Ischemic Stroke and Transient Ischemic Attack After Head and Neck Radiotherapy
A Review

Chris Plummer, PhD; Robert D. Henderson, PhD; John D. O’Sullivan, MD; Stephen J. Read, PhD

Background and Purpose—Cerebrovascular disease can complicate head and neck radiotherapy and result in transient ischemic attack and ischemic stroke. Although the incidence of radiation vasculopathy is predicted to rise with improvements in median cancer survival, the pathogenesis, natural history, and management of the disease are ill defined.

Methods—We examined studies on the epidemiology, imaging, pathogenesis, and management of medium- and large-artery intra- and extra-cranial disease after head and neck radiotherapy. Controlled prospective trials and larger retrospective trials from the last 30 years were prioritized.

Results—The relative risk of transient ischemic attack or ischemic stroke is at least doubled by head and neck radiotherapy. Chronic radiation vasculopathy affecting medium and large intra- and extra-cranial arteries is characterized by increasing rates of hemodynamically significant stenosis with time from radiotherapy. Disease expression is the likely consequence of the combined radiation insult to the intima-media (accelerating atherosclerosis) and to the adventitia (injuring the vasa vasorum). Optimal medical treatment is not established. Carotid endarterectomy is confounded by the need to operate across scarred tissue planes, whereas carotid stenting procedures have resulted in high restenosis rates.

Conclusions—Head and neck radiotherapy significantly increases the risk of transient ischemic attack and ischemic stroke. Evidence-based guidelines for the management of asymptomatic and symptomatic (medium- and large-artery) radiation vasculopathy are lacking. Long-term prospective studies remain a priority, as the incidence of the problem is anticipated to rise with improvements in postradiotherapy patient survival. (Stroke. 2011;42:2410-2418.)

Key Words: ischemic stroke ■ TIA ■ cerebrovascular disease ■ head and neck cancer ■ radiotherapy ■ radiation vasculopathy

Radiation vasculopathy is an underrecognized precursor to ischemic stroke in patients who have received head and neck radiotherapy (HNXRT) for the treatment of malignancy.1,2 Since the first histologic description of radiation-induced vascular injury,3 animal and human studies have aimed to characterize the acute and chronic effects of radiation on the cerebral vasculature.4–8 Small vessels (arterioles, venules, and capillaries), devoid of intervening muscularis and adventitial layers, are the most vulnerable to radiation-induced endothelial cell injury.9 This can lead to thrombotic occlusion and ischemia of the microvascular bed, resulting in cerebral radionecrosis.10 Corticosteroid use and advances in HNXRT delivery have helped limit the incidence of this problem.11,12 The 2 forms of post-HNXRT injury to medium and large arteries (external diameters >100 and >500 μm, respectively) are acute rupture and occlusive vasculopathy.13 Vessel rupture is rare nowadays with the advances in post-surgical wound care.14 Occlusive radiation vasculopathy, the subject of this review, is marked by its chronicity: years can span the interval from XRT exposure to the first cerebrovascular event (CVE).15 In children, and rarely in adults, it may be associated with the formation of netlike vessels and transdural anastomoses (moyamoya disease).16 Chronic radiation vasculopathy has attracted little research attention because it was considered rare and because patients would often succumb to their malignancy before the condition manifested itself.2 This is no longer the rule. More patients are now “outliving” their malignancies and are presenting with the long-term sequela of cancer treatment.17 Until relatively recently, the literature was dominated by anecdotal reports and case series on the subject. The purpose of this review is to provide an update on the problem by identifying key studies that have contributed most to our current understanding of the epidemiology, radiologic features, pathogenesis, and treatment of the disease.

Scope
This review focuses on studies that have attempted to systematically analyze the problem of ischemic stroke, tran-
sient ischemic attack (TIA), or carotid stenosis in patients who have received HNXRT where radiation fields have involved the large (common, internal, and external carotid) and/or the medium (anterior, middle, and posterior cerebral; vertebral; basilar) intra- and extra-cranial arteries. “Radiation vasculopathy” herein implies chronic occlusive cerebrovascular disease affecting medium- and large-diameter arteries. Head and neck cancer patients (adults and children) and breast cancer patients make up the treatment cohorts. Studies focusing on radiotherapy-related hemorrhagic stroke and small-vessel disease (radionecrosis) are not included. This avoids introducing further heterogeneity to an already multifactorial problem. Disease pathogenesis differs in radionecrosis, and post-XRT hemorrhagic stroke, though less common, carries its own order of confounding risk factors, including aneurysmal disease.18,19

### Methods

Web of Science and PubMed databases were searched by using the following terms and separators: “cerebrovascular disease” (or) “vasculopathy” (or) “stroke” (or) “ischemic stroke” (or) “transient ischemic attack” (or) “carotid stenosis” (and) “head (or) neck cancer” (or) “malignancy” (or) “radiotherapy” (or) “radiation.” Priority was given to controlled prospective trials and to larger retrospective trials published within the last 30 years (until June 2010). Medium arteries (anterior, middle, and posterior cerebral; vertebral; basilar) and/or large arteries (common, internal, and external carotid) had to be included in the XRT field. Case reports were excluded, as were other documented forms of XRT-related cerebrovascular disease (small-vessel disease, hemorrhagic stroke, and aneurysmal disease with or without hemorrhage). Studies were grouped and are discussed according to epidemiology, pathogenesis, and management. The search revealed 99 studies on stroke, TIA, or rates of carotid stenosis in patients who had previously received XRT for primary or secondary cancers of the head and/or neck region: epidemiology (n = 17), imaging (n = 19), pathogenesis (n = 21), management (n = 16), and case reports (n = 22). The latter were excluded. From the total number of pediatric studies remaining (n = 15), cancer types were as follows: optic pathway gliomas 50%, craniopharyngiomas 20%, medulloblastomas 10%, and other suprasellar tumors 20%. Of the remaining adult studies (n = 58), cancer types were as follows: nasopharyngeal carcinomas 40%, lymphomas 20%, pituitary adenomas 10%, breast cancers 10%, and oral cancers 10%. Cancer type was not specified in 1 study. Refer to Table 1.2-1.2–3.3 and the Figure (for epidemiology; all studies were retrospective) and Table 2.4–2.4–5.5 (for imaging; only 2 studies were prospective).

