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Management of Radiation Induced Carotid Stenosis in Head and Neck Cancer[1]

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Abstract

OBJECTIVES: Presentation of radiation-induced lesions in carotid arteries of patients with head and neck squamous cell carcinoma (HNSCC) and the evaluation of the effectiveness of endovascular treatment of symptomatic stenoses. *MATERIALS AND METHODS:* We retrospectively analyzed 26 patients who underwent surgery and subsequently cervical radiotherapy (RT) for HNSCC, focusing on radiation-induced vascular disease in neck arteries—from the latency period to the occurrence of neurological events—and the endovascular treatment of the internal carotid artery (ICA) and/or of common carotid artery (CCA) stenoses. The vascular lesions were diagnosed with Doppler ultrasonography and selective digital angiography. Patients with >70% stenoses of ICA and/or CCA were scheduled for carotid artery stenting (CAS). They were followed-up with neurological examinations and Doppler ultrasonography at 6, 12, and 24 months after stenting. *RESULTS:* Radiation-induced vascular diseases occurred in the ICA in 22 patients (85%), CCA in 15 (58%), and in ECA in 15 (58%). The stents were implanted in 25 ICA and 17 CCA. Thirteen patients (50%) had one stent, eight (30%) had two stents, four (15%) had three stents, and one patient had five stents. Overall, 46 stents were implanted. Technical success was achieved in all patients. No cerebrovascular events occurred in the 24-months follow-up. *CONCLUSION:* RT in patients with HNSCC holds a significant risk factor of developing carotid artery stenosis and cerebrovascular events. Carotid stenting is preferable mode of treatment for radiation-induced stenosis. A screening program with doppler ultrasonography enables pre-stroke detection of carotid stenosis.

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Introduction

RT plays an essential role as an adjuvant therapy in patients operated for HNSCC. It can also be an independent treatment method with the aim of possible larynx preservation. The treatment combining radical cervical dissection and high-dose radiation has significantly improved the survival rate of these patients. However, this therapy can be harmful to the arteries by generating radiation-induced vascular diseases. The inflammatory reaction in the carotid artery generates or accelerates atherosclerosis, resulting in carotid stenosis [1–5].

Carotid stenosis carries a high risk of causing neurological events, such as transient ischemic attack (TIA) or ischemic stroke. Therefore, radiation-induced carotid artery disease has become an important

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clinical issue in patients with HNSCC. There are several studies demonstrating that patients with head and neck malignancies receiving RT have a higher incidence of carotid stenosis, and experience neurological events more often than the average general population [2,6–9].

In a review published by Plummer et al., based on 99 studies, irradiation for the HNSCC doubled the risk of TIA and ischemic stroke [10]. Lam et al., states that patients irradiated for nasopharyngeal carcinoma registered a higher rate of carotid stenosis than the non-irradiated cohort, with severe carotid stenosis exceeding 50%, solely in the irradiated patients [11]. In a recently published review by Fernández-Alvarez et al., they reported the incidence of carotid artery stenosis, within the range of 18% to 38%, in patients with head and neck cancer treated with radiation. It was only up to 9.2% among the non-irradiated patients [12].

Patients after RT with confirmed carotid stenosis who developed symptoms of cerebral ischemia, should be referred to surgical or endovascular treatment to restore normal blood flow in the affected arteries and to prevent further neurological events. The risk of surgical treatment for carotid stenosis is increased due to multilevel inflammatory and fibrotic lesions in the arterial wall and the scarring of neck tissues. Therefore, endovascular methods bypass those obstacles and could be considered as the treatment of choice in cases of radiation-induced carotid stenosis.

The aim of this study is to analyze the radiological features of radiation-induced lesions in carotid arteries in patients treated for HNSCC and to evaluate the effectiveness of endovascular treatment of symptomatic carotid arteries stenoses.

Material and Methods

The study included 26 consecutive patients admitted to the University Hospital No 4 in Lublin with cerebrovascular symptoms previously treated for HNSCC with surgery followed by RT. Out of the 26 patients, 11 had laryngeal cancer, 9 hypopharyngeal cancer, and 6 oropharyngeal cancer. There were 20 men and 6 women. Their mean age was 61.4 years. The post-RT interval ranged from 27 to 50 months (mean 45.2 months). The patients received therapeutic radiation. The doses received in the volumes irradiated ranged from 58 Gy to 70 Gy with standard fractionation. The mean irradiation dose was 62 Gy.

