

The role of radiotherapy in the carotid stenosis



Ann. Ital. Chir., 2014 85: 533-536
pii: S0003469X14021022

Giovanni Simonetti^{***}, Enrico Pampana^{***}, Isabel Di Poce^{***}, Augusto Orsini^{****}, Federico Pugliese*, Sara Izzo*, Luigi Basso*, Virgilio Nicolanti*, Monir Al Mansour*, Pierfrancesco Di Cello*, Luciano Izzo*

* Department of Surgery "Pietro Valdoni" Rome University "Sapienza", Rome, Italy

**Department of Vascular Surgery, Latina, Italy

***Department of Radiology, Imaging molecular and radiotherapy Rome University "Tor Vergata", Italy

**** Presidente Società Italiana di Flebologia Clinica Sperimentale

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OBJECTIVE: Cervical radiation for head and neck cancer has been associated with an increased incidence of carotid arterial stenosis. Modern radiation therapy delivers higher doses with increasing long-term survival. In our study 50 patients with head and neck malignancies treated with radiotherapy are analyzed with colour Doppler ultrasonographic scanning of the carotid arteries. These patients were compared with a population of asymptomatic historical controls (40). These findings suggest that radiation has an adverse effect on large vessels. Colour Doppler follow-up may be indicated for patients receiving head and neck radiation therapy.

METHODS: 50-70 Gy is the local dose that all patients received, during a period of about 8 weeks. The ecodoppler scan of carotid arteries was performed in all patients with estimation of Common and internal carotid artery's intimal medial thickness (IMT). Stenosis grade were divided into low (0-30%), moderate (31-49 %) and severe ($>50\%$). In add we considered ematochimics and flogosys parameters. Patients recruited from a hospital Radiation-oncology-surgery department from April 2007 to September 2011, 90 consecutive head and neck cancer patients were enrolled in this study. 50 of these patients had previously undergone RT (RT group) and 40 had no RT (control group). All patients were screened with bilateral carotid arterial duplex ultrasonography. We defined disease as "normal or mild" if the carotid stenosis was $<50\%$, and "significant" if $>50\%$. The relationship between standard demographic risk factors and screening outcomes was then analyzed.

RESULTS: We found that severe carotid stenosis ($>50\%$) was higher (41%) in patients who underwent to radiotherapy than in control group. The Eco Doppler examination demonstrated that the most affected site was Internal Carotid Artery's fork. There were no differences in age or gender between the two groups. The RT group had a significantly higher plaque score than the non-irradiated group. Bilateral plaque score was significantly correlated with age, hyperlipidemia, and RT. This analysis showed that in RT patients >50 years old, age was inversely correlated with plaque score; however, in RT patients ≤ 41 years old, age was positively correlated with plaque score.

CONCLUSIONS: Literature evidences about this subject are few and similar to ours. Moritz et al found a severe carotid stenosis in 30% of irradiated and 5.6% in the control group. Lam found carotid stenosis in 78.9% of irradiated and 21.6% in the other group. We can conclude that radiotherapy is able to induce atherosclerotic lesions only in sites included in radiation field. Should be important to perform pre and post radiotherapy Carotid Artery Ecodoppler of patients who are going to undergo cervical radiotherapy. The prevalence of carotid arterial disease in patients with prior cervical radiation therapy is clinically significant and warrants aggressive screening as part of routine preradiation and postradiation care. Focused screening of this high-risk population may be cost effective and medically beneficial in terms of risk factor modification and stroke prevention.

KEY WORDS: Carotid stenosis, Cervical radiotherapy, Stroke prevention

Pervenuto in Redazione Dicembre 2012. Accettato per la pubblicazione Maggio 2013

Correspondence to: Luciano Izzo, Via Giuseppe Tomasi di Lampedusa 9, 00144 Roma (e-mail: luciano.izzo@uniroma1.it)

Introduction

In last five years radiotherapy's role, in treatment of head and neck cancer was outlined. Radiotherapy's vascular complications are well known. Ionized effect of X-ray over vessel's wall, produce, direct and indirect damages. Direct damages are characterized from perivascular fibrosis, middle necrosis and intimal hyperplasia. Indirect damage is vasculature occlusion¹.