### Table 1. Prevalence of Ischemic Stroke and Transient Ischemic Attack After Head and/or Neck Radiotherapy

<table>
<thead>
<tr>
<th>Year</th>
<th>First Author/Reference No.</th>
<th>XRT</th>
<th>Dose, Gray</th>
<th>Cancer</th>
<th>Cases, No.</th>
<th>Treatment Categories</th>
<th>Controls</th>
<th>CVE Risk (Attributed to XRT)</th>
<th>XRT to CVE, Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Smith20</td>
<td>HN</td>
<td>Not given</td>
<td>Oral/Phnx/Slv</td>
<td>6862</td>
<td>1983 XRT, 2823 SU+XRT, 2056 SU</td>
<td>SU/A/S</td>
<td>TIA or stroke RR = 1.7–4.4</td>
<td>21.4 (0–10)</td>
</tr>
<tr>
<td>2002</td>
<td>Haynes21</td>
<td>HN</td>
<td>64°</td>
<td>Oral/Phnx/Lx/Slv</td>
<td>413</td>
<td>All XRT</td>
<td>A/S</td>
<td>Stroke RR = 2.1</td>
<td>4.6 (0.2–12)</td>
</tr>
<tr>
<td>2002</td>
<td>Dorrestein2</td>
<td>HN</td>
<td>50–66</td>
<td>Lx/Slv</td>
<td>367</td>
<td>All XRT</td>
<td>A/S</td>
<td>Stroke RR = 5.6; RR = 10.1 at &gt;10 y</td>
<td>10.9 (1.3–21.0)</td>
</tr>
<tr>
<td>1981</td>
<td>Elerding2</td>
<td>HN</td>
<td>40–50</td>
<td>Oral/Phnx/HD/NHL</td>
<td>910</td>
<td>All XRT (&gt;5-y Sv)</td>
<td>A/S/G</td>
<td>Stroke RR = 0.39</td>
<td>9° (1.5–18)</td>
</tr>
<tr>
<td>2009</td>
<td>Debruin23</td>
<td>N</td>
<td>30–40</td>
<td>HD</td>
<td>2200</td>
<td>609 XRT, 187 ChRx, 1405 ChRx+XRT</td>
<td>A/S/G</td>
<td>TIA RR = 3.1; stroke RR = 2.2</td>
<td>17.4 (5.1–37.6)</td>
</tr>
<tr>
<td>2006</td>
<td>Moser24</td>
<td>N</td>
<td>28–60</td>
<td>NHL</td>
<td>462</td>
<td>189 XRT, 273 ChRx</td>
<td>A/S/G</td>
<td>Stroke RR = 2.3</td>
<td>3.7 (1.6–5.1)</td>
</tr>
<tr>
<td>2006</td>
<td>Woodward25</td>
<td>N</td>
<td>Not given</td>
<td>Breast</td>
<td>5752</td>
<td>471 BXRT+N0XRT, 5281 BXRT</td>
<td>BXRT</td>
<td>Stroke HR = 1.0 at 10 and 15 y</td>
<td>FULL 7.5 (5–15)</td>
</tr>
<tr>
<td>2006</td>
<td>Hooning26</td>
<td>N</td>
<td>40–50</td>
<td>Breast</td>
<td>4368</td>
<td>2765 NXRT, 934 other XRT, 516 SU</td>
<td>A/S/G</td>
<td>TIA HR = 1.4, stroke HR = 1.0</td>
<td>FULL 17.7 (10–20+)</td>
</tr>
<tr>
<td>2006</td>
<td>Jagsi27</td>
<td>N</td>
<td>62°</td>
<td>Breast</td>
<td>820</td>
<td>222 BXRT+N0XRT, 598 BXRT</td>
<td>A/S/G</td>
<td>TIA or stroke RR = 1.9</td>
<td>5.4 (0.1–16.9)</td>
</tr>
<tr>
<td>2005</td>
<td>Bowers28</td>
<td>N</td>
<td>40°</td>
<td>HD</td>
<td>1926</td>
<td>1598 XRT, 328 ChRx</td>
<td>Siblings</td>
<td>Stroke RR = 5.6</td>
<td>17.5 (6–29)</td>
</tr>
<tr>
<td>2009</td>
<td>Erridge29</td>
<td>H</td>
<td>45°</td>
<td>Pituitary</td>
<td>385</td>
<td>All XRT, 288 SU+XRT</td>
<td>A/S/G</td>
<td>Stroke RR = 1.45 (M), RR = 2.2 (F)</td>
<td>0.6–27.4</td>
</tr>
<tr>
<td>2006</td>
<td>Keene30</td>
<td>H</td>
<td>35°</td>
<td>Glioma/MB/other</td>
<td>244</td>
<td>All XRT</td>
<td>Nil</td>
<td>Stroke or TIA, 5%</td>
<td>3° (1–8)</td>
</tr>
<tr>
<td>2002</td>
<td>Bowers28</td>
<td>H</td>
<td>27–90</td>
<td>Glioma/MB/other</td>
<td>807</td>
<td>All XRT</td>
<td>Nil</td>
<td>Stroke, 1.6% XRT (P = 0.007)</td>
<td>2.3 (0.3–15.8)</td>
</tr>
<tr>
<td>2002</td>
<td>Erfurth31</td>
<td>H</td>
<td>41°–46°</td>
<td>Pituitary</td>
<td>342</td>
<td>All SU+XRT (31 deaths)</td>
<td>SV/A/G</td>
<td>Stroke death (P &gt; 0.05)</td>
<td>10° (6–40)</td>
</tr>
<tr>
<td>1999</td>
<td>Brada4</td>
<td>H</td>
<td>45°</td>
<td>Pituitary</td>
<td>331</td>
<td>All XRT, 250 SU+XRT</td>
<td>A/S/G</td>
<td>Stroke RR = 4.1</td>
<td>FULL 15° (0.5–33)</td>
</tr>
<tr>
<td>1998</td>
<td>Grill43</td>
<td>H</td>
<td>55°</td>
<td>Optic glioma</td>
<td>69</td>
<td>All XRT</td>
<td>Nil</td>
<td>Stroke or TIA, 13%</td>
<td>3° (0.6–5.7)</td>
</tr>
<tr>
<td>1989</td>
<td>Flickinger2</td>
<td>H</td>
<td>35–62</td>
<td>Pituitary</td>
<td>156</td>
<td>All XRT, 118 SU+XRT</td>
<td>A/S/G</td>
<td>Stroke incidence (P = 0.08)</td>
<td>3.2–14.6</td>
</tr>
</tbody>
</table>

