R. Basiratnia MD[1]
A. Gokizadeh MD[1]
A. Hekmatnia MD[2]
I. Fani MD[3]

Ultrasonographic Carotid Changes in Patients with Hodgkin's Disease after Radiotherapy: A Historical Cohort Study

Background/objective: Radiotherapy is the most effective treatment for Hodgkin's disease in early stages. However, it can cause various side effects in radiated tissues, e.g., vascular structures. One of the effects of radiation on vessels is atherosclerosis. The primary objective of this study was to compare the atherosclerotic changes of carotid arteries, expressed as the mean intima-media thickness (IMT), in patients with Hodgkin's disease after radiotherapy with a matched non-exposed group. We also tried to see whether there is a correlation between the time elapsed since the last radiotherapy session and the prevalence and severity of atherosclerosis. Moreover, we tested if radiation can augment the effect of age, as an independent risk factor for atherosclerosis.

Patients and Methods: In two groups of 50 patients, sonography of the common and internal carotid arteries in bifurcation of the artery was performed and the IMT was measured for both groups of patients exposed and unexposed to radiation.

Results: The mean±SD IMT was significantly higher in exposed (0.67±0.22 mm) than unexposed (0.51±0.07 mm) group. There were early atherosclerotic changes, diagnosed based on the vessel morphology, in 18% of exposed and none of the unexposed group. Correlation of IMT with age is stronger in the exposed than in the unexposed group. (r=0.61 in the exposed vs. 0.22 in the unexposed).

Conclusion: Atherosclerotic changes are more prevalent in post-radiotherapy patients that may indicate the necessity of regular and careful follow-up of these patients for the early diagnosis of vascular pathologies and considering suitable screening and therapeutic interventions for prevention of cerebral complications. Ultrasound could be a suitable technique for screening and early detection of atherosclerosis considering it's relatively low cost and non-invasiveness.

Keywords: radiotherapy, ultrasound, Hodgkin's disease, atherosclerosis

Introduction

Radiotherapy is the most effective treatment for Hodgkin's disease in early stages of the disease with a five-year survival of more than 85%.[1] However, according to inherent hazards of radiotherapy, several local side effects are expected that are related to the direct tissue injuries caused by irradiation.

Side effects of radiation on blood vessels include intimal thickening, medial degeneration and foam cells infiltration that results in vascular stenosis and occlusion—a pathologic process known as "atherosclerosis". The most sensitive layer of vessel is intima and its thickening is dose-dependant.[2]

These alterations, ultimately lead to plaque formation and fibrosis, fat infiltration, destruction of intima and formation of thrombus in small vessels.

In large vessels like carotid artery, a high prevalence of stenosis in the form of scar is observed years after neck radiotherapy.[3]

According to previous studies on Hodgkin's disease, in patients who undergo radiotherapy, carotid abnormalities, e.g., intima-media thickening (IMT) is

1. Assistant Professor, Department of Radiology, Isfahan University of Medical Sciences, Isfahan, Iran.
2. Associate Professor, Department of Radiology, Isfahan University of Medical Sciences, Isfahan, Iran.
3. Department of Radiology, Isfahan University of Medical Sciences, Isfahan, Iran.

Corresponding Author:
Reza Basiratnia
Address: Department of Radiology, Al-Zahra General Hospital, Soffeh Street, Isfahan, Iran.
Tel: +98 311-6685555
Fax: +98 311-6255555
E-mail: basiratnia@med.mui.ac.ir

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significantly more common than the control groups.[4-6] Asymptomatic stenosis of carotid is a risk factor for cerebrovascular events and therefore, early diagnosis of stenosis in these patients is of paramount importance.[7-9] For example, these patients are potential candidates for endarterectomy.[10]

Sonography is considered an appropriate diagnostic modality for the diagnosis of vascular disorders, as it is non-invasive, readily available and relatively cheap. Ultrasonographic detection of thickening of more than 0.8 mm in intima-media complex is considered abnormal and may indicate the earliest signs of atherosclerosis.[11]

The primary objective of this research was to study the atherosclerotic changes in patients with Hodgkin's disease after radiotherapy as compared to new cases of Hodgkin's disease at the same stage of the disease, before radiotherapy. We also evaluated the hypothesis that atherosclerosis becomes more prevalent and severe as time passes from radiotherapy. We also tested whether radiation can augment the effect of age, as an independent risk factor for atherosclerosis.

Patients and Methods

In this historical cohort study, 50 patients aged 19–30 years at the time of the study, presented with early-stage Hodgkin's disease earlier who were treated by radiation therapy, were selected from the records of the Department of Radiotherapy of Isfahan Seyydo-Shohada Hospital. These patients had undergone radiotherapy 5–15 years before our investigation and had received a total dose of 3500–4000 cGy. This interval was chosen based on findings of previous investigations, to allow for detectable atherosclerotic changes to take place.[4-6] The patients were asymptomatic and in complete remission of Hodgkin's disease at the time of the study. Those with neck tumor, smoking, diabetes mellitus or hyperlipidemia were excluded from the study. Fifty age-matched (age: 15–30 yrs) new cases of Hodgkin's disease presented also in early stages of the disease who had not received radiotherapy, were selected as the control unexposed group. The same exclusion criteria was applied to this group of patients. Both groups were called for an ultrasonographic study performed by an experienced sonologist using Dronier/5200 apparatus with a 7.5 MHz linear probe. The apparatus was set for carotid. Our sonologist was unaware of the status of the patients regarding their exposure to radiation. Selected parts of common carotid arteries including proximal of internal carotid arteries, one cm before bifurcation of common carotid and the space between them were assessed in supine position. IMT in proximal and far point of images was measured and the mean value of three measurements was calculated.

