Radiation therapy (RT) is beneficial for patients with cancer but may cause unwanted long-term effects and complications. In 1978, Silverberg et al. (1) described 9 patients with atherosclerotic carotid artery disease associated with RT for head and neck cancer (HNC). Since then, several studies have demonstrated that RT in patients with HNC is associated with: 1) increased intimal medial thickness of the carotid wall; 2) narrowing of the lumen; 3) occurrence of new atherosclerotic plaques; and 4) worsening of pre-existing plaques (2–6). The evolution of carotid disease is associated with the increased risk of stroke and cardiovascular events (7,8). Most effects of RT have been investigated in adult patients. However, the increased risk also extends to the pediatric population. Children treated with RT who have survived cancer display significant signs of premature arterial aging during young adulthood (9). Although discrepancies exist about the prevalence of events in different reported series, data about the preceding RT-related effects on the carotid artery are consolidated. Monitoring and protection of carotid arteries in patients with HNC to be treated with RT should be considered mandatory. However, most data available today reflect past RT techniques, protocols, and doses and are expected to differ from future data reflecting the recent implementation of carotid-sparing techniques and protocols that create RT plans with sharp dose gradients, depending on the complex planning of RT for the different HNCs (10,11).

The pathobiological profile of RT-related carotid disease is still a matter of research. Pathological studies of samples removed at carotid endarterectomy are providing nonconcordant results: on the one hand, carotid stenotic lesions in patients with previous cervical radiation seem to be less inflammatory and more fibrotic than carotid atherosclerotic lesions in nonirradiated patients (12); on the other hand, vulnerable plaques with large necrotic cores seem to be more common in patients treated with RT than in non-RT-treated control groups (13). High plaque vulnerability in RT plaques is associated with increased risk of events. Large cores, a thin cap, inflammation, and more recently, angioneogenesis and intraplaque neovascularization (IPN) and hemorrhage (14,15) are all factors potentially contributing to plaque vulnerability; imaging can detect and monitor most of them in vivo.

**INTRAPLAQUE NEOVASCULARIZATION**

IPN is common in atherosclerotic plaques, where it is promoted by hypoxia and inflammation (16,17). The origin of IPN is still a matter of research: newly formed capillary vessels can originate from CD34-positive cells entering plaques (analogous to inflammatory cells) or from adventitial vessels. Newly formed vessels limit the effects of plaque hypoxia and favor the afference of monocyte-macrophage cells (CD68 positive) functionally deputed to clearing lipids and digesting toxic agents like hemoglobin. Most newly formed vessels in plaques are tiny and leaky; they lack mural pericytes and smooth muscle cells surrounding and supporting the endothelial cells (Figure 1). The “immature neovessels” are prone to structural instability and permissiveness for extravasation of blood contents into the plaque (14,15). Plaque hemorrhage has been recognized as a contributor to plaque...
(A) A large lipid-rich carotid atherosclerotic plaque with angioneogenesis: newly formed vessels are specifically immunostained with anti-CD34 antibodies (objective ×20). (B to E) Corresponding low-magnification views (objective ×4) of the same plaque; rectangle shows the area magnified in A. (B) The Movat pentachrome shows the plaque composition with a very large core and hemorrhage; rectangle shows the area magnified in A. (C) Anti-CD34 immunostain; rectangle shows the area magnified in A. (D) Anti-glycoforyn A immunostain showing the hemorrhage-related content of the core; rectangle shows the area magnified in A. (E) Large number of macrophages (anti-CD68 immunostain); rectangle shows the area magnified in A.
instability and is strictly linked with angioneogenesis (14–17). The in vivo identification of IPN in carotid plaques may inform about the potential risk or presence of plaque hemorrhage (nonselectively detectable in vivo). Contrast-enhanced ultrasonography (CEUS) is routinely used to assess IPN in carotid atherosclerotic plaques (18). Plaque angiogenesis has been correlated with the presence of clinical symptoms in patients treated with endarterectomy for carotid artery stenosis (19) and is associated with timing of ischemic neurological events (20). Indirect evidence of the presence of IPN in carotid plaques is emerging from studies of angiogenesis inhibitors in cancer. In patients treated with angiogenesis inhibitors (e.g., human recombinant endostatin [Endostar]), enhanced intensity of CEUS performed before and 1 month after treatment showed that carotid soft plaque IPN was reduced by the antiangiogenesis treatment (21). Therefore, novel RT technologies and cancer treatment protocols may modify future scenarios of RT-related carotid disease and call for systematic investigation and monitoring of carotid artery disease.