Note that “ refers to medians and “ refers to means for both dose (Gray) and time (years). Numbers in parentheses in the final column refer to the time range in years. CVE indicates cerebrovascular event; Phnx, pharynx; Sv, salivary gland; SU, surgery; A/S/G, age/sex/geography matched; RR, relative risk; FULL, follow-up interval; Lx, larynx; y, year(s); HD, Hodgkin disease; NHL, non-Hodgkin lymphoma; SV, survivors; ChRx, chemotherapy; BXRT, breast radiotherapy; HR, hazard ratio; M, males; F, females; and MB, medulloblastoma; H, head; N, neck; TIA, transient ischemic attack; XRT, radiotherapy.
Epidemiology

Head and Neck XRT

Squamous cell carcinoma of the head and neck was the most common pathology treated by HNXRT in these studies. Smith et al.20 used a medical record database to analyze CVEs from a cohort of 6862 head and neck cancer patients. They calculated a CVE hazard ratio of 1.5 for XRT alone versus surgery (with or without) XRT and a hazard ratio of 1.7 to 4.4 for XRT versus no XRT. Because there was no significant difference for cardiovascular events, the authors surmised that baseline vascular risk was comparable between subgroups. Although unable to cite XRT protocols, they argued that the higher CVE rate in the XRT-alone subgroup was the consequence of the higher mean XRT dose typically used to treat inoperable head and neck cancers. Unfortunately, like many such studies published to date, no distinction was made between ischemic and hemorrhagic stroke. Haynes et al.21 also using a database registry, identified 20 post-HNXRT ischemic strokes from a cohort of 413 head and neck cancer patients. On the basis of expected stroke rates from a different (Scandinavian) population, they calculated a relative risk of 2.09 for stroke in the HNXRT cohort. Although no dose effect was seen, the XRT dose range was narrow (59.4 to 76.8 Gray), and the mean follow-up was brief (2.1 years). Dorresteijn et al.2 used fewer ischemic strokes from a comparable number of patients (14 of 367) yet calculated a much higher RR of stroke (5.6) in their treatment cohort, again relative to geographically distant (Oxfordshire) baseline data. The higher RR may relate to the longer follow-up (median, 10.9 years from XRT to stroke) and the younger age at treatment. The authors mentioned their study as the first to show a significantly elevated risk of stroke after HNXRT. They pointed to the benchmark study by Elerding et al.22 in which 910 HNXRT survivors evidenced only a “trend” (6.9%) toward ischemic stroke against a matched population; the mean interval from XRT to stroke was comparable (9.0 years), but the total XRT dose was lower (40 to 50 Gray).

Neck XRT

Lymphoma and breast cancer were the main tumor types targeted by neck XRT (NXRT) in these studies. Debrun et al.23 looked at CVE risk in >5-year survivors of Hodgkin disease (HD). The median time to CVE (TIA or ischemic stroke) was 17.4 years. Mantle field XRT (combination mediastinal-NXRT) for HD (1651 of 2014 XRT patients) was judged to be an independent risk factor for ischemic stroke and/or TIA (88 cases; hazard ratio=2.5) when compared with the CVE rate for HD without supradiaphragmatic XRT (7 cases, 303 patients). The hazard ratio for the NXRT-alone HD cohort was 2.3 (5 cases, 136 patients), but the 95% CI crossed 1.0 (0.7 to 7.6). The RR for TIA after any XRT was 3.1; for stroke, it was 2.1. Most of the risk was borne by younger patients (age <30 years at XRT). Of the CVEs with an identifiable mechanism (58 of 88), 32 cases (55%) were attributed to large-artery disease, and 21 (36%) were considered cardioembolic (the latter arguably potentiated by mediastinal XRT). Whereas chemotherapy was received by most patients (72%), it did not appear to elevate CVE risk. Bowers et al.26 studied stroke incidence in >5-year survivors of HD after mantle XRT (1387 of 1598 XRT patients). The patients’ 3846 siblings served as the control population. The RR of stroke in the treatment group was 5.6 (24 patients had a stroke versus 9 in the sibling group). The median time to stroke was 17.5 years. The chief criticism of this study is the reliance on self-reporting of stroke by a questionnaire mailed to participants. Clinical verification of the diagnosis, stroke subtype (ischemic versus hemorrhagic), and stroke etiology were not detailed. Stroke risk in non-Hodgkin lymphoma after mediastinal-NXRT was addressed by Moser et al.24 as part of a broader study on XRT-related cardiovascular disease. Against a well-matched control population, the RR of stroke was 2.3 in the NXRT subgroup (168 patients) but 0.6 in the group treated by chemotherapy alone (273 patients). Although a subanalysis suggested that the RR rose with increasing XRT dose (0.7 at <30 Gray, 2.2 at 30 to 40 Gray, and 8.6 at >40 Gray) and the time from XRT (2.1 at 3-year follow-up and 2.5 at 5-year follow-up), it again unclear whether all.

