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Ultrasound Evaluation of Carotid Arteries in Patients Post Radiotherapy

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ABSTRACT

OBJECTIVE: To assess in a cross-sectional study if radiotherapy to the carotid area has any effect on the intima- medial thickness of the common carotid artery.

METHOD:

A cross sectional study comparing the intima-medial thickness of common carotid artery of forty subjects who received radiotherapy for head and neck cancer with forty matched healthy subjects who no history of irradiation to head and neck and meeting the inclusion and exclusion criteria of the study .Data obtained was statistically analysed on SPSS 10.0.

RESULTS:

Intima-medial thickness(IMT) was found to be significantly higher(p value< 0.0001) in post radiotherapy patients compared to healthy subjects with a short follow up interval (mean duration 1year 2months)

There is no significant difference (p value 0.95)in the IMT between cases treated with combined chemo-radiotherapy and cases treated with radiotherapy alone.

CONCLUSION:

Patients who have had radiotherapy for treatment of head and neck malignancy are at increased risk of accelerated atherosclerosis in common carotid artery which inturn can lead to cerebrovascular accidents. Common carotid IMT was increased after radiotherapy to the head and neck in subjects with no other major risk factors for atherosclerosis. As changes in carotid IMT are the earliest indicators of atherosclerosis, routine ultrasound of the carotid arteries is advisable for patients who have received radiotherapy to the head and neck

KEYWORDS: Radiotherapy Intima-medial thickness(IMT) Carotid Ultrasound

INTRODUCTION

Radiotherapy(RT) as a single modality or in combination with surgery has been widely used in the treatment of head and neck tumors for many years, and this has resulted in marked improvement in survival of patients with these tumors, who previously had a dismal prognosis. Successful treatment increases survival but also puts the patient at risk of radiation-related side effects. Of these, vascular side effects are serious and may be life-threatening [1].

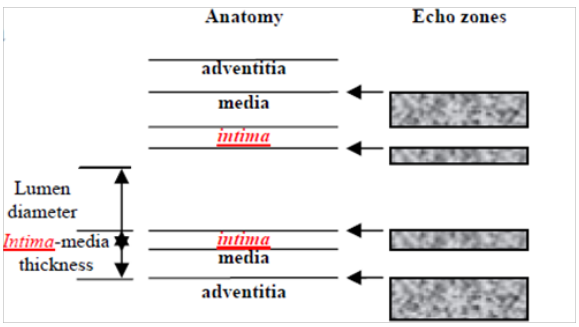
The downside of this success in treatment advances is the occurrence of long-term treatment related complications. Vascular disease, like ischemic stroke, is one of the most important determinants of late morbidity and mortality after RT.

The underlying pathogenetic mechanism in RT-related vascular changes is partly different from classical atherosclerosis. Whereas classical atherosclerosis is merely a disease of the intimal layer predominated by inflammation and lipid storage; RT related vascular changes affect all the three arterial layers (i.e. the intima, the media and the adventitia). On the one hand, already existing atherosclerotic lesions seem to worsen by RT, but RT itself can also induce atherosclerotic changes in atherosclerotic-naive, young patients Histological examination showed endothelial damage in an early post-RT stage. In the chronic phase, this probably leads to a cascade of inflammatory reactions that result in the proliferation of the endothelial (i.e. intima) layer, fibrosis of the medial layer, and obliteration of the vasa vasorum in the adventitial layer. The combination of these changes will eventually lead to narrowing of the arterial lumen. Correspondingly, thickening of the inner wall, expressed as the intima-media thickness (IMT), seems to be an independent predictor of cerebrovascular disease[2]. RT could lead to enhancement of the IMT progression which in turn can result in carotid artery stenosis and consequently to ischemic cerebrovascular disease.

Patients who have undergone RT often show occlusive carotid disease at different locations compared to patients with classic age-related atherosclerosis. In general, these occlusive lesions are more extensive after RT and are often found outside the bifurcation: in the common carotid artery, the distal internal carotid artery, or the external carotid artery, which corresponds to the full radiation area.

The traditional dogma that radiation related changes take 10–15 years to reach clinical significance has been questioned. Induction of a thrombosis of the carotid has been postulated to explain the early (within 36 months) appearance of symptoms in young patients (age 25–40 years), although work in the laboratory has documented ``physiological aging'' and plaque formation in the carotid within days of radiation exposure [3].

