo-mediada (FMD) e o índice de rigidez aórtica (ASI).*

METODOLOGIA: *Um total de 75 funcionários, 35 expostos à radiação devido à sua ocupação e 40 como grupo de controle, foram incluídos em nosso estudo monocêntrico. Os dados demográficos, de FMD, rigidez aórtica e ecocardiográficos dos dois grupos foram comparados.*

RESULTADOS: *Não houve diferenças significativas nos dados demográficos. Os valores médios de FMD, em geral, foram mais baixos no grupo de exposição à radiação [7,89 (2,17-21,88) e 11,69 (5,13-27,27) p=0,09]. O valor de FMD foi significativamente menor no grupo laboratorial com cateter do que no exposto à radiação (p=0,034) e no de controle (p=0,012). No entanto, não houve diferença estatisticamente significativa entre o grupo laboratorial sem cateter e exposto à radiação e o grupo de controle (p=0,804). Além disso, não houve diferença estatisticamente significativa quanto ao valor de ASI entre os grupos (p=0,201).*

CONCLUSÃO: *Observamos que a FMD é menor entre funcionários que trabalham em setores hospitalares associados à radiação. Isso pode ser um marcador inicial de disfunção endotelial induzida por radiação.*

PALAVRAS CHAVE: *Radiação. Endotélio vascular. Exposição ocupacional. Exposição à radiação.*

REFERENCES

1. Cuzick J, Stewart H, Peto R, Baum M, Fisher B, Host H, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. Cancer Treat Rep. 1987;71(1):15-29.
2. Madan R, Benson R, Sharma DN, Julka PK, Rath GK. Radiation induced heart disease: pathogenesis, management and review literature. J Egypt Natl Canc Inst. 2015;27(4):187-93.
3. Swerdlow AJ, Higgins CD, Smith P, Cunningham D, Hancock BW, Horwich A, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. J Natl Cancer Instit. 2007;99(3):206-14.
4. Jaworski C, Mariani JA, Wheeler G, Kaye DM. Cardiac complications of thoracic irradiation. J Am Coll Cardiol 2013;61(23):2319-28.
5. Agewall S. Is impaired flow-mediated dilatation of the brachial artery a cardiovascular risk factor? Curr Vasc Pharmacol. 2003;1(2):107-9.
6. Paris F, Fuks Z, Kang A, Capodieci P, Juan G, Ehleiter D, et al. Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice. Science. 2001;293(5528):293-7.
7. Eren M, Gorgulu S, Uslu N, Celik S, Dagdeviren B, Tezel T. Relation between aortic stiffness and left ventricular diastolic function in patients with hypertension, diabetes, or both. Heart. 2004;90(1):37-43.
8. Erol MK, Yilmaz M, Oztasyonar Y, Sevimli S, Senocak H. Aortic distensibility is increasing in elite athletes. Am J Cardiol. 2002;89(8):1002-4.
9. Yasmin, McEniery CM, Wallace S, Mackenzie IS, Cockcroft JR, Wilkinson IB. C-reactive protein is associated with arterial stiffness in apparently healthy individuals. Arterioscler Thromb Vasc Biol. 2004;24:(5):969-74.
10. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA; Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr. 2002;15(2):167-84.
11. Korkmaz H, Onalan O. Evaluation of endothelial dysfunction: flow-mediated dilation. Endothelium. 2008;15(4):157-63.
12. Konings AW, Hardonk MJ, Wieringa RA, Lamberts HB. Initial events in radiation-induced atheromatosis I. Activation of lysosomal enzymes. Strahlentherapie. 1975;150(4):444-8.
13. Van der Meeren A, Squiban C, Gourmelon P, Lafont H, Gaugler MH. Differential regulation by IL-4 and IL-10 of radiation-induced IL-6 and IL-8 production and ICAM-1 expression by human endothelial cells. Cytokine. 1999;11(11):831-8.
14. Bhattacharya S, Asaithamby A. Ionizing radiation and heart risks. Semin Cell Dev Biol. 2016;58:14-25.
15. Taunk NK, Haffty BG, Kostis JB, Goyal S. Radiation-induced heart disease: pathologic abnormalities and putative mechanisms. Front Oncol. 2015;5:39.
16. Beckman JA, Thakore A, Kalinowski BH, Harris JR, Creager MA. Radiation therapy impairs endothelium-dependent vasodilation in humans. J Am Coll Cardiol. 2001;37(3):761-5.
17. Sugihara T, Hattori Y, Yamamoto Y, Qi F, Ichikawa R, Sato A, et al. Preferential impairment of nitric oxide-mediated endothelium-dependent relaxation in human cervical arteries after irradiation. Circulation. 1999;100(6):635-41.
18. Bilora F, Pietrogrande F, Campagnolo E, Rossato A, Polato G, Pomerri F, et al. Are Hodgkin and non-Hodgkin patients at a greater risk of atherosclerosis? A follow-up of 3 years. Eur J Cancer Care (Engl). 2010;19(3):417-9.
19. Sincer I, Mansuroglu AK. A review of cardiovascular disease induced by radiation. Experimental Biomedical Research 2018;1:1-5.
20. Prosnitz RG, Chen YH, Marks LB. Cardiac toxicity following thoracic radiation. Semin Oncol. 2005;32(2 Suppl 3):S71-80.
21. Abdelaal E, Plourde G, MacHaalany J, Arsenault J, Rimac G, Déry JP, et al; Interventional Cardiologists at Quebec Heart-Lung Institute. Effectiveness of low rate fluoroscopy at reducing operator and patient radiation dose during transradial coronary angiography and interventions. JACC Cardiovasc Interv. 2014;7(5):567-74.
22. Yildiz A, Gur M, Yilmaz R, Demirbag R. The association of elasticity indexes of ascending aorta and the presence and the severity of coronary artery disease. Coron Artery Dis. 2008;19(5):311-7.
23. Gujral DM, Shah BN, Chahal NS, Bhattacharyya S, Senior R, Harrington KJ, et al. Arterial stiffness as a biomarker of radiation-induced carotid atherosclerosis. Angiology. 2016;67(3):266-71.
24. Mettler Jr FA, Moseley Jr RD. Medical effects of ionizing radiation. Orlando: Grune & Stratton; 1985. 304p.
25. Elmaraezy A, Ebraheem Morra M, Tarek Mohammed A, Al-Habaa A, Elgebaly A, Abdelmotaleb Ghazy A, et al. Risk of cataract among interventional cardiologists and catheterization lab staff: a systematic review and meta-analysis. Catheter Cardiovasc Interv. 2017;90(1):1-9.