Figure. Relative risk (RR) of stroke and transient ischemic attack (TIA) after head and/or neck radiotherapy. The RR of stroke and/or TIA after radiotherapy to the head and neck (HN), neck (N), or head (H) with 95% confidence intervals (CIs) is shown. The vertical axis represents an RR of 1.0. CI values were not given for Brada et al.1 The group of articles published in 2006 by Woodward et al.25 Hooning et al.26 and Jagsi et al.26 examined the effect of adjuvant NXRT in breast cancer (all CI values cross RR 1.0). Also refer to Table 1. Yr indicates year; A/S, age- and sex-matched control: no cancer, no radiotherapy (XRT); and SU, surgery-only cohort: no XRT.
Table 2. Imaging Studies for Ischemic Stroke and Transient Ischemic Attack After Head and/or Neck Radiotherapy

<table>
<thead>
<tr>
<th>Year</th>
<th>First Author/Reference No.</th>
<th>XRT</th>
<th>Dose, Gray</th>
<th>Cancer</th>
<th>Cases (All XRT)</th>
<th>Controls</th>
<th>Imaging Parameter</th>
<th>XRT to ix, Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Chang44</td>
<td>HN</td>
<td>70'</td>
<td>Not specified</td>
<td>192</td>
<td>98 (CA, no XRT)</td>
<td>Plaque, &gt;50% to &gt;70% stenosis</td>
<td>2.0’ (0.3–19.1)</td>
</tr>
<tr>
<td>2005</td>
<td>Dorresteijn35</td>
<td>HN</td>
<td>40–66</td>
<td>Parotid, PleoAd</td>
<td>42 (XRT side)</td>
<td>42 (non-XRT side)</td>
<td>IMT</td>
<td>9.8’ (3.4–27.2)</td>
</tr>
<tr>
<td>2005</td>
<td>Brown36</td>
<td>HN</td>
<td>60’</td>
<td>Parotid, SCC</td>
<td>44 (XRT side)</td>
<td>44 (non-XRT side)</td>
<td>&gt;50% stenosis</td>
<td>7.5’ (4–23)</td>
</tr>
<tr>
<td>2004</td>
<td>Cheng50 (pros)</td>
<td>HN</td>
<td>60 H, 60 N</td>
<td>NasoPhrx, Lrx</td>
<td>95 (asxic &lt;50% stenosis)</td>
<td>75 (no CA, asxic &lt;50% stenosis)</td>
<td>&lt;50% to &gt;50% stenosis change</td>
<td>7.6’, FUI 3’ (0.5–5.7)</td>
</tr>
<tr>
<td>2004</td>
<td>Steele38</td>
<td>HN</td>
<td>55–77</td>
<td>SCC, Lymph</td>
<td>40</td>
<td>Nil</td>
<td>&gt;50% stenosis</td>
<td>10.2’</td>
</tr>
<tr>
<td>2002</td>
<td>So39</td>
<td>HN</td>
<td>Not stated</td>
<td>NasoPhnx</td>
<td>51</td>
<td>51 (No CA; A/S)</td>
<td>IMT</td>
<td>7.7’ (4–18)</td>
</tr>
<tr>
<td>2001</td>
<td>Lam40</td>
<td>HN</td>
<td>60’</td>
<td>NasoPhnx</td>
<td>80</td>
<td>58 (NasoPhnx, no XRT)</td>
<td>&gt;50% stenosis</td>
<td>(4–26)</td>
</tr>
<tr>
<td>2000</td>
<td>Muzaffar41 (pros)</td>
<td>HN</td>
<td>60’</td>
<td>SCC</td>
<td>36</td>
<td>No CA; A/S</td>
<td>IMT, plaque, PSV</td>
<td>FUI 1, 2 y</td>
</tr>
<tr>
<td>2000</td>
<td>Cheng45</td>
<td>HN</td>
<td>64–72 H, 45–66 N</td>
<td>NasoPhnx</td>
<td>96</td>
<td>96 (A/S)</td>
<td>&gt;70% stenosis</td>
<td>6.5’ (1–28)</td>
</tr>
<tr>
<td>1999</td>
<td>Cheng44</td>
<td>HN</td>
<td>&lt;66.5–55</td>
<td>Oral/Phnx/Lx/Sw</td>
<td>240</td>
<td>108 (A)</td>
<td>&gt;70% stenosis</td>
<td>6.0’ (0.5–27.8)</td>
</tr>
<tr>
<td>1999</td>
<td>Carmody44</td>
<td>HN</td>
<td>&lt;50%</td>
<td>NasoPhnx, Lrx</td>
<td>23 males</td>
<td>46 males (A)</td>
<td>&gt;70% stenosis</td>
<td>6.5’ (SD = 1.8)</td>
</tr>
<tr>
<td>1998</td>
<td>Dubec45</td>
<td>HN</td>
<td>60’</td>
<td>SCC, Thy, Lymph</td>
<td>45</td>
<td>No CA; no A/S</td>
<td>&gt;50% stenosis</td>
<td>?, but &gt;5</td>
</tr>
<tr>
<td>1992</td>
<td>McGuirt46</td>
<td>HN</td>
<td>60’</td>
<td>Oral/Phnx/Lx</td>
<td>29</td>
<td>9 (no CA)</td>
<td>IMT</td>
<td>8.5’ (3–17)</td>
</tr>
<tr>
<td>1990</td>
<td>Moritz47</td>
<td>HN</td>
<td>&gt;50</td>
<td>SCC</td>
<td>53</td>
<td>38 (CA, no XRT)</td>
<td>&gt;50% stenosis</td>
<td>2.4’</td>
</tr>
<tr>
<td>2009</td>
<td>Meekse48</td>
<td>N</td>
<td>20–66</td>
<td>HD, RMS</td>
<td>30</td>
<td>30 (no CA; A/S)</td>
<td>IMT</td>
<td>15’ (6–35)</td>
</tr>
<tr>
<td>2008</td>
<td>Woodward49</td>
<td>HN</td>
<td>50’</td>
<td>Breast</td>
<td>46 (ipsilat to XRT)</td>
<td>46 (contralat to XRT side)</td>
<td>IMT, plaque, PSV</td>
<td>14.6’</td>
</tr>
<tr>
<td>1999</td>
<td>King50</td>
<td>N</td>
<td>22.5–40</td>
<td>HD</td>
<td>42</td>
<td>42 (No CA; A/S)</td>
<td>IMT, &gt;70% stenosis</td>
<td>13’ (5.1–22.8)</td>
</tr>
<tr>
<td>1997</td>
<td>Omura51 (rev)</td>
<td>H</td>
<td>54’</td>
<td>Optic glioma, other</td>
<td>32</td>
<td>Nil</td>
<td>MRA</td>
<td>1.3–14</td>
</tr>
<tr>
<td>1995</td>
<td>Bitzer52 (rev)</td>
<td>H</td>
<td>52’</td>
<td>Optic glioma, other</td>
<td>40 (most children)</td>
<td>Nil</td>
<td>MRA</td>
<td>85% cases &lt;8</td>
</tr>
</tbody>
</table>