All patients were admitted to the hospital on account of cerebrovascular symptoms, experienced during the last 6 months: 20 patients had TIA episodes and 6 had suffered ischemic strokes. Out of these 26 patients, 7 have been smokers for at least 10 years, 6 were treated for hypertension (5 of them were smokers), and 3 had hypercholesterolemia (2 were hypertensive). The initial diagnosis of carotid stenosis was based on the Doppler ultrasonography. Bilateral examination of internal carotid artery (ICA), external carotid artery (ECA), common carotid artery (CCA), and vertebral arteries was performed with a Logiq 7 GE scanner, using a linear HD 6-12 MHz transducer. Patients in whom Doppler ultrasonography showed a stenosis >70% of ICA and/or CCA, were scheduled for carotid artery stenting (CAS). Every stenting procedure began with a bilateral cerebral digital subtraction angiography (DSA) of the CCA, ICA, vertebral, and subclavian artery. The length of stenosed carotid segment from the most proximal visible narrowing of the vascular lumen to the most distal part of the stenotic segment was measured on the lateral DSA projection. Besides the detailed evaluation of the stenosed segments, the status of the arteries was analyzed with regards to changes in the vessel diameter, local dissections, segmental dilatations, and outline of the vessel lumen.

The relation of the latency period and patient's age with the number of affected arteries in each patient, as an indication of the advancement of radiation-induced vascular disease, was evaluated. The dataset was analyzed using the TIBCO Software Inc. (2017) Statistica, version 13. The Spearman's rank correlation test was conducted for testing the relationship between the two quantitative variables.

Post the angiographical confirmation of >70% carotid stenosis, endovascular intervention was undertaken. CAS was performed under local anesthesia. Distal neuroprotection (Accunet—Abbott Vascular or Filter-Wire EZ—Boston Scientific) was used in the ICA and/or the CCA stenting procedure. In all cases tapered (Acculink—Abbott Vascular) stents were implanted. Post-procedural angiograms were obtained to confirm precise stent placement and the patency of the carotids and the intracranial arteries. The complete restoration of the arterial lumen diameter was regarded as a technical success of the treatment. The patients were placed on 75 mg of acetylsalicylic acid and 75 mg of clopidogrel, daily for 4 weeks.

An independent neurologist assessed the perioperative neurological status of the patients, before and after the stent implantation. All the patients were followed-up with a neurological examination and a Doppler ultrasonography 6, 12 and 24 months after the endovascular treatment. Restenosis was defined as a reduction of the artery diameter by over 50%.

Results

In our study we found radiation induced arterial lesions in all treated patients. They were multifocal and included stenoses, segmental dilatations, and local dissections, occasionally resembling fusiform aneurysms. Stenosis was occupying long segments of arteries, where the arterial lumen had smooth outlines, except in 14 cases where surface ulcerations were present (Figure 1.). The mean length of the ICA stenosis was 19.16 (SD 3.42) mm and 31.16 (SD 10.60) mm on the CCA.

An angiography identified radiation-induced vascular disease in the ICA for 22 patients (85%), in the CCA for 15 (58%), and in the ECA for 15 (58%) cases (Table 1). The effects of irradiation were observed in the vertebral arteries in 2 cases (7.7%), combined with lesions in the ICA. Stenosis was diagnosed in the subclavian arteries in 5 patients (19%). In all of them it coexisted with CCA lesions. Occlusion of ICA was present in 4 patients and of the ECA in 3 cases.

The number of affected arteries in an individual patient did not correlate with the patient's age or the time interval from RT (Table 2).

