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Evaluation of radiation – Induced carotid artery stenosis after supraclavicular irradiation in patients with breast carcinoma

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ABSTRACT

Objective: To screen breast cancer patients for carotid artery stenosis (CAS) after supraclavicular irradiation and study its possible effect on the pathogenesis.
Methods: The study included 114 patients who received supraclavicular irradiation. They were recruited from the follow up clinic at Minia University Hospital and Minia Oncology Center from January 2015 to December 2016. Evaluation was by Carotid duplex ultrasonography.
Results: In 28% of patients, CAS was more on the irradiated side than the non-irradiated side in the same patient. The degree of stenosis was severe on the irradiated side in 81.2% versus only 9.4% on the non-irradiated side. There was no significant difference except for the presence of co-morbidity. In nine patients with no co-morbidity, supra-clavicular irradiation was considered to be the only possible factor responsible for stenosis.
Conclusion: Supraclavicular irradiation may play a role in the pathogenesis of carotid stenosis in about 1/3 of breast carcinoma patients. The presence of co-morbidity has an additive role in radiation induced CAS. This stresses the importance of regular examination of the carotid artery by duplex ultrasonography. Every effort should be considered to minimize the dose to carotid artery within the clinical target volume by its proper delineation especially in high risk patients.

1. Introduction

Irradiation on the carotid area is a significant risk factor of developing carotid artery stenosis (CAS) and subsequent cerebrovascular events [1]. The exact mechanism of radiation-induced carotid artery disease is not clear [2]. It is believed to be due to a combination of direct vessel wall injury leading to intimal proliferation, necrosis of media and fibrosis around the adventitia resulting in accelerated progression of normal atherosclerosis pathophysiology [3]. However, some histopathological studies indicate differences to “classical” atherosclerosis, thus pathogenesis of chronic radiation vasculopathy is still under discussion [4].

In cases of head and neck malignancies treated by radiation therapy, a consistent difference in carotid intima-medial thickness (CIMT) and CAS between irradiated and unirradiated carotid arteries was documented [3,4]. CIMT significantly increased in the first 7 years after radiation therapy. Moreover, the incidence rate of stroke was six-fold increased [5]. Thus, patients treated with radiation therapy for head and neck malignancies have proven sustained risk of developing atherosclerosis of the carotid arteries and future stroke. Therefore, focused screening of this high-risk population may be cost effective and medically beneficial in terms of risk factor modification and stroke prevention [6,7].

Studying radiation induced CAS and the possible subsequent cerebrovascular events in patients with breast carcinoma subjected to supraclavicular irradiation is even more complicated. This is because of the superadded long-term side effects of adjuvant cancer therapy. It is well documented that breast cancer therapy such as anthracyclines, chest wall radiotherapy, or trastuzumab may induce cardiovascular toxicity. This may affect disease-free survival, and ultimately, overall survival [8,9]. In addition, tamoxifen may play a role in increasing the risk of thromboembolic complications, including deep venous thrombosis, pulmonary embolism and cerebral vascular events [10–12].

The current study evaluates the impact of supraclavicular irradiation in patients with breast carcinoma on the CIMT. The prevalence CAS among our patients and the possible associated risk factors are studied and analyzed aiming for early detection and management of such adverse effect. This approach may minimize treatment related morbidity and mortality.

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2. Patients and methods

The current work included females with confirmed diagnosis of breast carcinoma with a minimum duration between diagnosis and assessment of 30 months. Patients were collected from the follow up clinic in Minia University Hospital and Minia Oncology Center during the period between January 2015 to December 2016. Patients with a past history of cerebral infarction or symptoms suggestive of cardiovascular dysfunction, bilateral breast cancer were excluded from the study. Eligible patients should be asymptomatic. They were subjected to clinical, laboratory and radiologic examination to exclude disease recurrence. Eligible patients with chronic co-morbidity such as diabetes, hypertension and/or altered lipid profile should be controlled on medications. All patients were treated with systemic combination chemotherapy (FAC or FAC Docetaxel) after surgical intervention (modified radical mastectomy or wide excision with axillary evacuation). Tamoxifen and/or aromatase inhibitor was prescribed for hormone receptors positive patients.

2.1. Technique of irradiation

Eligible patients included in the current study had received supraclavicular irradiation using 2D, 6 Mv photon Linear Accelerator up to total dose 4500–5000 cGy/20–25 sessions/4–5 weeks. Irradiation was given through a direct field to the supraclavicular region and the dose was calculated as a given dose.

The supraclavicular field borders

- Upper border: thyro-cricoid groove.
- Medial border: at or 1cm across midline extending upward following medial border of Sternomastoid muscle to thyro-cricoid groove.
- Lateral border: insertion of deltoid muscle.
- Lower border: matched with upper border of tangential fields [13].