Risk factors for atherosclerotic plaque are irreversible how age, sex and familiarity and reversible how smoke, hypertension, diabetes, obesity, dyslipidemia and stress.

The aim of our study was to evaluate prevalence of carotid stenosis in patients with head and neck malignant tumours treated with radiotherapy.

Material and Methods

In our study, we examine a first group of 90 patients with head and neck cancer. Of 90 patients examined, only 50 underwent cervical radiotherapy (31 male and 19 female, middle age 62,8 range 29-84 years). A second group of 40 patients (21 male and 19 female, middle age 63,7 years old), with the same clinical characteristics but not underwent to radiotherapy, was employed as control group (Table I).

Neoplasia was localized in larynx, laterocervical space, tongue, submandibular gland, oropharynx, hypopharynx. All patients included in our study were effected external radiotherapy on laterocervical region with Linear Accelerator (LINAC) of 6-15 MeV (PRECISE), with compliance technique. We administered 50 – 70 Gy divided into 5 – 6 weeks. Middle space out after radiotherapy was 36,7 months (vs 11,1 months). All patients carotid arteries were evaluated with EcoDoppler B-mode scan model Vision Esaote 50 L, with multifrequency linear probes of 7,5 MHz – 10 MHz. Doppler's exam of epicardial trunks, was executed on standard projections, with bilateral estimation of Common and Internal Carotid Artery's Intimal Medial Thickness (IMT) of Common Carotid Artery (CCA) and Internal Carotid Artery (ICA). Carotid obstruction extent was classified in low (between 0-30%), moderate (between 31-49%), severe (between $\geq 50\%$).

We considered hematological and biological blood parameters how glycaemia, HDL, LDL, total cholesterol,

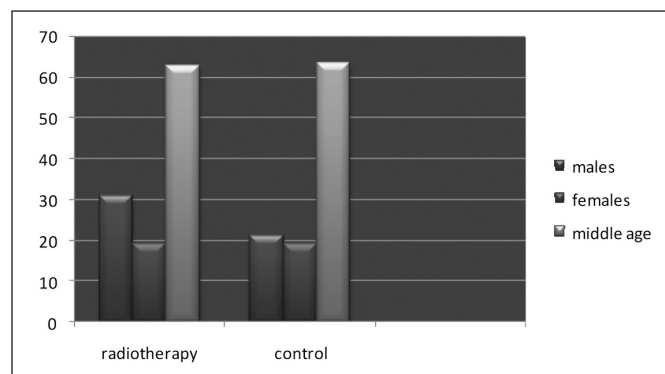


Fig. 1: Demographic characteristics of the sample.

TABLE I - Atherosclerotic's risk factors

Characteristics	Stenosis $\geq 50\%$	
	Radiotherapy	Control
No	10	11
Smoking	9	9
Cardiovascular disease	9	7
Age > 60 years	15	11
Diabetes mellitus	7	2

TSH, fT3, fT4, Complement's fractions, C protein, ESR. We be careful to atherosclerotic's risk factors (Table II).

Results

We found that severe carotid stenosis ($\geq 50\%$) was higher (41%) in patients underwent to radiotherapy than in control group (16.6%). The Eco Doppler examination demonstrated $\geq 50\%$ stenosis in 41% of radiated patients and 16,6 % of unirradiated patients (Table 4). Ecocolor-doppler's pictures show atherosclerotic plaques with disomogeneous morphological aspect, with hypercholesterolemic aspect at carotid's fork on Internal Carotid Artery (ICA) origin.

Discussion

Atherosclerosis was considered only depot of fat in vessel wall. Recently we considered endothelial dysfunction how induced by LDL, modified by free radicals. High pressure, smoke, toxic and wall stress compete with this atherogenic process². With this new pathogenetic hypothesis, we can evaluate the role of drugs, how ACE-inhibitor³, cannabis derived (δ -9-THC)⁴, COX2-inhibitor ASA⁵ and vaccinal strategies, to decrease atherosclerotic process. Recently experiment and study of Moritz et al.⁶ (1990) over modify LDL, show CB2 cannabis receptor into ath-

