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
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

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

<table>
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<tr>
<th>Year</th>
<th>First Author/Reference No.</th>
<th>XRT Dose, Gray</th>
<th>Cancer, Cases, No.</th>
<th>Treatment Categories</th>
<th>Controls</th>
<th>CVE Risk (Attributed to XRT)</th>
<th>XRT to CVE, Years</th>
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<td>2008</td>
<td>Smith20</td>
<td>HN Not given</td>
<td>Oral/Phnx/Slv 6862</td>
<td>1983 XRT, 2823</td>
<td>SU; A/S</td>
<td>TIA or stroke RR = 1.7–4.4</td>
<td>2.4 (0–10)</td>
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<td>2002</td>
<td>Haynes21</td>
<td>HN 64</td>
<td>Oral/Phnx/Lnx/Slv 413</td>
<td>All XRT</td>
<td>A/S</td>
<td>Stroke RR = 2.1</td>
<td>4.6 (0.2–12)</td>
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<td>2002</td>
<td>Dorresteijn2</td>
<td>HN 50–66</td>
<td>Lnx/Slv 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>
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<tr>
<td>1981</td>
<td>Elerding23</td>
<td>HN 40–50</td>
<td>Oral/Phnx/HD/NHL 910</td>
<td>All XRT (&gt;5-y Sv)</td>
<td>A/S/G</td>
<td>Stroke (P = 0.39)</td>
<td>9 (1.5–18)</td>
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<tr>
<td>2009</td>
<td>Debruin23</td>
<td>N 30-40</td>
<td>HD 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>
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<td>2006</td>
<td>Moser24</td>
<td>N 28–60</td>
<td>NHL 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>
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<td>2006</td>
<td>Woodward25</td>
<td>N Not given</td>
<td>Breast 5752</td>
<td>471 BXRT + NxRT, 5281 BXRT</td>
<td>BXRT</td>
<td>Stroke HR = 1.0 at 10 and 15 y</td>
<td>7.5 (5–15)</td>
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<td>2006</td>
<td>Hooning26</td>
<td>N 40–50</td>
<td>Breast 4368</td>
<td>2765 N XRT, 934</td>
<td>A/S/G</td>
<td>TIA HR = 1.4, stroke HR = 1.0</td>
<td>17.7 (10–20+)</td>
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<tr>
<td>2006</td>
<td>Jagsi27</td>
<td>N 62</td>
<td>Breast 820</td>
<td>222 BXRT + NxRT, 598 BXRT</td>
<td>A/S/G</td>
<td>TIA or stroke RR = 1.9</td>
<td>5.4 (0.1–16.9)</td>
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<td>2005</td>
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<td>HD 1926</td>
<td>1589 XRT, 328 ChRx</td>
<td>Siblings</td>
<td>Stroke RR = 5.6</td>
<td>17.5 (6–29)</td>
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<td>2009</td>
<td>Erridge29</td>
<td>H 45</td>
<td>Pituitary 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>
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<tr>
<td>2006</td>
<td>Keene30</td>
<td>H 35</td>
<td>Glioma/MB/other 244</td>
<td>All XRT</td>
<td>Nil</td>
<td>Stroke or TIA, 5%</td>
<td>3” (1–8)</td>
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<tr>
<td>2002</td>
<td>Bowers28</td>
<td>H 27–90</td>
<td>Glioma/MB/other 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>Erfurth21</td>
<td>H 41–46</td>
<td>Pituitary 342</td>
<td>All SU + XRT (31 deaths)</td>
<td>SV; A/S/G</td>
<td>Stroke death (P &gt; 0.05)</td>
<td>10 (6–40)</td>
</tr>
<tr>
<td>1999</td>
<td>Brada1</td>
<td>H 45</td>
<td>Pituitary 331</td>
<td>All XRT, 250 SU + XRT</td>
<td>A/S/G</td>
<td>Stroke RR = 4.1</td>
<td>FU 15” (0.5–33)</td>
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<tr>
<td>1998</td>
<td>Grill12</td>
<td>H 55</td>
<td>Optic glioma 69</td>
<td>All XRT</td>
<td>Nil</td>
<td>Stroke or TIA, 13%</td>
<td>3” (0.6–5.7)</td>
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<tr>
<td>1989</td>
<td>Flickinger33</td>
<td>H 35–62</td>
<td>Pituitary 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>
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</tbody>
</table>

Note: * 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; Slv, salivary gland; SU, surgery; A/S/G, age/sex/geography matched; RR, relative risk; FUI, follow-up interval; Lnx, 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; MB, medulloblastoma; H, head; N, neck; TIA, transient ischemic attack; XRT, radiotherapy.

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.

Results

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 1.2.20–33 and the Figure (for epidemiology; all studies were retrospective) and Table 2.34–51 (for imaging; only 2 studies were prospective).
## Discussion

### 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 (RR) 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 al²² identified 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. Debruijn 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.²⁴ 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.²⁵ 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 is 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.,²⁶ Hooning et al.,²⁸ and Jagai et al.²⁹ 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.

![Figure](https://stroke.ahajournals.org/)

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events were ischemic. Three recent studies\textsuperscript{25–27} 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.\textsuperscript{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 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).

### 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 al\textsuperscript{29} 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 al\textsuperscript{31} 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.