Overall there were 46 stenoses diagnosed and treated. In the ICA 25 stents were implanted and 17 in the CCA. In 1 patient with occluded ICA, a stent was placed in the ECA to increase collateral flow through the ECA-ICA anastomoses. Stenoses in the vertebral arteries were not significant and did not require treatment. In 13 patients (50%) 1 stent was implanted, 2 stents in 8 (30%) cases and 3 stents in 4 (15%) cases and 5 stents in 1 patient. In 5 patients the length of the stenotic segments required implantation of two stents to cover the lesion. The remaining multiple stents were used to treat single stenoses at various sites of the same patient. Out of the 5 patients with stenosis in the subclavian artery coexisting with carotid stenosis, 3 were symptomatic and were stented.

Technical success of carotid stenting was achieved in all patients (Figures 1, 2). There were no complications related to the procedure recorded.

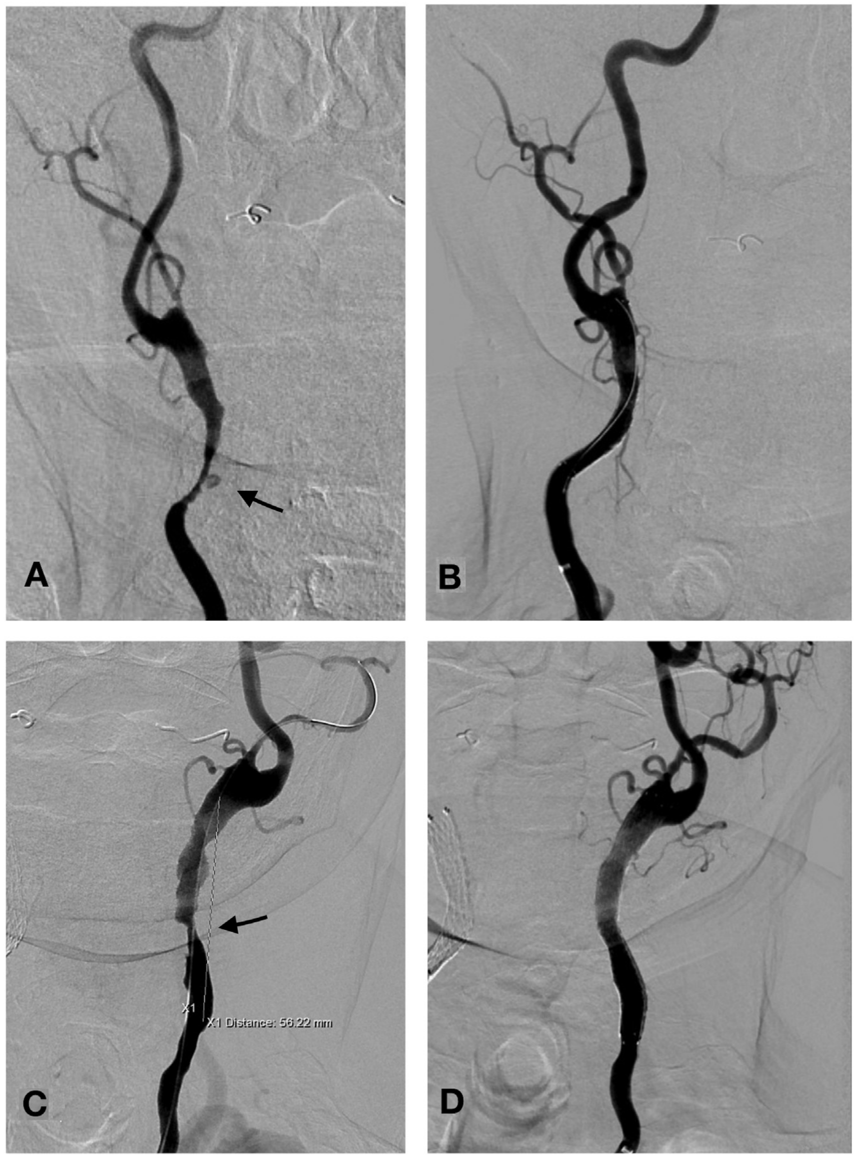

Figure 1. Male, 63 years old, 52 months after laryngeal cancer resection and RT. The right CCA arteriography shows severe stenosis and ulcerationin in the middle segment (arrow). Critical stenosis of the ECA ostium (A). Control arteriography demonstrates technically successful stent placement in the CCA (B). The left CCA arteriography discloses critical stenosis in the middle segment (arrow) (C). Control angiography confirms adequate stent placement (D).