Measurement of the intima–media thickness (IMT) of the common carotid artery is feasible with today's high-resolution ultrasound machines. When the ultrasound beam is at right angles to the carotid walls, two white lines are seen in the vessel, particularly on the far wall. The first line corresponds to the blood–intima boundary and the second to the outer media–adventitia region. The IMT is the distance between these two interfaces(fig 1) [4]. Change in IMT of the carotid arteries has become well established in epidemiological studies as a marker of the early changes of atherosclerosis[4]. It has also proven to be a powerful predictor of future cerebrovascular disease [5]



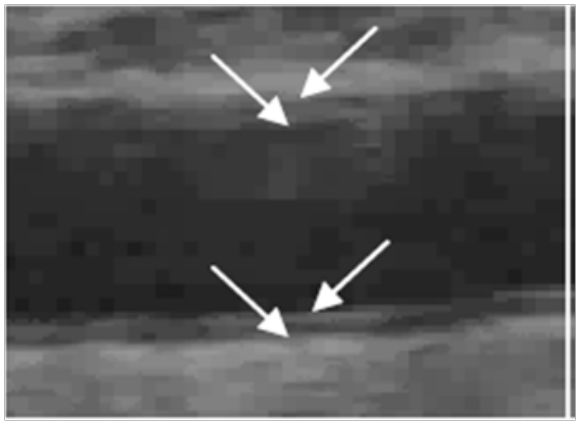


Fig 1:Correspondence of anatomical structure of carotid artery(CA) to the zones of acoustic reflections: **above** scheme of CA anatomy and ultrasound image of echo zones; **below** - typical B-scan image of CA. White arrows corresponds to the blood–intima boundary and the second to the outer media–adventitia interface.

This study was conducted to determine if irradiation to the carotid area for treatment of head and neck malignancy has any latent effect on IMT of the common carotid artery in comparison with non-irradiated subjects matched for age, sex and race.

MATERIAL AND METHODS

Forty subjects were recruited from outpatient clinics of Acharya Tulsi Regional Institute of Oncology, PBM Hospital Bikaner Rajasthan using a purely purposive sampling method. Radiotherapy charts were reviewed to confirm that the carotid arteries were within the irradiated field.

Forty healthy adult subjects were recruited for the control group. They had no history of irradiation to the head and neck and met the inclusion and exclusion criteria for the control group. Age, sex and race of the control group were matched those of the irradiated group.

INCLUSION CRITERIA

Inclusion criteria for the irradiated group were:

1) Radiation therapy to the carotid area for treatment of malignancy
2) Radiotherapy to have occurred at least 1 year before the ultrasound examination.

Inclusion criteria for the control group were:

1) No history of radiation to head and neck region
2) Same age, gender and race as the irradiated patients.

EXCLUSION CRITERIA

Exclusion criteria for the irradiated and non-irradiated groups were:

1) History of previous cardiovascular disease
2) History of connective tissue disorder or vascular disease
3) Diabetes mellitus
4) Hypertension.

INSTRUMENTATION

Sonological examination of the carotid and the vertebral arteries was done using a L&T SEQUINA color Doppler scanner with a linear band probe of frequency 6.6 to 14 MHz's

METHODS

Ultrasound of both common carotids and proximal portions of internal and external carotid arteries were performed in transverse and longitudinal planes. The intima-media thickness is defined as the distance between the echogenic line blood intima interface and the line representing the media adventitia interface. The intima-medial thickness was measured along the posterior wall of the common carotid in the longitudinal plane by using an anterolateral approach with the transducer head perpendicular to the vessel. Measurements of the intima-medial thickness were performed on magnified, static images with electronic calipers. The intima-medial thickness were recorded three times at each of the six sites: the proximal, middle and distal common carotid artery, the mean intimomedial thickness was calculated.

The vessel wall at the common carotid artery bifurcation and in the proximal portions of the internal and external carotid arteries were subjectively assessed due to difficulty in obtaining consistent images perpendicular to ultrasound beam.

OBSERVATIONS AND RESULTS

A total of 80 patients with head and neck malignancies underwent ultrasound evaluation of carotid arteries. Of these 40 subjects had received radiotherapy to neck, 40 were controls. Of the 40 subjects in each group, 37 were males and 3 were females.

Mean age among cases was 50.52 $\pm$ 7.12 SD with age ranging from 32-67 years and among controls was 50.55 $\pm$ 7.72 with age ranging from 34 – 63 years

The mean dose of radiotherapy for patients for head and neck (except Hodgkins lymphoma) cancer was 64.7 Grays, the patients of Hodgkins lymphoma received a mean dose of 40 Grays.

