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# Radiation-Induced Arterial Injury in the Upper Limb

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## Abstract

In recent years, radiation combination therapy for malignant tumors has improved cancer survival, thereby increasing the importance of radiation therapy. In 1959, radiation-induced arterial injury (RIAI) was first reported by Thomas as a condition in which stenosis and obstruction of the blood vessels arise within the irradiated area following radiation therapy; there have been several subsequent reports regarding this.

Although RIAI has been examined and reported, to date, there have been few reports of RIAI in the arteries of the upper limbs, and it cannot be said that the clinical features and treatment of this condition have been thoroughly examined and established. In particular, irradiation for breast cancer can cause stenosis and obstruction in the area extending from the subclavian artery to the axillary artery; however, the associated symptoms resemble the symptoms of lymphedema and neuropathy following surgery for breast cancer, and it is assumed that diagnosis is difficult, and many patients has been overlooked. Thus, in the event of such patients, careful examination should be performed with RIAI in mind.

Irradiation can cause arteriosclerosis, and therefore, it is important that RIAI becomes common knowledge; further examinations should also be conducted in a larger sample size.

**Keywords** Radiation-induced arterial injury; Radiation therapy; Breast cancer

## Introduction

In recent years, radiation therapy has been widely administered for malignant tumors, and it is a particularly important treatment in breast cancer. To date, studies have been conducted on RIAI as a complication following radiation therapy; however, there are few reports of such injury to the arteries of the upper limbs, and it cannot be said that the clinical features of this condition are fully understood. Therefore, we would like to examine and discuss the clinical features, effective diagnostic methods, and effective treatment methods for RIAI in the upper limbs.

## Overview

RIAI was first reported by Thomas [1] as a condition in which radiation therapy causes stenosis and obstruction of the great vessels. Incidence and prevalence of radiation induced subclavian artery stenosis

To date, it has been considered that RIAI is rare after radiation therapy. However, because of advanced imaging technology and the fact that clinicians have become aware of the concept of RIAI, reports of RIAI have increased.

Lam [2] compared newly diagnosed patients with nasopharyngeal cancer patients before and after they underwent radiation therapy and reported that arterial stenosis was more common in the irradiated area of the post-radiation group compared with that of the pre-radiation group (56/71 vs. 11/51). Furthermore, arterial stenosis of 50% or more was only observed following radiation therapy.

In addition, the probability of carotid stenosis of 70% or more after radiation therapy is 6.3% according to Elerding [3] and 11.7%–16% according to Cheng [4]. It is also reported that the symptom due to this vascular stenosis appears in 14.6% of the cases [4].

Most reports of RIAI examine the carotid artery [3,5-11]. However, there are few reports of RIAI in the arteries of the upper limbs, including the axillary artery and subclavian artery.

According to our search of the literature, there have been 13 reports of 21 RIAI in the upper limbs, including the axillary artery and subclavian artery cases from 1974 to 2015 [12-24].

Breast cancer is the most common non-dermatological cancer among women in the US, with an estimated 60,290 noninvasive (in situ) and 231,840 newly diagnosed invasive cancers and 40,290 fatal cases in 2015 [25]. Furthermore, the results of two randomized controlled trials from Denmark and Canada were reported in 1997 [26,27], which suggested that post-mastectomy radiation therapy (PMRT) combined with systemic chemotherapy for breast cancer not only reduced the rate of localized recurrence but also improved survival in the high-risk group. A systematic review conducted by the Early Breast Cancer Trialists' Collaborative Group in 2005 [28] also confirmed that in the high-risk group with lymph node metastasis, PMRT not only improved the rate of local control but also increased survival. Furthermore, it has been reported that following breast-preserving surgery, the rates of local control and survival were improved by post-operative irradiation, irrespective of axillary lymph node metastasis.

Therefore, the importance of radiation therapy for breast cancer has increased in recent years. According to the "Japanese Structure Survey of Radiation Oncology in 2009 (first report)" by the Japanese Society for Radiation Oncology (JASTRO) database committee, in the new patients who underwent radiation therapy, breast cancer was the most common cancer type (23.3%) based on the primary lesion [29].

RIAI in the carotid artery and RIAI in the subclavian to axillary arteries must have the same mechanism of onset. Therefore, considering the number of case reports, it is likely that many patients are not diagnosed, and we believe that clinicians need to be more aware of this condition.

## Pathogenesis

The general mechanism of action can be broadly divided into three stages.

