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Effects of Neck Radiation Therapy on Carotid Arteries in Patients with Head and Neck Carcinoma

Hosein Aghamiri [1], Amin Rahmani [2], Mir Ramin Khatib Shahidi [1], Shaghayegh Kamian [2], Ahmad R Mafi [2]✉

[1] Neurology Department, Shahid Beheshti University of Medical Sciences, Imam Hosein Hospital, Tehran, Iran
[2] Radiation Oncology Department, Shahid Beheshti University of Medical Sciences, Imam Hosein Hospital, Tehran, Iran

Abstract

Background: Radiotherapy is a main treatment modality for cancers of the head and neck (HNC). However, it can cause a number of complications, including carotid artery damage. This study aimed to determine the effect of head and neck radiotherapy on carotid Doppler ultrasound findings in patients with HNC treated at Imam Hossein University Hospital. **Materials and Methods:** This research is a descriptive-longitudinal and prospective study conducted in 2022 on patients with HNC undergoing neck radiotherapy. In this study, before the initiation of radiotherapy, the patients underwent neck carotid artery Doppler ultrasound and various parameters including peak systolic velocity (PSV), end-diastolic velocity (EDV), internal carotid artery/common carotid artery (ICA/CCA) PSV, the number of plaques, intimal thickness, and percentage of carotid diameter stenosis, were recorded. The Doppler ultrasound was repeated six months later, addressing the same characteristics, and the collected data were compared. **Results:** Of 49 investigated patients, 32 (65.3%) were male (mean age=59.46 years). PSV, EDV, and ICA/CCA ratios showed no statistically significant difference 6 months following the completion of radiotherapy compared to the initial investigation. On the other hand, the percentage of carotid artery stenosis, the middle intimal membrane thickness, and the number of vascular plaques increased significantly ($P<0.05$). **Conclusion:** Carotid artery stenosis due to radiotherapy seems to be a common complication; however, radiotherapy probably has minimal effects on other ultrasound parameters of carotid arteries including EDV, PSV, and ICA/CCA ratio.
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Keywords: Radiotherapy; Ultrasound Results; Carotid Arteries; Head and Neck Cancer

Introduction

Based on recent data, lip, oral cavity, and pharyngeal cancers are responsible for approximately 3.2 percent of global cancer deaths [1]. Head and neck cancers (HNC) are the seventh most common cancer worldwide, encompassing malignancies originating from various areas such as the skin, nasal cavity, oral cavity, pharynx, and larynx. The most prevalent type of HNC is squamous cell carcinoma, with other types including adenocarcinomas, adenoid cystic carcinomas, lymphomas, and plasmacytoma [2-5]. They account for approximately 4% of malignancies with a 10-50% five-year recurrence rate [6, 7] and

✉ **Correspondence to:**
Ahmad R Mafi, Radiation Oncology Department, Shahid Beheshti University of Medical Sciences, Imam Hosein Hospital, Tehran, Iran.
Telephone Number: 0098-02123871
Email Address: ahmadrmafi123@yahoo.com

are responsible for about half a million annual deaths worldwide [8-11]. HNC treatment typically involves a combination of surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy [4, 5, 8, 12-14]. Radiotherapy is a key treatment modality for HNCs, although it can lead to complications such as carotid artery stenosis [15, 16]. As radiotherapy more often affects the cells with a higher proliferation rate (epithelial, and endothelial cells), these cells are more prone to develop radiation-induced complications [7, 17].

Despite improvements in the planning and delivery of radiotherapy, carotid artery stenosis remains one of the notable adverse effects of radiotherapy in HNC survivors [18-20]. Previous studies have demonstrated that significant changes can occur in the carotid arteries and other vessels following head and neck radiotherapy [21, 22]. Carotid artery Doppler ultrasound is a reliable, sensitive, and non-invasive method for the diagnosis of carotid artery disorders [23, 24]. This study aims to explore the impact of neck radiotherapy on carotid artery Doppler ultrasound results in HNC patients.