Note that ‘ix’ indicates investigation; CA, cancer; PleoAd, pleomorphic adenoma; IMT, intima-media thickness; SCC, squamous cell carcinoma; pros, prospective study; NasoPhnx, nasopharynx; Lrx, larynx; asxic, asymptomatic; FUI, follow-up interval; Lymph, lymphoma; A/S, age/sex matched; PSV, peak systolic velocity; y, year(s); Phnx, pharynx; Slv, salivary gland; SD, standard deviation; Thy, thyroid; HD, Hodgkin disease; RMS, rhabdomyosarcoma; ipsilat, ipsilateral; contralat, contralateral; MRA, magnetic resonance angiography; rev, review study; H, head; N, neck; TIA, transient ischemic attack; XRT, radiotherapy.

Events were ischemic. Three recent studies25–27 have looked at CVE risk after adjuvant NXRT in patients with breast cancer. The largest study compared long-term stroke risk between 2 breast cancer cohorts: 471 patients treated with breast XRT and NXRT versus 5281 patients treated with breast XRT alone.25 Although freedom from hospitalization for stroke did not differ between the cohorts at both 10 and 15 years, data were not matched against a non-XRT cohort, as breast XRT can predispose to cardiomyopathy and, potentially, to cardioembolic stroke.52 Hooning et al52 did compare their 4368 breast cancer (10-year) survivors with a demographically matched population to determine the RR for both TIA and stroke. The median follow-up was 17.7 years. Neither event was more likely in patients exposed to adjuvant NXRT (supraclavicular and/or internal mammary nodes). Jagisi et al27 analyzed the records of 820 breast cancer patients, 222 of whom underwent supraclavicular XRT (median follow-up, 6.8 years) and also found that NXRT had no independent impact on CVE risk.

Head XRT

Pituitary tumors in adults and optic pathway gliomas in children were the main tumor types targeted by head XRT (HXRT) in these studies. Erridge et al29 looked at CVE risk in patients previously irradiated for pituitary adenoma (385 patients). Against a well-matched control population, the RR for stroke was 1.45 in males and 2.2 in females. Data on stroke subtype and mechanism were lacking. Erfurth et al31 did attempt to identify the stroke syndrome resulting in death in their cohort of 342 pituitary tumor patients who had undergone postoperative HXRT. This was a detailed but highly selective case-control study, in which data from 31 stroke-related deaths were compared with data from 2 control groups: 62 of 311 post-HXRT survivors matched for tumor type and XRT protocol, and 32 non-XRT patients matched for stroke syndrome. Despite the hard end point, records were incomplete: of the 20 of 31 files retrieved, 6 of 20 could not be classified as ischemic or hemorrhagic; 13 of 14 were ischemic; and 11 of 13 involved the anterior circulation. HXRT did not emerge as an independent predictor of stroke-related death or stroke syndrome against either control group. Gonadotropin insufficiency, a known vascular risk factor,53 appeared to add to stroke mortality risk in females, but as the authors pointed out, a synergistic effect with HXRT could not be excluded. Brada et al1 by contrast, subjected all patients from their initial pituitary adenoma cohort (331 cases) to
multivariate analysis of stroke risk after HXRT and came to a different conclusion: that HXRT increases stroke risk (RR = 4.1 against a matched population) and that it does so in a dose-dependent manner; that is, the greatest risk was conferred by doses >50 Gray. This study suffers from a lack of detail on both stroke syndrome and HXRT protocol. Stroke syndrome was better described by Flickinger et al in their study of 156 pituitary adenoma cases after HXRT (6 of 7 known ischemic). They did not see an increase in the incidence of stroke in the treatment cohort against matched population data. A causal link between HXRT and CVEs in children is more readily demonstrated, as pediatric stroke is rare and there are fewer confounding risk factors for CVEs. The largest study, by Bowers et al, calculated an incidence of 1.6% (13 of 807) for ischemic stroke 0.3 to 15.8 years after HXRT for various brain malignancies (TIA was not assessed). Most strokes (9 of 13) reflected large-artery intracranial disease within the original HXRT field. Keene et al found a higher incidence (5%) of post-HXRT CVEs in their cohort of 244 children with primary brain malignancy, but here TIA was included (9 TIAs, 2 strokes). All events were referable to those vessels (medium or large artery) that had been exposed to the maximum XRT field. Grill et al looked at a more select cohort of 69 children treated for optic pathway glioma. Clinical and/or radiologic evidence of occlusive vasculopathy was seen in 13 children. The anterior cerebral circulation was involved in all patients, 11 of whom had neurofibromatosis type 1, a recognized risk factor for cerebral circulation was involved in all patients, 11 of whom had neurofibromatosis type 1, a recognized risk factor for vasculopathy for reasons that remain unclear; 9 of 13 cases evidenced disease progression (median follow-up, 7 years), with death or severe disability occurring in 8 of 9 patients.

