Neck Irradiation: A Risk for Carotid Atherosclerosis

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Abstract

Background: Radiation injury to the carotid arteries, with resultant stenosis and stroke, is a well-known long-term sequel for cervical radiotherapy (RT), the objective of the present study is to determine whether irradiation is an independent risk factor for carotid atherosclerosis and propose guidelines for patients follow-up.

Design: A retrospective case control study.

Patients and Methods: Tow groups of head and neck cancer patients matching in age, sex, smoking and incidence of diabetes mellitus and hypertension. Group I twenty eight post neck irradiation treated patients and a 22 cancer patients with no history of irradiation therapy (group II). Both groups subjected to physical examination, laboratory assessment including total lipid profile, fasting blood sugar and HbAlc. Carotid duplex study was done to all patients assessing intima-media thickness, plaque existence and lumen reduction.

Results: Patients in group I (radiotherapy treated cancer patients) show statistical significant difference in numbers of TIAs and the audible carotid bruit (p value 0.04). Measurement of Intima-Media thickness by carotid duplex show statistical significant increase in thickness in group I compared to group II (p value 0.001).

Conclusion: Neck irradiation should be considered a risk factor for occlusive carotid artery disease and yearly duplex scanning follow-up for all patients after neck irradiation is recommended.

Key Words: Carotid duplex – Cancer neck – Intima – Media thickness.

Introduction

Radiation injury to the carotid arteries, with resultant stenosis and stroke, is a well-known long-term sequel for cervical radiotherapy (RT) [1]. The following factors may influence such injury: Type of radiation, number of fractions, dose and time interval from treatment [2]. The vascular injury induced by irradiation involves all layers of the vessel wall and is characterized by endothelial cell proliferation, medial scarring and loss smooth muscle and adventitial fibrosis [3]. Irradiation may also accelerate the development of atherosclerosis.

Earlier diagnosis and better treatment options have lead to improvements in cancer-specific survival for most tumor types, but this also results in an increased number of patients at risk of developing treatment related side effects. At least one-half of all cancer survivors will have received radiotherapy during their treatment and vascular injury is the major cause of late radiation morbidity [4].

However, since atherosclerosis is common, it may be difficult to distinguish irradiation-induced from atherosclerotic vascular disease.

The aim of the present study were to determine weather irradiation is a risk factor for development of carotid stenosis; to assess the effect of neck irradiation on the severity of carotid arterial disease and to propose guidelines for follow-up of post-neck irradiation patients.

Patients and Methods

This study included 50 patients with cancer of variables areas of the head and neck; they are recruited from the cancer unit, out patient clinic in Kasr El Aini hospital. Twenty eight of them had finished radiotherapy treatment sessions, with the last session was more than 4 years ago (group I) and the remaining 22 patients had no history of exposure to irradiation (group II), all patients gave their informed consent.

Both groups were subjected to the following:

1- Complete history taking with special emphasis on type of cancer, mode of treatment, number of sessions of radiotherapy, date of last session (patients with their last session less than four years before the date of examination were excluded) coexisting illness and history suggestive of neurological deficit.

2- Complete physical examination.
3- Laboratory investigations:

a- Total lipid profile including total cholesterol, triglycerides, LDL and HDL. Cholesterol determination was done using cholesterol CHOD-PAP enzymatic colorimetric test which was done on Hitachi auto Analyzer. Fasting samples were assayed for triglycerides using BM Hitachi 911 by enzymatic colorimetric method. The ldl concentration is Calculated according to Friedwald formula. HDL determination was Done using Biosystems cholesterol HDL precipitating reagent on Hitachi auto analyzer.

b- Fasting blood sugar was done for all subjects and glycosylated Hemoglobin (HbAIc) was done for diabetic patients.

4- Carotid duplex study: Duplex examination of the extra cranial portion of the carotid arteries using an ultrasound scanner HDI 5000 ultrasound system measurements of intima media thickness, assessment of plaque existence and blood flow recording was recorded.

