Acoustic neuromas following childhood radiation treatment for benign conditions of the head and neck

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Childhood radiation exposure has been associated with an increased risk for developing several neoplasms, particularly benign and malignant thyroid tumors, but little is known about the risk of developing acoustic neuromas. The aim of this study was to confirm whether there is a risk for acoustic neuromas and, if so, to determine its magnitude and duration. We investigated the time trend and dose-response relationships for acoustic neuroma incidence in a cohort of 3,112 individuals who were irradiated as children between 1939 and 1962. Most of the patients were treated to reduce the size of their tonsils and adenoids and received substantial radiation exposure to the cerebellopontine angle, the site of acoustic neuromas. Forty-three patients developed benign acoustic neuromas, forty of them surgically resected, far in excess of what might be expected from data derived from brain tumor registries. The mean dose (±SD) to the cerebellopontine angle was 4.6 ± 1.9 Gy. The relative risk per Gy was 1.14 (95% confidence interval 1.0–1.3). The earliest case occurred 20.4 years after exposure and the latest 55 years after exposure (mean 38.3 ± 10.1 years). Our study provides support for an association between acoustic neuromas and childhood radiation exposure. Although acoustic neuromas are usually benign and often asymptomatic, many cause significant morbidity. Following childhood radiation exposure, they appear after a long latency and continue to occur many decades afterward. Any symptoms of an acoustic neuroma in a patient with a history of radiation to the head and neck area should be investigated carefully, and the threshold for employing imaging should be lowered. Neuro-Oncology 10, 73–78, 2008 (Posted to Neuro-Oncology [serial online], Doc. D06-00157, December 13, 2007. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2007-047)

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Introduction

For the last 30 years, we have been studying a cohort of irradiated patients to determine health risks related to their exposure. We have reported on the increased incidences and dose-response relationships for benign and malignant thyroid tumors, benign and malignant salivary gland tumors, and benign parathyroid tumors. We also have described an increased frequency of acoustic neuromas and schwannomas in other parts of the body in this cohort. An association between radiation exposure and schwannomas, including acoustic neuromas, has been suggested by reports of cases in radiation-exposed cohorts and sporadic case reports. Only recently, however, have the dose-response relationship between radiation and schwannomas and the effects

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of other risk factors been investigated.17 Studies of schwannomas have been limited because the tumors are rare, and usually only symptomatic ones are clinically diagnosed. This is the first report to evaluate radiation-related acoustic neuromas specifically. We describe the dose-response relationship for acoustic neuromas and observe that cases continue to occur as late as the fifth decade after exposure.

Subjects and Methods

The cohort consisted of 4,296 patients who received conventional radiation therapy for benign conditions in the head and neck area before their 16th birthday, between 1939 and 1962. We began following this cohort in 1974 and have described it, including the details of the radiation treatments, previously.18,19 Briefly, the large majority of patients were irradiated for "enlarged" tonsils and adenoids through symmetric fields centered on the posterior pharynx. Typically, treatments were delivered in three weekly sessions with a total dose of 7.5 GY or 9 GY. In the current study 3,112 (72.4%) subjects with adequate follow-up information, defined previously as reliable information about whether or not the subject had thyroid surgery, and estimated radiation dose to the cerebellopontine angle are included. Follow-up efforts occurred uniformly without regard to dose. Subjects were informed about the potential risk of Schwann cell tumors and specifically acoustic neuromas starting about 1986, but no early detection screening has been conducted. The diagnosis of acoustic neuroma was confirmed by a review of the operative reports, pathology reports, and, when available, original pathology slides.

Radiation doses to the cerebellopontine angle, the site of acoustic neuromas, were estimated. Approximately 12% of the study population received more than one course of treatment. Typically these subjects received retreatment to the posterior pharynx or treatment to a second area in the head and neck region. In 87 subjects (3.0%) where the doses administered to the left and right sides differed, the mean dose to the right and left sides was used for analysis.