Comment
Despite the aforementioned limitations of these studies, HNXRT and NXRT do appear to at least double the RR of TIA or stroke; the exception is adjuvant NXRT for breast cancer, where carotid XRT exposure is usually minimal. The evidence for increased CVE risk after HXRT is more substantial when exposure occurs in childhood versus adulthood (where data remain conflicting), but the magnitude of the increase is unclear, largely owing to the heterogeneity for both tumor type and XRT protocol across the few pediatric HXRT studies available.

Imaging
Most studies were cross-sectional, with results based on nonserial carotid ultrasound scanning (USS), and most were based on patients who had undergone HNXRT.

Head and Neck XRT
Cheng et al performed carotid duplex imaging on 240 patients who had received XRT for various head and neck tumors after a mean interval of 6.0 years (range, 0.5 to 28 years). Significant stenosis (>70%) of either the internal or common carotid artery (ICA or CCA) was seen in 28 patients (against 0 of 108 “healthy” controls); 10 of 28 patients were symptomatic. Multivariate analysis suggested that age >60 years, interval from XRT >5 years, and XRT for either nasopharyngeal or laryngeal cancer were independent risk factors for the development of significant stenosis. A subsequent similarly designed study of 96 nasopharyngeal carcinoma patients by the same group replicated these findings, with >70% stenosis measured in 16% of patients. Whereas the earlier study is 1 of the largest of its kind to date, XRT protocol data are missing, sonographic interpretation was not blinded, and patients were only “asked” about previous possible CVEs. Despite this, a similarly sized study by Chang et al (290 patients) lends weight to the results. Head and neck cancer patients were consecutively recruited (198 after XRT, 92 before XRT). From a combination of plaque score (percentage vessel occlusion plus plaque distribution) and degree of stenosis (peak systolic velocity) on USS (interpreter blinded), the interval from XRT and XRT dose were seen to be correlated (P<0.01) with both outcome measures (higher plaque scores; stenosis >50% in 38 of 198 XRT patients, >70% in 17 of 198 XRT patients versus 0 of 92 pre-XRT patients). The interval from XRT to USS was short (mean, 2.0 years), and pre-XRT patients were not reassessed after XRT, which would have been useful. These results are also consistent with findings from 5 smaller studies. Moritz et al studied 91 patients with head and neck cancer (53 after XRT, 38 with no XRT). Extracranial carotid stenosis >50% was detected in 30% (16 of 53) of the XRT patients versus 6% (2 of 38) in the non-XRT group. There was a nonsignificant trend for a higher-grade stenosis with increasing time from XRT (the mean XRT to USS interval was only 2.4 years).

Lam et al also described a 30% prevalence of carotid stenosis (>50% occlusion of the ICA/CCA) among 80 nasopharyngeal carcinoma patients after XRT, 9 of whom were symptomatic. No patient in their pre-XRT cohort met this criterion. Steele et al detected a similar prevalence of significant (>50%) carotid stenosis in their cohort of 40 HNXRT patients (40%, or 16 patients). The interval to USS was longer (mean, 10.2 years); 6 of 16 patients had unilateral complete occlusion, and 6 of 16 patients had significant bilateral disease. Unfortunately, no detail on plaque or stenosis distribution was given, and although 3 patients experienced a stroke after XRT, there was no mention of stroke territory. Carmody et al also found a higher prevalence of carotid disease (>70% stenosis) in their HNXRT cohort (5 of 23 patients, 22%; 4 patients symptomatic) against an age-matched population (2 of 46 patients, 4%; 1 patient symptomatic). The mean retrospective interval to USS was 6.5 years. They went further by repeating the sonography in a subset of patients from each group (16 of 23 versus 18 of 46 patients; the mean prospective interval was 1.6 years). The mean velocity increase was significantly higher in the XRT group (19% versus 1%, P<0.05). Dubec et al screened 45 patients after a minimum of 5 years after XRT and observed a >50% stenosis of either the ICA or CCA in 17 patients (38%). They noted an expected prevalence of 4% of such stenosis in asymptomatic disease, but this was drawn from unmatched historical data.