Doppler ultrasonography in 24 patients who came for control evaluation, 6 and 12 months after the stenting, showed no restenosis and good flow in all the stented arteries. There were 21 patients, examined after 24 months, with normal cephalad blood flow in stented arteries. New radiation-induced arterial lesions developed in a different carotid artery in 2 patients, and in 1 patient they developed in the subclavian artery. All the patients who came for follow-up examination were free of new neurological symptoms. None of the patients reported cerebrovascular events during a 24-months follow-up.

Table 1. Distribution of Stenoses in the Carotid arteries in 26 Patients after Radiotherapy for Head and Neck Cancer.

Carotid Arteries	No Patients with Post-RT Lesions
Internal (ICA)	4
Internal and Common (ICA + CCA)	5
Internal and External (ICA + ECA)	7
Common (CCA)	2
Common and External (CCA + ECA)	2
Internal and External and Common (ICA + ECA + CCA)	6

Discussion

It has long been acknowledged that ionizing radiation induces changes in the arterial wall, with the first observations dating back to the introduction of X-rays into clinical practice. The exact pathogenesis of post-irradiation arterial disease is still unclear. According to present knowledge, radiation directly affects the highly sensitive endothelial cells leading to apoptosis and senescence and results in changing normal vascular homeostasis [13,14]. It contributes to a systemic chronic inflammatory state that, together with the normal aging processes, leads to accelerated atherosclerosis. As a result, arterial stenoses develop, leading to an increased tendency for thrombi formation. The clinical significance of these changes is

Table 2. Spearman's Rank Correlation Test of the Relationship Between Number of Affected Arteries and Two Quantitative Variables: Age and Latency from RT.

	Spearman Rank Correlation			
	n	R	t(n-2)	*P*
Age and number of affected arteries	26	-0.108161	-0.533004	0.598932
Latency from RT and number of affected arteries	26	0.347370	1.814770	0.082079

$P < .05000$ considered as statistically significant.

particularly perilous in the arteries supplying the brain because they generate a high risk of ischemic brain damage [14–17].

It has been confirmed in the radiological imaging of the present study that vascular lesions, after radiotherapy for HNSCC, can occur in all neck arteries. These lesions presented a remarkable variation of angiographic symptoms, from occlusion through critical stenosis to aneurysmatic dilatation. They were found in all segments of the carotid arteries, primarily in the CCA and proximal segments of the ICA and ECA. A remarkable variation of radiological symptoms and the multifocal appearance of radiation-induced vascular diseases have been also reported in the literature [11,18,19].

We found that the radiological appearance of vascular lesions, induced by radiation, differ from those in the course of atherosclerosis. Post-radiation lesions were occupying significantly longer segments of arteries and were often multifocal in comparison to lesions caused by atherosclerosis, which are usually unifocal, located in the CCA bifurcation and in the initial segment of the ICA. The observations of other authors were similar to ours [13,18,19]. The length of radiation induced stenosis segment has not been commonly evaluated. Sano N et al. showed that stenosis lengths in CCA were significantly longer in the radiation induced stenosis group then in the non-irradiated patients with atherosclerotic stenosis (32.8 +/− 30.0 mm vs 6.9 +/− 5.1 mm) [20]. This is close to the values found in our study, where the mean length of CCA stenosis was 31.16 +/− 10.60 mm.

Differences in the radiological appearance of radiation-induced vascular lesions and atherosclerotic lesions was explained by Fokkma et al., in studies comparing atherosclerotic plaques for RT patients and non-RT patients. Evaluation of various histopathological factors (calcification, collagen, macrophages, smooth muscle cells, atheroma, micro-vessels, and intraplaque hemorrhage) justified their conclusion that carotid lesions in patients with previous cervical radiation are less inflammatory and more fibrotic than carotid atherosclerotic lesions in non-radiated patients [21].