TABLE I - Demographic characteristics of the samples

Characteristics	Radiotherapy	Control
No	50	40
Males	31 (79,4%)	21 (74,1%)
Females	19 (20,6%)	19 (25,9%)
Middle age	62,8 (S.d.8.6)	63,7 (S.d. 8.4)

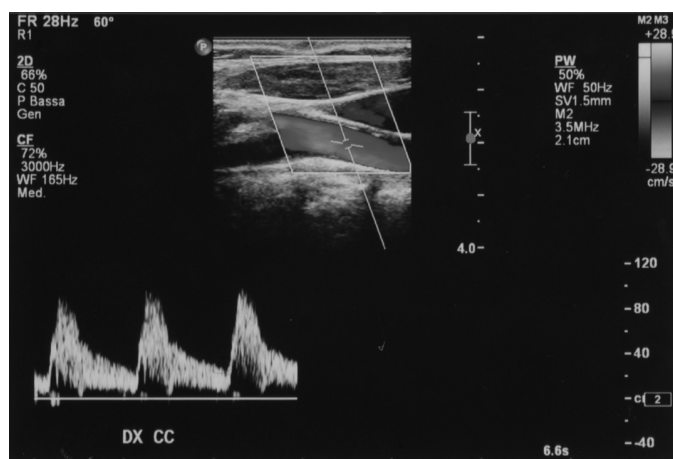


Fig. 2: Longitudinal axis CCA - ICA (plaque, under blue color of ecoDoppler).
Eco- doppler exam long trasverse vessels axis, showed plaques at carotid's fork on External Carotid Artery (ECA) origin.

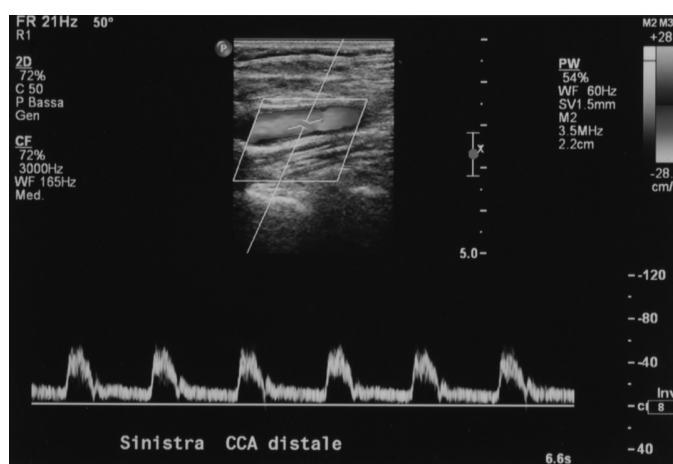


Fig. 3: Trasversal axis. Plaques at carotid's fork on External Carotid Artery (ECA) origin ECA-ICA.

erosclerotic lesions and his hypothetical role in ApoB-100 immunization. In this study, Moritz show high incidence of carotid's stenosis in patients underwent to radiotherapy for head and neck cancer.

Lam's et al study (2001) with 71 patients radiated for nasopharynx cancer, compared with a control group of 51 patients with cancer but not radiated. Carotid's stenosis prevalence tax in radiated patients was 78.9% compared to 21.6% of control group. 35% of patients show stenosis gredu higher than 50% whereas any patient of control group had this rate ⁷.

Muzaffar's et al study (2000) with 35 patients, over ralisation between carotid's intimal thickness and stenosis grade, show intimal increase in radiated parients. Intimal thickness measured before and 2 years after radiotherapy.

He found increase of intimal thickness, 1 year after raditherapy with progression of atherosclerotic process following year ⁸.

Literature datum, agree with our's and show how radi0therapy induced vasal stenosis.

Conclusions

Atherosclerosis connected with radiotherapy, is hystological similary at the same natural process but clinically distinct. In fact this process is radiate's limited and smaller join with risk factors ⁹.

Atherosclerotic process isn't only fad depot in vesse wall but local flogistic process. In fact, we can use anti-flogistic drugs to reduce process progression.