First, it is considered that irradiation causes endothelial dysfunction [30]. Endothelial cell damage accelerates vascular permeability, and serum mucopolysaccharide is deposited on the endothelium, causing intimal hyperplasia. In addition, it has been reported that radiation exposure subsequently activates nuclear factor-kappa B [31] and can cause inflammation due to oxidative stress [32]. It has been reported that inflammatory markers can rise soon after radiation exposure, which may be useful predictors of angiostenosis caused by RIAI; however, further evaluation of this finding is needed [33].

Second, vasa vasorum damage causes focal necrosis of the media, resulting in fibrosis, adventitial chronic inflammation, and so forth [34,35].

These changes ultimately promote arteriosclerosis, which leads to stenosis and obstruction.

## Clinical features and symptoms

Clinical features of RIAI include the following: the irradiation site and the lesion site coincide, lesions can occur with relatively low radiation doses of approximately 40–80 Gy, several years may pass from irradiation until the appearance of symptoms, and the lesions pathologically appear to be the same as arteriosclerotic lesions [5,6,36-42]. It has been reported that the time from irradiation until the appearance of symptoms can range from 3 to 24 years, with a mean of 14.7 years [22].

Furthermore, it has also been reported that angiographic findings reveal the poor development of collateral circulation [23,24], which is attributed to the possible impact of dissecting tissue in the area extending from the subclavian to axillary arteries, such as the pectoral muscle and axillary blood vessels, during surgery for breast cancer. In addition, peripheral ischemic symptoms can be more severe than those in normal arteriosclerosis, which should be given due attention.

Symptoms often include fatigability of the arms, numbness, and coldness due to arterial stenosis [14,16,17,19,22-24].

The reason why it has been scarcely reported on RIAI in the arteries of the upper limbs may be that they are overlooked because the symptoms of stenosis such as fatigue and numbness of the upper limb are resembled with the symptoms of lymphedema and nerve disorders that frequently occur after mastectomy. We believe this may prevent the detection of RIAI in the upper limbs [24].

## Diagnosis

RIAI is often difficult to differentiation from atherosclerosis. However, the feature of RIAI is fundamentally matches the lesion exposed radiation. Therefore, it is important to check whether the patient have received radiation therapy in the past.

Diagnosis is confirmed upon the observation of numbness, coldness, and fatigability of the upper limbs, as well as an absent or weak pulse. The bilateral difference in blood pressure of the upper limbs is assessed. In the event of a bilateral difference in blood pressure, ultrasonography and contrast-enhanced computed tomography or angiography is useful.

The ankle–brachial index is also a non-invasive useful test [24].

## Treatment

The most frequently reported revascularization method is bypass surgery [12,14,15,17,18,20-23]. Mellièr [20] examined the outcomes of bypass surgery for subclavian or axillary artery stenosis caused by RIAI in four patients and reported that in all four patients, the surgery was successful. Similar good surgical outcomes were obtained in all the reports that we evaluated [12,14,15,17,18,20-23]. Only one patient was reportedly able to progress well with only medical therapy and exercise [19].

However, there are not reported whether medical treatment from the early stage is effective for prevent the progression of RIAI or not. Therefore, we should be considered about the medical treatment for RIAI hereafter.

On the other hand, there are relatively few reports of revascularization using PTA rather than bypass surgery, and we could find only five cases in our literature search [13,16,20,21,24]. We reported on a case in which calcification of the lesion was extremely severe, adequate dilatation by plain old balloon angioplasty (POBA) was difficult, and although not unsuccessful, adequate dilatation could not be achieved [24]. Furthermore, one case in the four successful bypass surgery cases that have been reported by Mellièr [20] is initially unsuccessful case by PTA. Hans [21] reported that symptoms reappeared 3 years and 9 months after POBA and that progress was good after bypass surgery.

As a result, in RIAI-induced arteriosclerosis, severe calcification can make it extremely difficult to perform revascularization using PTA, and good mid-to-long-term outcomes may not be anticipated. Therefore, bypass surgery, for which there have been many successful cases, should probably be considered first.

Effective treatment methods should be further examined in a larger sample size.

## Conclusion

Although radiation therapy is currently an important treatment method for cancer, there is no doubt that it carries the risk of arteriosclerosis. In recent years, radiation combination therapy has improved cancer survival, thereby increasing the importance of radiation therapy. We believe that it is important for RIAI to be widely recognized. Further studies with a larger sample size should be performed. Radiation therapy, particularly for breast cancer, causes obstruction in the subclavian artery, the symptoms of which resemble

those of lymphedema and neuropathy following surgery for breast cancer, and requires careful examination.

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