Two groups have tried to limit the problem of vascular risk confounders by comparing left and right carotid sonography findings when the XRT plane has been oblique enough to spare the contralateral vessel (as with XRT for parotid cancer). Borrestein et al calculated the intima-media thickness (IMT) to be 0.3 mm greater on average at the irradiated...
carotid for 42 patients, a difference that more than doubled (0.67 mm) beyond 10 years after XRT. Brown et al. saw a higher but nonsignificant overall rate for >50% stenosis of the irradiated carotid in their cohort of 44 patients, a rate that appeared to quadruple in the subgroup treated >15 years previously (2.13 vs 5.3 patient-years, \( P < 0.01 \); subgroup patient count not given). In both studies, 4 patients gave a history of CVE in the territory of the irradiated vessel.

IMT has also been studied after HNXRT for nasopharyngeal carcinoma, in which both carotids are typically involved in the field. So et al. found that the CCA IMT was significantly greater for both carotids in 51 HNXRT patients, by a mean of 1.5 mm, against a control group otherwise matched for vascular risk. Although the interval to USS ranged from 4 to 18 years (mean, 7.7 years), all XRT patients were CVE-free. This result agrees with the earlier study by McGuirt et al. who performed CCA measurements on a smaller asymptomatic cohort of 29 patients after a similar post-XRT interval (3 to 17 years; mean, 8.5 years) but who used 9 recently diagnosed (pre-XRT) patients as the control group. IMT was greater in the post-XRT group, by a mean of 0.38 mm (\( P = 0.003 \)), a difference that remained significant after adjusting for confounders (age, smoking, and hypertension). Sonography was unblinded, a drawback common to both studies.

As the first of only 2 genuinely prospective imaging studies on this problem, Muzzafar et al. followed up 36 head and neck cancer patients after XRT. There was a 0.17-mm IMT increase (for the right and left CCA/ICA) at 1 year and a further 0.06-mm (left CCA/ICA) to 0.16-mm (right CCA/ICA) increase in the subsequent year in a subset of 12 patients, 21 times the rate suggested by age- and sex-matched population data. No significant change was seen for either new plaque formation or degree of stenosis, albeit >75% stenosis was seen in the only 2 symptomatic patients. The authors suggested that the earliest post-XRT change on Doppler criteria is the IMT. The second study, by Cheng et al., examined the rate of progression of ICA/CCA stenosis in 95 head and neck cancer patients with mild asymptomatic disease at baseline after XRT (15% to 49% stenosis; mean follow-up, 3 years). Against a control group of 75 patients matched for degree of stenosis but not matched for age and sex, a shift in the degree of stenosis to >50% was more common in the XRT group (\( P = 0.035 \)); the greatest shifts were seen in those who had undergone XRT >6 years earlier (RR = 3.1). The figure on the actual rather than the 50% categorial change would have been useful.

**Neck XRT**

Woodward et al. in a study mislabeled “prospective” (the design was cross-sectional), found no difference between irradiated and contralateral carotid Doppler characteristics (IMT, stenosis) in 46 breast cancer patients who received unilateral adjuvant NXRT to the supraclavicular nodes >8 years previously. Meeske et al. examined 30 asymptomatic young adults who had received NXRT when <20 years old; most had HD, and the mean XRT to USS interval was 15 years. There were 3 significant findings: (1) the prevalence of CCA plaque for the irradiated versus nonirradiated side was 18% versus 2%; (2) CCA IMT was 0.05 mm greater for patients, against an age- and sex-matched control group; and (3) there was a linear increase in CCA IMT with increasing time from XRT. Similar findings were reported by King et al. in their asymptomatic cohort of 42 HD survivors (0.08-mm CCA IMT difference against age- and sex-matched controls; mean XRT to USS interval, 13 years).

**Head XRT**

Omura et al. retrospectively analyzed the magnetic resonance imaging and magnetic resonance angiographic results of 32 tumor-free children who underwent HXRT for primary intracranial malignancy. Six patients experienced a CVE (3 TIs, 3 strokes) 2 to 13 years after HXRT. Four patients had optic glioma tumors without a known neurofibromatosis type 1 mutation. The magnetic resonance angiographic results were abnormal in every case (all relevant territory, all anterior circulation) but were never abnormal in the asymptomatic patients, in whom the scan was repeated a median of 8 times. There were 2 other interesting findings: (1) moyamoya changes were seen only in the TIA patients and (2) the mean HXRT exposure was significantly higher in the CVE subgroup (61 Gray versus 50 Gray). Bitzer and Topka reviewed 41 cases of intracranial medium- and large-vessel occlusive disease after HXRT. The most common indication was pediatric optic glioma (15 cases). In 35 of 41 cases, the first CVE occurred within 8 years of treatment; the XRT dose range was broad (10 to 100 Gray). In line with the findings of Omura et al., anterior circulation vasculopathy (terminal ICA, proximal middle and/or anterior cerebrials) was typical: only 4 of 41 cases involved the posterior circulation, and moyamoya changes (70% cases) heralded a better clinical outcome, perhaps via collaterals limiting the ischemic penumbra.