Data were analyzed using Cox proportional hazards regression methods, as implemented by the Epicure 2.11 computer software program (Hirosoft International, Seattle, WA, USA), with age at treatment as the entry time and age at event or age at end of follow-up as the event or censoring time.18 The score test was used to test for a linear trend of risk over continuous doses.18 Dose categories for relative risks (RR) were defined as <4.45, 4.45–<4.75, 4.75–<5.35, and >5.35 Gy. These were selected according to quartiles for the cases, modified to account for cases with equal doses. Since there was no unexposed reference group available for analysis, the lowest quartile was used as the reference category. We chose to use quartiles based on the number of cases rather than the number of subjects to create a stable reference group with enough cases while emphasizing lower doses. Confidence intervals for the estimated βs by Cox analysis were computed using likelihood-based methods.19 We evaluated variations in the dose-response relationship within categories of age at first radiation exposure and sex. The Kaplan-Meier method was used to plot tumor-free survival. For this purpose, time to event was defined as the date of the first radiation treatment until surgery for an acoustic neuroma or the date of last contact. Nonparametric group comparisons were performed with the Mann-Whitney test.

Clinical Findings

During follow-up, 43 of the 3,112 members of the study cohort developed acoustic neuromas. Forty cases were histologically confirmed and three cases were diagnosed on the basis of radiographic evidence, without surgical confirmation. The initial acoustic neuroma was on the right side in 25 cases, the left side in 15 cases, bilateral in 1 case, and unknown in 2. No patients were treated with radiation as their primary therapy, but three recurrences were treated with gamma knife therapy. These occurred 3, 4, and 18 years after the initial surgery.

One case of bilateral acoustic neuromas was detected radiographically in a patient who had other Schwann cell tumors diagnosed earlier. It is not known whether these tumors occurred as a result of neurofibromatosis type 2 or radiation exposure. In one case, a second acoustic neuroma was diagnosed 10 years after the first, but information as to whether it was ipsilateral or contralateral was not obtained.

The demographic and treatment characteristics of the cohort and the 43 individuals who developed acoustic neuromas are shown in Table 1. No differences were observed when patients who developed acoustic neuromas were compared with the rest of the cohort, with respect to the proportion of males (62.8% vs. 60.1%) and the other demographic characteristics shown in the table.

The distribution of radiation doses to the cerebellar pontine angle is shown in Fig. 1. The dose range was narrow, with an interquartile range of 4.4–4.9 Gy. The mean dose to the cerebellopontine angle was 4.62 Gy for the 3,069 cohort members who did not develop acoustic neuromas and 5.27 for the 43 members who did. The difference between the means of the doses was significant by the t-test, and the distribution of the doses was statistically different as determined by the Mann-Whitney test (both p < 0.05). The Kaplan-Meier plot of the acoustic neuromas in Fig. 2 shows that after 20 years cases have accrued throughout the follow-up period. The first acoustic neuroma occurred 20.4 years after exposure, and the tumor with the longest latency, the time interval between exposure and the occurrence of an acoustic neuroma, occurred after 55 years.

Dose-Response Relationships

Based on Cox regression, there was a statistically significant trend with dose (Table 2). The relative risk per
relationship for acoustic neuromas and strongly support a causal role for radiation. They also show that acoustic neuromas continue to occur into the fourth and fifth decades after exposure (Fig. 2). Recently, the secular trend for acoustic neuroma incidence in the United States has been investigated. The findings were derived from data obtained from 11 collaborating brain tumor registries and, independently, from the Los Angeles County Cancer Surveillance Program. The authors of this investigation concluded that the incidence has been increasing, and they suspect that it is due to the introduction of more precise diagnostic methods. Our findings presented here tentatively raise the possibility that radiation exposure may have contributed to this trend.