All patients gave their informed consent.

Statistical methods:

Statistical analysis was done using a commercially available soft ware package (SPSS version 6.13 for windows, SPSS, Chicago and I11. Data was described in terms of mean ± standard deviation. Comparisons of the two groups were done using Student t test. Results were described as statistically significant or non significant considering a p value of less than 0.05 as statistically significant and a p value of less than 0.01 as highly significant.

Results

This work included tow groups of head and neck cancer patients, group I radiotherapy treated patients were 16 males (57%) and 12 females (43%), with mean age of 57±6.17 years. They were almost with group II non-radiotherapy treated cancer patients (59% male and 41% female) with mean age of 57±6.21 years.

It was found that; 10 patients out of 28 in group I (35.7%) and 5 patients out of 22 in group II (22.7%) were diabetic, 32% of group I and 27% of group II were hypertensive.

On history taking 6 patients in group I (radiotherapy treated) gave a positive history of Transient Ischemic attacks (TIAs) and only one patient had cerebrovascular stroke (CVS), while only one patient in group II matched age, sex and medical history (diabetes and hypertensive) had positive history of TIAs and one patient had CVS.

On clinical examination carotid bruit was detected in 6 patients (21 %) of group I, compared to one patient (4.5%) in group II, this was statistically significant. All clinical data shown in Table (1).

Table (1): Clinical characteristics of patients and control groups.

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Group I (n=28)</th>
<th>Group II (n=22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57±6.17 yrs</td>
<td>57±6.21 yrs</td>
<td>1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>16M/12F</td>
<td>13M/9F</td>
<td>0.45</td>
</tr>
<tr>
<td>HTN</td>
<td>9</td>
<td>6</td>
<td>0.35</td>
</tr>
<tr>
<td>Smokers</td>
<td>8</td>
<td>5</td>
<td>0.32</td>
</tr>
<tr>
<td>TIAs</td>
<td>6</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Bruit</td>
<td>6</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Last dose of radiotherapy</td>
<td>6.17±1.32 yrs</td>
<td>NIL</td>
<td></td>
</tr>
</tbody>
</table>

On studying the laboratory parameters including fasting blood sugar, HbAIc in diabetic patients and total lipid profile, we found that; there were no values of statistical significance between the tow groups, as shown in Table (2).

Table (2): Laboratory findings of patients and control group.

<table>
<thead>
<tr>
<th>LAB Finding</th>
<th>Group I (n=28)</th>
<th>Group II (n=22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS</td>
<td>136.1±55.5</td>
<td>126.3±62.76</td>
<td>0.55</td>
</tr>
<tr>
<td>HbAIc</td>
<td>6.07±1.34</td>
<td>5.98± 9.24</td>
<td>0.78</td>
</tr>
<tr>
<td>TC</td>
<td>207±25.08</td>
<td>207.4±32.48</td>
<td>0.95</td>
</tr>
<tr>
<td>TG</td>
<td>104.2±23.22</td>
<td>103.5±13.96</td>
<td>0.88</td>
</tr>
<tr>
<td>LDL</td>
<td>102.7±12.19</td>
<td>107.4±12.89</td>
<td>0.19</td>
</tr>
<tr>
<td>HDL</td>
<td>39.6±4.03</td>
<td>38.4±6.31</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Regarding the results of carotid duplex represented in Table (3) the IMT in patient groups was 1.07±.166 compared to 0.909±.165 in control subjects with a statistically significant p value of 0.001.

Table (3): Results of carotid duplex study in both groups.

<table>
<thead>
<tr>
<th>Duplex finding</th>
<th>Group I (n=28)</th>
<th>Group II (n=22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT</td>
<td>1.07±0.166</td>
<td>0.909±0.165</td>
<td>0.001</td>
</tr>
<tr>
<td>% Reduction</td>
<td>14.9±24.3</td>
<td>4.18±13.6</td>
<td>0.089</td>
</tr>
<tr>
<td>Plaques P/A %</td>
<td>28.6±71.4</td>
<td>9.1/90.9</td>
<td>0.06</td>
</tr>
</tbody>
</table>
by medial degeneration and adventitial fibrosis

Complications that may result from cervical RT include by fewer atherosclerotic risk factors and diseases.