The mean duration since the completion of radiotherapy was 1year 2.3 months, the minimum duration of 1 year and a maximum of 1year and 4 months.

The sites of malignancy were alveolus(1) base of tongue,(6) buccal mucosa(2), hodgkins lymphoma(5), larynx-glotic(3), Larynx- Supraglotic(3),nasopharynx (6)oropaharynx(3), post cricoid(1), pyriform fossa(5), tongue(2),tonsil(2). The control cases were matched to simlar areas.

Table 1: Comparison of IMT values among cases and controls for the effect of Radiotherapy :

Study Group	Mean IMT (mm)	Standard deviation	t value	p value
Group I (post radiotherapy cases) (N= 40)	0.803	0.16	5.85	0.0001
Group II (Controls) (N=40)	0.633	0.09		

There is a significant difference in the IMT between cases and controls. IMT is significantly higher in cases post radiotherapy.(FIG 2 and FIG 3)

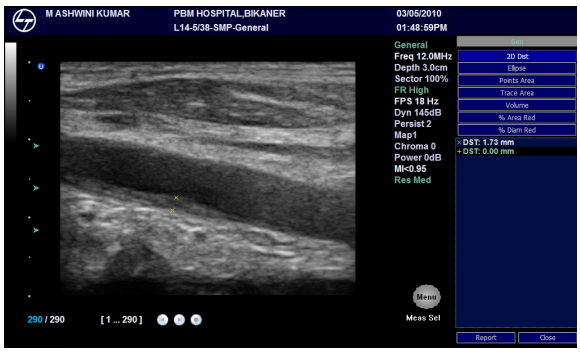


Fig2 : Increased intima-medial thickness(1.73mm) of mid common carotid artery post radiotherapy

Fig 3: Longitudinal ultrasound image of the CCA in a control case.The intima-medial thickness(0.51mm) is depicted by electronic calipers. The near caliper shows the intima-lumen interface and the far caliper shows the media- adventitia interface

Table : 2 Comparison of IMT values post radiotherapy and new case of Hodgkins lymphoma:

Study Group	Mean IMT (mm)	Standard deviation	t value	p value
Group I (post radiotherapy cases) (N=5)	0.67	0.07	3.6	0.0006
Group II (Controls) (N=5)	0.54	0.04		

There is a significant difference in the IMT between cases and controls of patients with Hodgkins disease. IMT is significantly higher in cases post radiotherapy.

Table : 3 Comparison of IMT values among Smokers and Non Smokers:

Study Group	Smoker /Non Smoker	Mean IMT (mm)	Standard deviation	t value	p value
Group I (post radiotherapy cases)	Smokers (n=27)	0.855	0.17	3.27	0.002
	Non Smokers (n=13)	0.695	0.06		
Group II (Controls)	Smokers (n=25)	0.66	0.09	3.16	0.003
	Non Smokers (n=15)	0.577	0.061		

(* p < 0.05 - Significant)

There is a significant difference in the IMT between smokers and non smokers in both the groups. IMT is significantly higher in smokers than in non smokers in both the groups

Table : 4 Comparison of IMT values in patients treated with or with chemothrapy

Study Group	Mean IMT (mm)	Standard deviation	t value	p value
Cases treated with combined chemo-radiotherapy (n=34)	0.80	0.17	0.0546	0.957
Cases treated with radiotherapy alone (n=6)	0.804	0.13		

There is no significant difference in the IMT between cases treated with combined chemo-radiotherapy and cases treated with radiotherapy alone.

DISCUSSION

The study documents that there is thickening of the intima-media thickness of the common carotid artery in patients with a history of radiation to the head and neck compared with fully matched non irradiated subjects (p<0.001). High-resolution B-mode instruments allow the measurement of the thickness of Intima-media complex. Thickening of this complex might represent the initial step of atherosclerosis and hence its measurement is of clinical importance [06].

It has been postulated that RT induces acute endothelial damage, which in turn causes endothelial proliferation[07] as well as chronic fibrosis of the media and occlusive changes of the vasa vasorum of the adventitia. These changes will produce atherosclerotic like plaques resulting in vascular stenosis and thrombo-embolic processes.