From the clinical point of view, and for patient safety, awareness of the latency period from radiation to symptomatic vascular damage is very important. Post-irradiation changes in the vessels develop over time. There are divergent opinions regarding the length of this period [18,22–27]. Cheng et al. demonstrated an 8.5 times greater risk of having severe carotid stenosis in patients irradiated over 5 years ago than in those with a shorter history [24]. Brown et al., observed no increase in carotid stenosis incidence in the first 10 post-irradiation years, but a significant increase of its incidence in patients irradiated 10–15 years (P = .03) and more than 15 years ago (P = .003) ago [22]. Dorresteijn et al. reported a median interval of 10 years to a stroke, in head and neck cancer patients irradiated with 60-70 Gy [4,7]. On the contrary Kim et al., found that vascular changes were not associated with the interval from radiotherapy and were observed even within a year after RT [18].

In our study, the mean interval from RT to symptomatic stenosis was 3 to 7 years and the shortest time was less than 2 years. This indicates that radiation-induced carotid artery stenosis in patients with HNSCC can occur much earlier than 5 to 10 years post RT. The present study did not reveal any relation of the latency period with the number of affected arteries, which is indicative of the advancement of radiation-induced vascular disease. Therefore, it is recommended that patients with HNSCC after RT are followed-up with screening programs for the early detection of radiation-induced vascular disease.

The treatment of atherosclerotic carotid stenosis is dominated by surgical interventions, although endovascular methods are playing an increasing role [27,28]. Radiation-induced stenosis in carotid arteries exposes classical surgical procedures to major challenges. Post-irradiation vascular disease often involves multiple arteries and locations. Dissection in the previously operated and irradiated neck, harboring scars and distorted anatomy, is particularly demanding. It has been reported that adhesion of different tissues and more diffuse plaques add to the difficulty of the procedure and increase the risk of cranial nerve injury [16,27,29]. Tallarita et al. showed that open surgery in patients with prior radical neck dissections was difficult and generated thrice as more complications [30].

Under these circumstances, percutaneous endovascular therapy became an attractive option. However, endovascular procedures in this group of patients are also technically demanding. Detailed recognition of the type and location of the lesions has to be established for meticulous treatment planning. Availability of a variety of stents and an adequate interventional radiology suite are necessities. The present series showed that meeting these requirements enabled technical success of the treatment without complications in all cases.

Long-term outcomes of carotid stenosis treatment in patients, irradiated for head and neck malignancies, have been rarely reported and present diverse results [31–35]. Some studies report that restenosis is more frequently observed after irradiation than in non-radiated patients. Protac et al. informed that the rate of restenosis within 3 years post stenting was much higher in patients after RT (75%) versus patients without RT (20%) [34]. A lower rate of restenosis (21%) within a mean of 28 months was reported by Harrod-Kim et al. [32]. In studies based on 5 and 7 patients, no restenosis was found, however during a very short follow-up of 9.3 and 6 months respectively [31,33].

Satisfactory results of carotid stenting in the presented series, in comparison with the published data, may result from technical improvements, development of new stents, delivery techniques, and cerebral protection devices. The progress in endovascular treatment warrants the use of carotid stenting as an optimal treatment option in radiation-induced carotid stenosis.

There are some limitations in our study. It is known that atherosclerosis develops particularly in patients harboring risk factors like advanced age, hypercholesterolemia, arterial hypertension, diabetes mellitus, and smoking. Similar risk factors are present in HNSCC patients. Therefore, it has to be considered that carotid stenosis is more likely to develop in those patients, regardless of the damaging effects of radiation. None of our patients reported neurological symptoms or events before RT; therefore no diagnostic examination of carotid arteries was carried out. Although carotid stenosis in patients irradiated for HNSCC, presented features typical for post-radiation lesions, the presence of previous atherosclerotic changes cannot be excluded.

Conclusion

RT in patients with HNSCC carries the risk of developing carotid artery stenosis of characteristic radiological features and may lead to cerebrovascular events. Carotid stenting seems to be a preferable treatment for radiation induced stenosis. Screening programs, with Doppler ultrasonography to secure early detection of pre-stroke carotid stenosis are recommended.