The above described supraclavicular irradiation field includes the common carotid artery CCA up to the bifurcation as illustrated in Fig. 1.

Patients included in the study were asked for consent to be subjected for examination for CAS.

2.2. Technique of examination for CAS

Doppler ultrasound examination was done using (Logiq P5, GE Medical Systems, Korea) with linear transducer (5–12 MHz). The examination was carried while the patient recumbent and her neck flat. The extra-cranial carotid artery was examined, including the common carotid artery in the neck up-to the carotid body (carotid bifurcation).

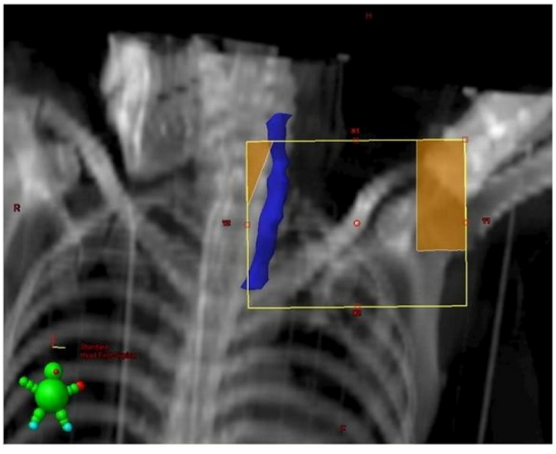

Fig. 1. Borders of supraclavicular field with delineation of CCA within (after Woodward et al. [14]).

The carotid artery was evaluated by gray scale ultrasound. Measurement of the intima media thickness (IMT), both anterior and posterior walls in both transverse and longitudinal planes, was done using the antero-lateral and postero-lateral approaches. Right and left common carotid arteries were examined for each patient during the same setting. As patients were treated unilaterally, the other side was used as a control to compare the Doppler measurements of irradiated side to those of non-irradiated side. Images were evaluated by 2 radiologists in consensus. For the purpose of the current study, if the intima media thickness of the common carotid artery is more than 0.7 mm the patient is considered to have carotid stenosis [15]. The degree of CAS was calculated as follows:

$$\text{CCA \% stenosis} = (1 - A/B) \times 100$$

where A is the minimal residual lumen area, and B is the area of the corresponding true lumen [16]. The degree of stenosis was considered: Mild < 30%, Moderate 30-70%, and severe > 70%.

Patients in the current study were classified into 2 groups according to the possibility of occurrence of radiotherapy related CAS.

Group A included patients in whom there was no detected stenosis on either side or if stenosis was equal on both sides.

Group B included patients in whom the degree of CAS was more on the irradiated side than on the non-irradiated side.

To study the impact of the supplementary role of patients' characteristics in radiation induced CAS, the demographic features of patients in both groups; A and B were studied and compared.

3. Statistical analysis

Comparisons between the two groups were tested using Chi-square test for categorical data. For quantitative data comparison between 2 groups was done using t-test. A p-value less than 0.05 was considered statistically significant.

4. Results

The current study included 114 females with confirmed diagnosis of breast carcinoma who received external beam irradiation to the supraclavicular region as a component of treatment, with a minimum duration between diagnosis and assessment of 30 months (range 30–77 months, median 38 months). It was found that in 28.1% (32/114) of patients, CAS was more on the irradiated side than on the non-irradiated side in the same patient (Group B) (Fig. 2).

In group A (82/114 patients, 71.9%), carotid artery measurements were normal in 36 patients, while varying degrees of CAS (but equal on both sides) were detected in 46 patients [mild in 13 patients (28.3%), moderate in 17 patients (36.9%) and severe in 16 patients (34.8%)]. Accordingly, the role of radiotherapy in the pathogenesis of CAS in this group could not be confirmed.

In group B (32/114), CAS was more on the irradiated side than on the other side. Among patients of this group, the degree of CAS was severe in 3/32-9.4% on the non-irradiated side versus 26/32-81.2% on the irradiated side (p, 0.001). Fig. 3 and Table 1. Moreover, atherosclerotic plaques were detected in 3 patients (9.4-3/32).

In sixteen patients of group B (16/32), the non-irradiated side was completely normal. Varying degrees of stenosis were detected on the irradiated side (mild 3 patients, moderate 3 patients and severe in 10 patients).

In the other 16 patients, the degree of stenosis on the non-irradiated side was mild in 3 patients, moderate in 10 patients and severe in 3 patients. While the degree of stenosis was severe on the irradiated side in all of them.

Comparing the demographic characteristics of patients in Group A with those in Group B showed that, there was no significant difference except for the prevalence of co-morbidity among patients of the two