Materials and Methods

This study is a descriptive-longitudinal prospective study conducted on 49 patients with HNC who were referred to the Department of Clinical Oncology, Imam Hossein Hospital and underwent head and neck radiotherapy in

Table 1. Demographic Characteristics of Patients Participating in the Study

Variable	Sub-Variable	Frequency	Percentage
Gender	Male	32	65.3
	Female	17	34.7
Marital status	Single	6	12.7
	Married	43	87.8
Educational level	Under diploma	9	18.4
	Diploma	12	24.5
	Associate	5	10.1
	Bachelor	19	38.8
	Master and higher	4	8.2
Occupation	Employee	11	22.4
	Freelancer	18	36.7
	Housewife	9	18.4
	Retired	11	22.4
Economic status	Poor	8	16.4
	Moderate	35	71.4
	Good	6	12.2
Place of residence	City	36	73.5
	Village	13	26.5
A family history of cancer	No	37	75.5
	Yes	12	24.5
Alcohol use	No	41	83.7
	Yes	8	16.3
Cigarette use	Yes	33	67.3
	No	16	32.7
Carotid arteries exposed to radiotherapy	Right	13	26.5
	Left	15	30.6
	Both sides	21	42.9

2022 and 2023. The inclusion criteria included patients with a definite diagnosis of HNC that needed radiotherapy to the neck area, who were willing to participate in the study. The exclusion criteria included patient death for any reason before the second investigation and consent withdrawal. A checklist was used to collect the data including demographic characteristics and ultrasound findings of the patients, including peak systolic velocity (PSV), end-diastolic velocity (EDV), ICA/common carotid artery (ICA/CCA) PSV, the number of plaques, intimal thickness, and percentage of carotid diameter stenosis, assessed before the initiation and 6 months after the completion radiotherapy. According to the of Akhan et al. [21] with assumption of Diameter stenosis of Less than 50% in pre-irradiation and post-irradiation, equal to 8.8% () and 51.1% (), respectively, α=0.01 and β=0.1 and by use of the following sample size formula, the obtained minimum sample size (n) is 28, but due to the fact that we had more samples in this study, 49 people were included in each of the groups under study.

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 [p_1(1-p_1) + p_2(1-p_2)]}{(p_1 - p_2)^2}$$

Statistical Method and Data Analysis

The data were analyzed using the Statistical Package for the Social Science-27 (IBM SPSS Statistics for Windows, version XX (IBM Corp., Armonk, N.Y., USA)). The results of quantitative data and qualitative data were reported as mean ± standard deviation and number (percentage), respectively. Paired t-test was used to compare the mean of quantitative variables (the middle intimal membrane thickness and the number of plaques) before and 6 months after radiotherapy. The McNemar test was used to compare the frequency distribution of qualitative variables (PSV, EDV, carotid diameter size, and the classified ICA-to-CCA ratio) before and 6 months after radiotherapy. The normality of the frequency distribution of the quantitative variables was assessed using the non-parametric Kolmogorov-Smirnov test, and the equality of variance of the groups was assessed via Levene's test. The significance level in the tests was considered 0.05 (Table-2).

Results

In this research, 49 patients (mean age=59.46 years) were studied, of which 32 (65.3%) were male. Table-1 demonstrates the demographic characteristics of the investigated patients. As seen in Table-3, the results of the McNemar statistical test demonstrated that EDV did not show a statistically significant

Table 2. Comparison of Peak Systolic Velocity in Carotid Arteries before and 6 Months after Radiotherapy

Carotid Type	PSV (CM/S)	Before Radiotherapy		6 Months After Radiotherapy		P-value
		Frequency	Percentage	Frequency	Percentage	
Right carotid	Less than 125	34	100	32	94.1	0.5*
	125-230	0	0	2	5.9	
	More than 125	0	0	0	0	
	Invisible	0	0	0	0	
Left carotid	Less than 125	36	100	35	97.2	1*
	125-230	0	0	1	2.8	
	More than 125	0	0	0	0	
	Invisible	0	0	0	0	
Sum of both	Less than 125	70	100	67	95.7	0.25*
	125-230	0	0	3	4.3	
	More than 125	0	0	0	0	
	Invisible	0	0	0	0	