**Comment**

Imaging studies, most based on Doppler USS in asymptomatic patients, repeatedly show an increased prevalence of hemodynamically significant carotid stenosis when there is a history of HNXRT. The earliest post-XRT effect is an increase in carotid IMT. Two prospective adult studies support the notion (from cross-sectional studies) of a rise in the incidence of carotid disease with time from XRT. One pediatric study lends favor to the argument (from case series) that moyamoya represents an adaptive post-HXRT response to intracranial medium- and large-artery vasculopathy. Perhaps the most convincing radiologic evidence to implicate HNXRT in the pathogenesis of TIA and ischemic stroke in these patients is the spatial distribution of the vascular disease itself: it signposts the XRT field. There is disproportionate involvement of the anterior versus posterior circulation, a reflection of the XRT portals used in the treatment of optic glioma, adult primary cerebral tumors, and pituitary tumors, which encompass the internal and external carotids and the proximal anterior and middle cerebral arteries. This can lead to lengthy stenoses with, for instance, extension of diseased segments well beyond the common carotid bifurcation after HNXRT.
Pathogenesis
The literature is confusing on this question. This is because no definitive clinicopathologic study exists on medium- and large-vessel XRT-related disease. Most of the evidence comes from animal studies and small case series. There are 2 lines of thought. Some authors have argued that chronic occlusive radiation vasculopathy is primarily an accelerated form of atherosclerosis; others have described it as a distinct disease entity shaped by the initial radiation insult to the vasa vasorum. Either way, it is the most radiosensitive mesenchymal cell common to both the artery proper and the vasa vasorum, the endothelial cell, that bears the brunt of any XRT field effect. Fonkalsrud et al used scanning electron microscopy to analyze the evolution of radiation vasculopathy in canine femoral arteries after a net dose of 40 Gray. By 48 hours, there was extensive endothelial damage with nuclear disruption, platelet aggregation, and fibrin deposition; the intima and media remained intact, but the adventitia already showed minor fibrosis and hemorrhage. By 1 week, no normal endothelial cells were seen, and by 3 weeks, there was destruction of the internal elastic lamina and marked thickening of the endothelium. By 6 weeks, the media was hypocellular. By 4 months, there was focal necrosis and fibrosis of the media, accompanied by chronic inflammation and minimal thrombosis of the adventitia. The medial and adventitial fibrosis narrowed the vessel lumen. It is this perivascular scarring, often combined with advanced ath- eroma of the endothelium, that is most commonly described in surgical case series. Documentation of disease evolution in the manner of Fonkalsrud et al in humans is clearly impossible, but Zidar et al described an autopsy case of a 35-year-old-man who succumbed to metastatic tonsillar carcinoma 20 months after XRT. Extensive focal inflammation and necrosis of the vasa vasorum and adventitium were seen. Atherosclerosis was mild. The authors argued, as have others, that it is the initial injury to the vasa vasorum that defines post-XRT vasculopathy and that distin- guishes it from spontaneous atheromatous disease. What remains unclear is the extent to which the subsequent development of a “clinically significant” stenosis (or even moyamoya) is under- pinned by a chronic inflammatory process (with cytokine release and fibrosis) versus a chronic ischemic one (with microthrombosis of the vasa vasorum and ischemia of the vessel wall). Moreover, whereas no XRT dose to the vessel wall can be considered “safe,” in practice there is no consensus on what might constitute a “safer” dosing regimen. This is because XRT dose ranges are too narrow within patient series to impart a statistical effect and because XRT protocols, which are often unsatisfactorily detailed, are difficult to compare across studies. In addition, whereas traditional vascular risk factor modification seems sensible, no single factor has been consistently designated as an essential “cofactor” in the pathogenesis of this disease. Indeed, a hallmark of radiation vasculopathy is its occurrence in patients who lack traditional vascular risk factors.

Management
No trial to date has adequately assessed the medical treatment options in primary or secondary stroke prevention in this select patient group. The effect of antiplatelet, anticoagulant, antihypertensive, or lipid-lowering therapy in limiting disease progression is therefore unclear. Most studies are retrospective surgical case series on patients with extracranial carotid stenosis and favor either stenting or endarterectomy. Neither approach is clearly superior, as no prospective head-to-head trial exists. A 3-year prospective study has suggested that postangioplasty restenosis rates are significantly higher than proposed. Freedom from restenosis was only 20% (23 XRT patients) versus 79% (127 “high-risk” non-XRT patients). Shin et al also showed that carotid angioplasty and stenting carry a higher restenosis rate in patients with radiation vasculopathy (4 of 18 patients, 22%) versus patients deemed at high risk for carotid endarterectomy for other reasons (most had a previous ipsilateral carotid endarterectomy; 3 of 78 patients, 3.8%, P=0.028). The 2-year restenosis-free survival was also lower in the post- HNXRT group (72.7% versus 95.9%, P=0.017). When technically feasible, bypass procedures, such as external to internal carotid bypass, have been successfully used for complex multifocal disease, as with moyamoya or with combined intra- and extra-cranial stenoses after HXRT. The use of synthetic bypass grafting material has improved the outlook for some of these patients. Rico et al saw no reocclusion after a median follow-up of 9.5 years among 18 patients who underwent prosthetic carotid bypass grafting. HNXRT strategies that better minimize radiation exposure to the carotids have also shown recent promise. Notwithstanding these considerations, timely management will rely on suspicion of the diagnosis in the first place. In post-XRT ischemic stroke, the differential diagnosis will often include tumor recurrence and radionecrosis. The absence of a mass effect and contrast enhancement on magnetic resonance imaging with evidence of arterial occlusion, either directly by magnetic resonance angiography or indirectly by diffusion-weighted imaging, will favor radiation vasculopathy. Positron emission tomography may be required to help distinguish radionecrosis and ischemic disease (hypometabolic) from tumor recurrence (hypermetabolic).

Conclusions
The relative risk of TIA or ischemic stroke is at least doubled by HNXRT. Chronic radiation vasculopathy affecting medium and large intra- and extra-cranial arteries is characterized by increasing rates of hemodynamically significant stenosis with time from XRT. Disease expression is the likely consequence of the combined radiation insult to the intima-media (endothelium) and the vasa vasorum (adventitia). Optimal medical treatment is not established, endarterectomy is confounded by a need to operate across scarred tissue planes, and stenting has resulted in high restenosis rates. Long-term prospective studies remain a priority, as the problem is anticipated to rise with improvements in post- XRT patient survival.

Disclosures
None.

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Ischemic Stroke and Transient Ischemic Attack After Head and Neck Radiotherapy: A Review

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