RT AND ANGIONEOGENESIS

The challenging question is whether RT exerts beneficial antiangiogenesis effects in cancer and adverse proangiogenic effects in plaques. Recent experimental studies showed that high doses of ionizing radiation on quiescent endothelial cells locally suppresses subsequent angiogenesis (22). In a review article on the effects of radiation on angiogenesis, Grabham and Sharma (23) described 3 potential (proangiogenic and antiangiogenic) mechanisms influencing vessel growth: 1) the proangiogenic effects of photons of electromagnetic radiation, increasing the expression of angiogenic factors; 2) the antiangiogenic effects of low linear energy transfer charged particles through decreased expression of angiogenic factors and motile tip activity; and 3) the antiangiogenic effects of high low linear energy transfer heavy ions (i.e., Fe) through an unknown mechanism affecting the later stages of tubulogenesis (23). Knowing whether and how different RT and combined RT and antiangiogenesis protocols for HNC exert proangiogenic or antiangiogenic effects is clinically relevant, particularly in patients with pre-existing atherosclerotic plaques.

In this issue of JACC, Shah et al. (24) report the results of a cross-sectional study with B-mode and CEUS of both carotid arteries on the RT-treated side and carotid arteries on the non-RT-treated side in 49 patients who had undergone RT for HNC ≥2 years before. The aim of the study was to assess the presence of IPN graded 0 (absent), 1 (present but limited to adventitia and plaque base), and 2 (extensive within the plaque body). The authors found IPN in 41% of carotid arteries on the non-RT-treated side and in 81% on the RT-treated side, with grade 2 IPN significantly higher in the latter than in the former (24). The merit of the study is focusing on IPN in post-RT carotid disease as a potential contributor to plaque progression and increased risk of stroke. IPN is common in atherosclerotic plaques and is related to the risk of intraplaque hemorrhage, which may contribute to plaque complications by modifying the composition of the plaque core. Intraplaque hemorrhage is a predictor of stroke (25) that does not correlate with the percentage of carotid stenosis/plaque size seen on magnetic resonance imaging (26) but rather to plaque composition (27), a feature that is especially relevant in cryptogenic stroke in patients with mild carotid plaques (28).

Baseline evaluation of both carotid arteries is essential in patients with HNC, because the carotid artery disease may not be symmetrical. Cross-sectional studies provide intrapatient control, but recent studies indicate that carotid atherosclerotic plaque size and composition are not symmetrically distributed: intraplaque hemorrhage is prevalent in left-sided carotid plaques, suggesting a greater vulnerability than in right-sided plaques, which are more calcified and therefore considered more stable (29).

CONCLUSIONS

Although more research is necessary to unravel the pathobiological characteristics of carotid plaques in patients treated with RT for HNC, the current scientific evidence strongly suggests the need for: 1) introducing systematic carotid imaging with CEUS in the pre-RT protocols to generate baseline images and data to be used as reference in the follow-up; 2) stratifying the risk of RT-related cerebrovascular events before starting treatment; 3) planning regular monitoring of carotid arteries, especially in patients with pre-RT atherosclerotic plaques; and 4) eventually administering medications preventing thrombotic complications or acting as anti-IPN agents (30).

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