PSV: Peak systolic velocity, McNemar Test*

Table 3. Comparison of End-diastolic Velocity in Carotid Arteries before and 6 Months after Radiotherapy

Carotid Type	EDV (CM/S)	Before Radiotherapy		6 Months After Radiotherapy		P-value
		Frequency	Percentage	Frequency	Percentage	
Right carotid	Less than 40	34	100	33	97.1	1*
	40-100	0	0	1	2.9	
	More than 100	0	0	0	0	
Left carotid	Less than 40	36	100	33	91.7	0.25*
	40-100	0	0	3	8.3	
	More than 100	0	0	0	0	
Sum of both	Less than 40	70	100	66	94.3	0.125*
	40-100	0	0	4	5.7	
	More than 100	0	0	0	0	

EDV: End-diastolic velocity, McNemar Test*

Table 4. Comparison of the Percentage of Carotid Artery Stenosis before and 6 Months after Radiotherapy

Carotid Type	percentage of Carotid Diameter Stenosis	Before Radiotherapy		6 Months After Radiotherapy		P-value
		Frequency	Percentage	Frequency	Percentage	
Right carotid	Normal	32	94.1	15	44.1	>0.001*
	Less than 50%	2	5.9	19	55.9	
	50-67	0	0	0	0	
	Above 70%	0	0	0	0	
Left carotid	Normal	33	91.7	19	52.8	>0.001*
	Less than 50%	3	8.3	17	47.2	
	50-67	0	0	0	0	
	Above 70%	0	0	0	0	
Sum of both	Normal	65	92.9	34	48.6	>0.001*
	Less than 50%	5	7.1	36	51.4	
	50-67	0	0	0	0	
	Above 70%	0	0	0	0	

McNemar Test*

change at 6 months after radiotherapy. Table-4 shows that radiotherapy can cause significant carotid artery stenosis (P<0.001). Among 65 carotid arteries with normal diameters before radiotherapy, 31 (47.7%) developed less than 50% stenosis after radiotherapy. Table-5, shows that ICA/CCA PSV ratio did not change significantly during the study period. Table-6, demonstrates that the mean score of the middle intimal membrane thickness and the number of plaques of carotid arteries had a statistically significant difference 6 months after radiotherapy (P<0.05).

Discussion

The impact of neck radiotherapy on the results of carotid artery Doppler ultrasound in patients with HNC is the subject of ongoing research. Radiotherapy is the main treatment modality for many head and neck malignancies, and many patients survive long enough to experience its complications such as carotid artery damage [21]. Results of this study, which examined the effects of radiotherapy on neck vessels, revealed that radiotherapy does not have a short-term impact on PSV, EDV,

Table 5. Comparison of the Ratio of PSV of the Internal Carotid Artery to PSV of the Common Carotid Artery before and 6 Months after Radiotherapy

Carotid Type	ICA/CCA PSV Ratio	Before Radiotherapy		6 Months After Radiotherapy		P-value
		Frequency	Percentage	Frequency	Percentage	
Right carotid	Less than 2	32	94.1	30	88.2	0.5*
	2-4	2	5.9	4	11.8	
	More than 4	0	0	0	0	
Left carotid	Less than 2	33	91.7	30	83.3	0.25*
	2-4	3	8.3	6	16.7	
	More than 4	0	0	0	0	
Sum of both	Less than 2	65	92.9	60	85.7	0.063*
	2-4	5	7.1	10	14.3	
	More than 4	0	0	0	0	

ICA/CCA PSV: Internal carotid artery/ common carotid artery peak systolic velocity, McNemar Test*

and ICA/CCA ratio, whereas it increases the rate of carotid artery stenosis, middle intimal membrane thickness, and the number of vascular plaques within 6 months following its completion.

Even prophylactic reduced-dose radiotherapy to the neck lymph nodes (45-46 Gy, 1.8-2 Gy per fraction) led to increased middle intimal membrane thickness and increased number of plaques, according to the results. Our results are similar to that of Carmody et al.'s study, suggesting that high-dose radiotherapy might be an important risk factor for accelerating carotid atherosclerosis [25]. In line with our research, Lam et al. in their study showed that patients with nasopharyngeal carcinoma are prone to develop radiation-induced carotid artery stenosis. As a result, regular follow-up ultrasound examinations seemed to be essential for early diagnosis and potential therapeutic interventions in this group of patients [26].