External radiotherapy treatment (RT) is standard treatment for early NPC (Nasopharyngeal carcinoma) and is also used for local recurrences and control of neck node metastasis [1], vascular complications that may result from cervical RT include temporal bone osteomyelitis with intrapetrosal carotid artery pseudo aneurysm and extra cranial carotid stenosis [4].

The long-term sequel or radiation exposure of the carotid arteries may take years to manifest clinically. The exact mechanism of radiation-induced carotid artery disease is not clear, although a combination of direct injury and vessel wall ischemia due to obliteration of the vasa vasorum may be responsible. Irradiation of the arteries of the neck induces direct vessel wall damage, with an acute phase of endothelial proliferation, followed by medial degeneration and adventitial fibrosis and thickening [5,6]. The results may be indistinguishable from atherosclerosis.

The present study demonstrated that the prevalence of carotid stenosis (% of lumen reduction) in patients previously treated by radiotherapy is not low (14.9±24.3%) compared to (4.18%±13.6%) in cancer patients not undergone RT with the consideration that the two groups of patients are matching in age, sex, smoking and the incidence of diabetes mellitus and hypertension. And as regard Intima-media thickness (IMT) it was 1.07%±0.166 in RT treated patients compared to 0.909±0.165 and this results show statistically high significance increase in IMT in RT treated patients.

Our results are in agreement with a two retrospective studies done by Dorrestijn LDA and colleague 2005 and Boogerd W, et al., 2000, in head and neck cancer patients have identified stenosis and reduced blood flow or increase intima-media thickness of the irradiation section of the carotid artery [7,8].

Also our results are in agreement with those of Stephen WK, et al., 1998, who found that; patients who had undergone RT more than 5 years earlier had a 15 time high chance of having stenosis of 70% or more in their carotid arteries than those with less than 5 years, with an over all prevalence of 26%. RT treated patients included in the present study were after 4 years of radiation therapy treat-

Discussion

The present study confirms that irradiation is a risk factor for atherosclerosis. The post-irradiation carotid artery disease was found to be accompanied by fewer atherosclerotic risk factors and diseases.

Our results shows significant incidence of transient ischemic attacks that given as a history in RT treated patients (21%) compared to only (4.5%) in non RT treated cancer patients who are matching in all risk factors for developing vascular complication (age, sex, smoking, diabetes mellitus and hypertension). The incidence of cerebrovascular stroke in both groups of patients was almost similar.

The increase in incidence of cerebrovascular insults we had reported are in agreement with a cohort study of > 1200 Dutch patients demonstrated a 6.3 relative risk (RR) of developing cardiovascular disease for the whole group and patients irradiated at age <21 years had even higher risk (RR, 13.6) [9]. Dorresteijn LD and colleague, had concluded from a later study done 2002, that; a 367 head and neck cancer patients irradiated at the Netherlands Cancer Institute showed a significantly increased risk of ischemic stroke in a relatively young population that would not normally be associated with atherosclerosis and the overall radiation risk of stroke in patient cohort was 5.6 times that expected and this increased to 10.1 after a follow-up of > 10 years [10].

Based on the above discussion, we recommend that follow-up of all patients who received neck irradiation should include yearly duplex scanning; beginning after completion of radiotherapy, of note is the heterogeneity of the indications for radiotherapy as well as the changes in dose, time and fractionation. These variables might implicate a different behavior of the post-irradiation arterial disease.

Future studies are needed to clarify the connection between the characteristics of the irradiation regimen and the biological behavior of the disease. Further investigation is needed to define the underlying molecular pathogenesis of radiation-induced atherosclerotic changes.

References