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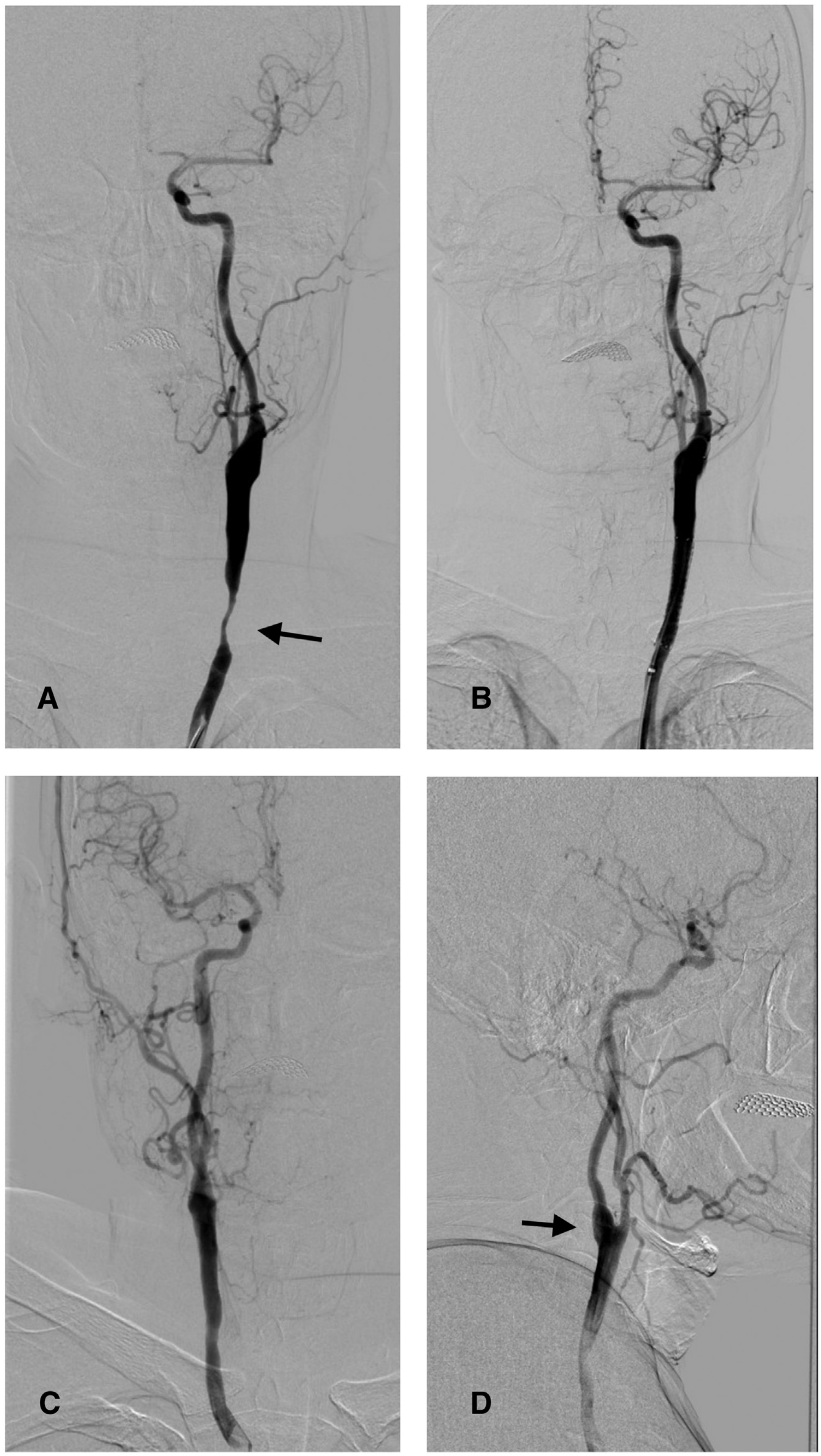

Figure 2. Male, 57 years old, 34 months after hypopharyngeal cancer resection and RT. The left CCA arteriography shows long, critical stenosis in the middle segment (arrow) and dilatation of the proximal segment. Stenosis of the ECA ostium (A). After CCA stenting restored artery diameter (B). The right CCA arteriography in coronal (C) and sagittal (D) projection. Hemodynamically insignificant irregularities of CCA lumen. Dilatation of the proximal segment of ICA (arrow).

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