This study was designed to evaluate the IMT of common carotid arteries in patients of head and neck cancer treated with radiotherapy in age and sex matched controls. Physical parameters like blood pressure and biochemical parameters like FBS, PPBS, lipid profile were reviewed and those with elevated values were excluded from the study.

The total therapeutic radiation dose ranged from 40 to 66 Gy and was delivered in fractions of 2.0 Gy. The patient's radiotherapy charts were reviewed so as to ascertain the inclusion of CCA in the radiated field.

A total of 40 patients treated with radiotherapy and 40 control subjects, newly diagnosed cases of head and neck cancer were evaluated. Each group had 37 males and 3 females.

Previous studies have shown that the IMT of irradiated individuals is higher than that of non-radiated individuals 8, 9. In this study also, the IMT was significantly higher in irradiated than in non-radiated individuals. In our study, the mean IMT post radiotherapy in this study was 0.80 + 0.167 SD mm while that of the non-irradiated was 0.63 + 0.09 SD mm. In previous studies by M Shariat et al and Kamil Muzaffar et al the mean IMT post radiotherapy was 0.74 and 0.84 while that of the non-irradiated were 0.46 and 0.67 mm respectively 10, 11.

The effect of dose of radiotherapy on the IMT was studied. The dose in our study ranged from 40 – 66 Gy. The patients could be categorized in two groups one constituting of patients of Hodgkin's lymphoma with a radiation dose of 40 Gy and other with patients with head and neck carcinomas with a dose of 64 – 66 Gy. There was a statistically significant increase in IMT in both groups as compared with respective controls. The mean IMT in the group with higher dose of radiotherapy (64-66 Gy) was 0.82 + 0.16 SD mm as compared with controls who had mean IMT of 0.65 + 0.09 SD mm. The mean IMT in the group with lower dose (40Gy) of radiotherapy was 0.68 + 0.7 SD mm as compared with controls who had mean IMT of 0.54 + 0.04 SD mm. thus showing a higher increase of IMT at 64-66 Gy from 40 Gy. Similar findings of relation of dose of radiotherapy and IMT were observed in a previous study by Maria Elena Gianicolo1et al 12, but Chung et.al13found no dose-effect relationship with RT dose.

The smokers had a significantly higher IMT both in the controls (0.66+0.09 SD v/s 0.57+0.061 SD) and cases (0.855 + 0.17 SD v/s 0.69 + 0.06 SD mm). Earlier studies have also show a significant increase in IMT in smokers by Viveca M. Bhat et al 14.

The IMT of those cases who received combined chemotherapy and radiotherapy (64 – 66 Gy) was 0.80 + 0.17 SD and those treated with only radiotherapy (64 – 66 Gy) was 0.80 + 0.13 SD. Our study did not show any difference in the IMT with or without chemotherapy. Similar results were shown by Leonard J. King 08.

The mean duration of interval since the completion of radiotherapy was 1year 2.3 months. Earlier studies had suggested a long latent period as long as 20 years for the effects of radiotherapy on carotid artery 15. Results for recent studies by Gianicolo and Kamil Muzaffar including this study show a significant increase in IMT with a short follow-up interval 7,11

None of the irradiated patients in this study had neurological symptoms. 15 (37.5 %) cases had abnormal IMT (>0.8 mm) [04]. There was only one (2.5 %) abnormal IMT measurement in the control group.

The potential for stroke is well recognised in patients with head and neck cancer and is generally considered a risk related to pre-existing atherosclerotic disease. As the IMT of the common carotid is a good predictor of stroke[02], our data and those from other reports should heighten awarenesss that patients who have had radiotherapy for treatment of head and neck malignancy are at increased risk of accelerated atherosclerosis in common carotid artery which inturn can lead to cerebrovascular accidents. As most patients in early changes in post radiation carotid injury are asymptomatic, early detection and monitoring is possible by routine ultrasound examination and measurement of IMT.

Also, recognition of the increased risk of developing accelerated atheromatous changes in the extracranial carotid arteries of patients irradiated for head and neck tumors should prompt a reassessment of risk-benefit implications of prophylatic neck irradiation.

CONCLUSION

Common carotid IMT was increased after radiotherapy to the head and neck in subjects with no other major risk factors for atherosclerosis.

There was also a positive relation of smoking and dose of radiotherapy on carotid artery injury. No effect of chemotherapy on IMT was evident.

As changes in carotid IMT are the earliest indicators of atherosclerosis, routine ultrasound of the carotid arteries is advisable for patients who have received radiotherapy to the head and neck

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