Table 1. Demographic characteristics of the individuals included in this study and those who developed acoustic neuromas

<table>
<thead>
<tr>
<th></th>
<th>Cohort</th>
<th>Acoustic Neuroma</th>
<th>No Acoustic Neuroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>3,112</td>
<td>43</td>
<td>3,069</td>
</tr>
<tr>
<td>Female (%)</td>
<td>1,240 (39.8)</td>
<td>16 (37.2)</td>
<td>1,224 (39.9)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>1,872 (60.2)</td>
<td>27 (62.8)</td>
<td>1,845 (60.1)</td>
</tr>
<tr>
<td>Birth date (median)</td>
<td>12/17/1942</td>
<td>2/3/1942</td>
<td>12/17/1942</td>
</tr>
<tr>
<td>Date at first treatment (median)</td>
<td>11/9/1946</td>
<td>2/17/1947</td>
<td>11/9/1946</td>
</tr>
<tr>
<td>Age at first treatment (median, years)</td>
<td>3.59</td>
<td>3.24</td>
<td>3.60</td>
</tr>
<tr>
<td>Range</td>
<td>0.00–15.83</td>
<td>0.66–15.81</td>
<td>0.00–15.83</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2.10–5.81</td>
<td>1.79–6.03</td>
<td>2.10–5.81</td>
</tr>
<tr>
<td>Dose (median, Gy)</td>
<td>4.60</td>
<td>4.70</td>
<td>4.60</td>
</tr>
<tr>
<td>Range</td>
<td>0.01–18.20</td>
<td>2.00–10.60</td>
<td>0.01–18.20</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>4.40–4.90</td>
<td>4.50–5.30</td>
<td>4.40–4.90</td>
</tr>
</tbody>
</table>

Gy (RR/Gy) was 1.14, with a 95% confidence interval of 1.0–1.3, and the risk was not significantly modified by gender.

There was a nonsignificant decrease in the magnitude of the dose-response relationship with increasing age at exposure. This relationship was seen using alternative statistical models (linear, power, linear-exponential) for the dose-response relationship (data not shown). There was no correlation between exposure dose and latency.

Discussion

The main findings of this study concern the association of childhood radiation exposure and acoustic neuromas. Our results are consistent with a linear dose-response relationship for acoustic neuromas and strongly support a causal role for radiation. They also show that acoustic neuromas continue to occur into the fourth and fifth decades after exposure (Fig. 2).

Recently, the secular trend for acoustic neuroma incidence in the United States has been investigated. The findings were derived from data obtained from 11 collaborating brain tumor registries and, independently, from the Los Angeles County Cancer Surveillance Program. The authors of this investigation concluded that the incidence has been increasing, and they suspect that it is due to the introduction of more precise diagnostic methods. Our findings presented here tentatively raise the possibility that radiation exposure may have contributed to this trend.

Fig. 1. Distribution of estimated doses (Gy) to the cerebellopontine angle for the 3,112 individuals included in this study.
The data from the 11 collaborating brain tumor registries and the Los Angeles County Cancer Surveillance Program give similar estimates for the incidence of acoustic neuromas during 1995–1998, that is, 0.6 and 0.8 cases per 100,000 person-years, respectively. These estimates give a projection of <1 expected case in the cohort studied here, even uncorrected for the lower rates in prior years.

Although the dose-response relationship confirms the association of radiation with acoustic neuromas, the risk estimate appears smaller than would be anticipated considering that 43 cases were observed in the cohort versus <1 case predicted from population-based rates. However, the lack of nonexposed subjects in this study, imprecision in the dose estimates, relatively narrow dose range, and uncertainty in which model best represents the data make it inappropriate to extrapolate to zero dose. Also contributing to this apparent difference may be the characteristics of the cohort and tumor ascertainment. The cohort is quite uniform in race and ethnicity, although these are not known to be factors in acoustic neuroma incidence. Also, even though most surgically resected acoustic neuromas are symptomatic, there may be differences in how frequently they are diagnosed based on access and use of medical services. The cohort has a relatively high educational and economic level, and cohort members are aware of their radiation exposure and the associated elevated risks of thyroid and other head and neck tumors, which may result in earlier or more accurate diagnoses. Age at radiation treatment is a strong modifier of the dose-response relationship for thyroid tumors in this cohort. A decreasing risk with increasing age at exposure also was seen for acoustic neuromas, but the association was not statistically significant.