### 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>
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<td>2009</td>
<td>Chang\textsuperscript{44}</td>
<td>HN</td>
<td>70’</td>
<td>Not specified</td>
<td>192</td>
<td>98 (CA, no XRT)</td>
<td>Plaque, &gt;50%/70% stenosis</td>
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<td>2005</td>
<td>Dorrestein\textsuperscript{35}</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>
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<td>2005</td>
<td>Brown\textsuperscript{36}</td>
<td>HN</td>
<td>60’</td>
<td>Parotid, SCC</td>
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<td>44 (non-XRT side)</td>
<td>IMT</td>
<td>7.5’ (4–23)</td>
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<td>Cheng\textsuperscript{37} (pros)</td>
<td>HN</td>
<td>60 H, 60 N</td>
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<td>75 (no CA, axsic &lt;50% stenosis)</td>
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<td>7.6’, FUI 3’ (0.5–5.7)</td>
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<td>80</td>
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<td>&gt;50% stenosis</td>
<td>(4–26)</td>
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<td>2000</td>
<td>Muzaffar\textsuperscript{41} (pros)</td>
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<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>Cheng\textsuperscript{42}</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>Cheng\textsuperscript{43}</td>
<td>HN</td>
<td>&lt;66:55</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>Carmody\textsuperscript{44}</td>
<td>HN</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>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>Dubec\textsuperscript{45}</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>McGuirt\textsuperscript{46}</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>Moritz\textsuperscript{47}</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>Meekse\textsuperscript{48}</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>Woodward\textsuperscript{49}</td>
<td>HN</td>
<td>50’</td>
<td>Breast</td>
<td>46 (ipsilateral to XRT)</td>
<td>46 (contralateral to XRT side)</td>
<td>IMT, plaque, PSV</td>
<td>14.6’</td>
</tr>
<tr>
<td>1999</td>
<td>King\textsuperscript{50}</td>
<td>N</td>
<td>22.5–40</td>
<td>HD</td>
<td>42</td>
<td>No CA; A/S</td>
<td>IMT, &gt;70% stenosis</td>
<td>13’ (5.1–22.8)</td>
</tr>
<tr>
<td>1997</td>
<td>Omura\textsuperscript{51}</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>Bitzer\textsuperscript{52} (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 ‘t’ refers to medians and ‘x’ refers to means for both dose (Gray) and time (years). Numbers in parentheses in the final column refer to the time range in years.

\(I_x\) indicates investigation; CA, cancer; PleoAd, pleomorphic adenoma; IMT, intima-media thickness; SCC, squamous cell carcinoma; pros, prospective study; NasoPhnx, nasopharynx; Lrx, larynx; axsic, asymptomatic; FUI, follow-up interval; Lymph, lymphoma; A/S, age/sex matched; PSV, peak systolic velocity; y, years; Phnx, pharynx; Slv, salivary gland; SD, standard deviation; Thy, thyroid; HD, Hodgkin disease; RMS, rhabdomyosarcoma; ipsilateral, ipsilateral; contralateral, contralateral; MRA, magnetic resonance angiography; rev, review study; H, head; N, neck; TIA, transient ischemic attack; XRT, radiotherapy.
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 Flinkinger et al.33 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
known ischemic). They did not see an increase in the
study of 156 pituitary adenoma cases after HXRT (6 of 7
patients who had received XRT for various head and neck
malignancies (TIA was not as-
clusive vasculopathy was seen in 13 children. The anterior
cerebral circulation was involved in all patients, 11 of whom
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,
HXRT 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.49
The evidence for increased CVE risk after HXRT is more
substantial when exposure occurs in childhood versus adult-
hood (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.38 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 subse-
quent similarly designed study of 96 nasopharyngeal carci-
noma patients by the same group replicated these findings,
with >70% stenosis measured in 16% of patients.42 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)34 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
(preference vessel occlusion plus plaque distribution) and
dergree 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 consis-
tent 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.40 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.38 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 sten-
sis distribution was given, and although 3 patients experi-
enced a stroke after XRT, there was no mention of stroke
territory. Carmody et al.41 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 symp-
tomatic). 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.45 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). Dorrestijn et al.46 calculated the intima-media thick-
ness (IMT) to be 0.3 mm greater on average at the irradiated
Woodward et al., 49 in a study mislabeled “prospective” (the Neck XRT/H11005 (RR 3.1). The figure on the actual rather than the 50% were seen in those who had undergone XRT (0.035); the greatest shifts P common in the XRT group (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., 37 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., 37 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, repeatedly show an increased prevalence of hemodynamically significant carotid stenosis when there is a history of HNXRT. 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., 31 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.15,59,64,65 Either way, it is described it as a distinct disease entity shaped by the initial radiation insult to the vasa vasorum.15,59,64,65 Either way, it is the most radiosensitive mesenchymal cell common to both the artery proper and the vasa vasorum, the endothelial cell,9 that bears the brunt of any XRT field effect. Fonkalsrud et al55 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.7,56,57,62 Documentation of disease evolution in the manner of Fonkalsrud et al55 in humans is clearly impossible, but Zidar et al59 described an autopsy case of a 35-year-old-man who succumbed to metastatic tonsillar carcinoma 20 months after XRT. Extensive focal inflammam- tion and necrosis of the vasa vasorum and adventitium were seen. Atherosclerosis was mild. The authors argued, as have others,55,64 that it is the initial injury to the vasa vasorum that defines post-XRT vasculopathy and that distinguishes 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.7,66

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 stenting67–71 or endarterectomy.14,72–75 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 al77 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.16,78 The use of synthetic bypass grafting material has improved the outlook for some of these patients. Rico et al79 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.80 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 imaging81 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).82

Conclusions

The relative risk of TIA or ischemic stroke is at least doubled by HNXRT. Chronic radiation vasculopathy affecting me- dium and large intra- and extra-cranial arteries is character- ized 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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