We compared scan pictures of radiate patients with the same of not radiated patients and we found major stenosis grade into radiated patients compare to not radiatd. We think be useful ecografic control of all patients with head and neck cancer, before they underwent cervical radiotherapy and after its. This sperimental methodology consent long time follow-up atherosclerotic post-actinic process. Now we can prevent atherogenic reversible risk factors with aimed therapy.

Riassunto

OBIETTIVO: Il trattamento radiante per il carcinoma di testa e collo è stata associata ad un'aumentata incidenza di stenosi carotidee. La moderna radioterapia offre dosi più elevate con incremento aumento della sopravvivenza a lungo termine. Nel nostro studio 50 pazienti con tumori maligni di testa e collo trattati con radioterapia sono stati analizzati con la scansione color-Doppler ultrasonografica delle arterie carotidee. Questi pazienti sono stati confrontati con una popolazione di controlli storici asintomatici (40). Questi risultati suggeriscono che la radiazione ha un effetto negativo sui grossi vasi. Un eco-Color Doppler di follow-up può essere indicato per i pazienti trattati con radioterapia della testa e del collo.
METODI: 50-70 Gy è la dose locale che tutti i pazienti hanno ricevuto durante un periodo di circa 8 settimane. La scansione Ecodoppler delle Arterie Carotidee è stata effettuata in tutti i pazienti con la stima dello spessore intimale mediale (IMT) dell'arteria carotide comune ed interna. Il grado di stenosi è stato diviso in: basso (0-30%), moderata (31-49%) e grave ($\geq 50\%$). In aggiunta abbiamo considerato parametri ematochimici e di flogosi. I pazienti sono stati reclutati da un Dipartimento ospedaliero di radiaterapia, oncologia e chirurgia dal mese di aprile 2007 a settembre 2011. Sono stati arruolati in questo studio 90 pazienti con cancro di testa e collo. Di questi pazienti, 50 erano stati precedentemente sottoposti a RT (gruppo RT) e 40 senza RT (gruppo di controllo). Tutti i pazienti sono stati sot-

toposti a screening con Ecografia Doppler delle Arterie Carotidee bilateralmente. Abbiamo definito la malattia come "normale o lieve" se la stenosi carotidea è stata <50%, e "significativa", se > 50%. La relazione tra i fattori di rischio demografici e gli esiti di screening è stata poi analizzata.

RISULTATI: Abbiamo trovato che la stenosi carotidea grave ($\geq 50\%$) è stata superiore (41%) nei pazienti sottoposti a radioterapia rispetto al gruppo di controllo. L'esame Eco Doppler ha dimostrato che il luogo più colpito è la biforcazione della Arteria Carotide Interna. Non ci sono state differenze di età o di genere tra i due gruppi. Il gruppo RT aveva un Punteggio di Placca significativamente più alto rispetto al gruppo non irradiato. Punteggio di Placca bilaterale è risultato significativamente correlato con l'età, iperlipidemia, e RT. Questa analisi ha mostrato che nei pazienti con RT > 50 anni, l'età è risultata inversamente correlata con il Punteggio di Placca, tuttavia, nei pazienti RT con età minore o uguale a 41 anni, l'età era positivamente correlata con il Punteggio di Placca.

CONCLUSIONI: Le evidenze nella letteratura su questo argomento sono poche e simili alla nostra. Moritz et al hanno trovato una grave stenosi carotidea nel 30% dei pazienti irradiati e del 5,6% nel gruppo di controllo. Lam ha trovato una stenosi carotidea nel 78,9% dei pazienti irradiati e del 21,6% nel gruppo di controllo. Si può concludere che la radioterapia è in grado di indurre lesioni aterosclerotiche solo nei siti inclusi nel campo di radiazione. Dovrebbe essere importante effettuare una Ecografia color-Doppler delle arterie Carotidee pre e post radioterapia carotidea nei pazienti in procinto di sottoporsi a radioterapia della testa e del collo. La prevalenza della malattia arteriosa carotidea in pazienti con precedente radioterapia cervicale è clinicamente significativa e garantisce lo screening aggressivo come parte della routine e del trattamento pre e post radiazione. Lo screening mirato di questa popolazione ad alto rischio può essere efficace e medicalmente vantaggioso in termini di modificazione dei fattori di rischio e prevenzione dell'ictus.

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