Apart from IMT criteria, atherosclerotic changes of carotid arteries are also classified morphologically as shown in Table 1.

Class I is considered normal—no atherosclerosis. Classes II and III are designated as early atherosclerosis. Classes IV, V and VI are categorized as advanced atherosclerosis. [4, 6, 8]

The mean IMT in exposed and unexposed groups was compared using *Student's t*-test. χ^2 test was used to compare the frequency of atherosclerosis between two groups. Pearson correlation coefficient was used to determine the correlation between carotid change and age and with the time elapsed since the last session of radiotherapy.

Results

The mean±SD of age in exposed group (32 males and 18 females) and unexposed group (30 males and 20 females) were 26.3±2.8 and 26.6±3.7 years, respectively ($p>0.05$). Sex distribution among the exposed and unexposed groups is shown in Table 2.

The mean±SD of time elapsed since the last session of radiotherapy was 7.5±2.5 (range: 5–15) years. The mean±SD of IMT in exposed and unexposed groups were 0.67±0.22 and 0.51±0.07 mm, respectively ($p<0.001$). Distribution of atherosclerotic changes in two groups based on their morphologic class is shown in Table 3. The number of patients with different classes of atherosclerosis was different between the exposed and unexposed groups (18% vs 0% respectively, ($p=0.005$).

Pearson correlation coefficient of IMT with age was 0.61 in exposed and 0.22 in unexposed group (for exposed and unexposed groups, respectively, 0.51 and 0.20 for males; and 0.71 and 0.24 for females) ($p<0.05$). Correlation coefficient between IMT and

Table1. Morphologic classification of atherosclerosis

Class	Description	
I	Clear visualization of all three layers of the vessel.	Normal
II	Discontinuity of intima and media, irregularity and loss of differentiation of layers from each other	Early Atherosclerosis
III	Visible microcalcification and plaque <2 mm	
IV	Plaque >2 mm	Advanced Atherosclerosis
V	Visible plaque with stenosis >50%.	
VI	Presence of plaque and stenosis with clinical symptoms	

Table 2. Sex Distribution among the exposed and unexposed group

sex	Exposed Group		Unexposed Group	
	Number	%	Number	%
Male	32	64	30	60
Female	18	36	20	40
Sum	50	100	50	100

Table 3. Distribution of the exposed and unexposed groups based on morphologic classification

MorphologicClass		I	II	III	IV	V	VI	Sum
Exposed	Number	41	6	3	-	-	-	50
	%	82%	12%	6%	-	-	-	100%
Unexposed	Number	50	-	-	-	-	-	50
	%	100%	-	-	-	-	-	100%

time between the last session of radiotherapy and sonography was 0.64.

Discussion

The exposed and unexposed patients did not differ significantly regarding age, as expected because they were matched for this variable ($p>0.05$). Therefore age is not considered as a confounder in our study. Furthermore, as noted in a recent article by Pourafkari et al. IMT in the third decade of life in normal Iranian population is well below the atherosclerosis threshold of 0.8 mm. Thereby, excluding the possibility of senile atherosclerosis in this age group, again we found that age and time are not to be considered as confounders .[12] In exposed group, based on our definition, overall nine (18%) patients were affected by early carotid atherosclerosis (Classes II or III). It is in keeping with previous studies like Elerding et al., who reported the figure of 22% (17 patients from 77 patients) and King's study who reported a frequency of 26% (11 patients from 42 cases).[4,6] In unexposed group, none of the patients had atherosclerosis.

The higher correlation coefficient between IMT and age (0.61) in the exposed group compared to the unexposed indicates that radiotherapy could augment the effect of age, as a risk factor for atherosclerosis.

One possible explanation is that radiation triggers a cascade of pathologic events that hastens the usual senile atherosclerosis and it does not stop after the discontinuation of radiation exposure and thus as time passes, atherosclerosis becomes more and more severe.The high correlation coefficient between IMT and radiotherapy-sonography time interval in the exposed group, revealed that the incidence of early atherosclerosis increases as the time passes from the last session of radiotherapy, Again confirming the above deduction.

We conclude that radiation can be considered as a risk factor for atherosclerosis and enhance the effect of other risk factors like age which may indicate the necessity of screening in these patients for early diagnosis of vascular alterations and implementing suitable therapeutic interventions for the prevention of cerebral complications. Sonography has benefits over other expensive and invasive methods and is a suitable technique for early detection of these vascular side effects. Other studies are needed to see if screening in these high risk patients is cost effective.

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