Elerding et al. by investigating the incidence of carotid artery disorders after external neck radiotherapy of head and neck cancer recommended that all survivors undergo non-invasive vascular studies in their follow-up visits, especially five years after radiotherapy had finished [27].

Dubec et al. in their study on 45 patients stated that radiotherapy adversely impacted large arteries and routine color Doppler examinations at follow-ups should be considered for patients receiving head and neck radiotherapy [28]. Results of another study evaluating carotid artery stenosis after radiation therapy for nasopharyngeal carcinoma demonstrated that patients had an increased risk of developing carotid artery stenosis approximately five years after completion of radiotherapy [29]. In their study investigating the impacts of radiotherapy on carotid arteries in patients with HNC, Akhavan et al. reported that radiotherapy increased the number of plaques in the arteries but had no significant effect on the middle intimal membrane thickness [21].

Other studies have indicated that radiotherapy can result in increased intima-media thickness and subsequently carotid artery stenosis, which increases the risk of cerebrovascular accidents, such as transient ischemic attack and stroke [30, 31].

The exact pathophysiology of radiation-induced carotid artery stenosis is still unknown. One important mechanism might be the dysfunction of endothelial cells that are highly sensitive to radiation. Damaged endothelial cells fail to function as a barrier against plasma lipoproteins. As a result, lipid filtration can activate the lysosomal system and result in the proliferation of endothelial cells [30].

In addition, radiation-induced atherosclerosis can cause carotid artery stenosis. Clinical evaluation of radiation-induced carotid injury includes diagnosis of newly formed lesions, adjustment of radiation and injury site, and consideration of the time between radiation and onset of symptoms [32]. It can be hypothesized that radiation-induced carotid stenosis

Table 6. Comparison of the Middle Intimal Membrane Thickness and the Number of Plaques in Carotid Arteries before and 6 Months after Radiotherapy

Variable	Carotid Type	Before Radiotherapy		6 Months After Radiotherapy		P-value
		Frequency	Percentage	Frequency	Percentage	
Middle intimal membrane thickness	Right carotid	0.67	0.22	0.77	0.12	0.027*
	Left carotid	0.81	0.14	0.88	0.08	0.017*
	Sum of both	0.74	0.12	0.83	0.20	0.001*
Number of vascular plaques	Right carotid	1.08	0.71	1.94	1.09	>0.001*
	Left carotid	1.02	0.60	2.13	1.04	>0.001*
	Sum of both	1.05	0.65	2.04	1.06	>0.001*

PairedT-test*

is a potentially fatal complication of head and neck radiotherapy, and that its diagnosis and treatment could be lifesaving for cancer survivors.

In this study, PSV, EDV, and ICA/CCA ratio remained stable in the patients. This is similar to the results of Akhavan et al. study that concluded that radiation therapy probably has minimal effects on carotid blood flow parameters [21]. In contrast to the results of our study, the results of the study by Mohammad Karim et al showed that the hemodynamic parameters of CCA change as a result of radiotherapy, and these changes can lead to late complications such as ischemic stroke [33].

A Comparison of the results of this study with previous studies indicates that the hemodynamic parameters of the common carotid arteries can change during radiotherapy and cause late complications. Meticulous attention to carotid arteries in radiotherapy planning and avoidance of hot spots can -to some extent- alleviate the impacts of radiation on carotid arteries. This sequela should not be considered benign and should be treated in the same way as other causes of carotid stenosis.

Conclusion

Carotid artery stenosis seems to be a common vascular complication of neck irradiation, and its long-term consequences may take years to manifest clinically. Radiotherapy probably has minimal effects on other ultrasound parameters of carotid arteries including EDV, PSV, and ICA/CCA ratio. A more accurate assessment of the studied parameters and the study of the clinical significance of these changes require a longer follow-up.

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Conflict of Interest

None declared.

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