To date, the most detailed dose-response analysis for schwannomas is the study of atomic bomb survivors in Hiroshima and Nagasaki. In slightly more than 80,000 individuals, including 32,600 with little or no exposure, 55 cases of schwannomas (including 22 spinal schwannomas) were observed and a significant dose-response

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**Table 2.** Acoustic neuromas, subjects, person-years, disease rates, relative risks (RR), and 95% confidence intervals (CI) by categories of estimated dose

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>&lt;4.45</th>
<th>4.45–&lt;4.75</th>
<th>4.75–&lt;5.35</th>
<th>&gt;5.35</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>7</td>
<td>15</td>
<td>11</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>Rate (×10,000)</td>
<td>1.8</td>
<td>3.5</td>
<td>4.1</td>
<td>3.9</td>
<td>3.2</td>
</tr>
<tr>
<td>RRb</td>
<td>1</td>
<td>2.2</td>
<td>2.8</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.9–5.4)</td>
<td>(1.1–7.3)</td>
<td>(0.7–5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>938</td>
<td>1,007</td>
<td>620</td>
<td>547</td>
<td>3,112</td>
</tr>
<tr>
<td>Person-years</td>
<td>39,365</td>
<td>43,025</td>
<td>26,585</td>
<td>25,759</td>
<td>134,734</td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td>3.0</td>
<td>4.6</td>
<td>4.9</td>
<td>7.1</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*RRs compared to <4.45 Gy dose group based on Cox regression, using age at treatment as entry time and age at event or at end of follow-up as survival time.

b*p-value for test of trend was 0.045.
relationship was demonstrated. The relative risk at 1 Sv (sievert) was 4.5. In nearly 11,000 persons irradiated as children for tinea capitis in Israel from 1948 to 1960, three acoustic neuromas were described in a 1988 report compared to none in the nonexposed comparison population of more than 16,000 people. In a Rochester, NY, study reported in 1976, a cohort of children whose thymus glands had been treated with radiation during the same era as the cohort in the current report included one acoustic neuroma. Results from these studies, however, are not directly comparable to those presented here. The atomic bomb survivor and Israel tinea capitis studies reported results for all schwannomas, whereas we have restricted our analysis to acoustic neuromas, and the doses in the present study are several-fold higher than those in the other studies.

Acoustic neuromas have not been reported as second tumors in survivors of childhood cancers whose treatment included radiation therapy to the head and neck region. There are several possible reasons for this. Some studies of second neoplasms depend on linkage to cancer registries to ascertain subsequent tumors, and although some cancer registries do obtain information on benign meningiomas, very few register acoustic neuromas. Other studies obtain information on previous tumors from self-reports on surveys. How accurately these ascertain acoustic neuromas is uncertain and probably depends on the precise wording of the questions and the level of medical knowledge of the study population. Our findings (Fig. 2) and those from the Israel tinea study9 and atomic bomb survivors11 emphasize the long latency of acoustic neuromas, much longer than for meningiomas. Acoustic neuromas develop asymptptomatically. When symptoms do occur, there often is a considerable lag before medical attention is sought and the diagnosis made. Thus, studies of second tumors, including the landmark Childhood Cancer Survivor Study, probably do not yet have sufficient follow-up to assess the occurrence of acoustic neuromas. As a result of these considerations, it should be mentioned that acoustic neuromas may emerge as a late problem in childhood cancer survivors.

Efforts have been made to identify other risk factors, besides radiation exposure, for developing acoustic neuromas. While two studies suggest that exposure to loud noise is a risk factor and one study suggests a history of nonmedullary thyroid cancer as a risk factor, no other risk factors have been identified with certainty. Much effort has gone into determining whether magnetic waves, from cell phones or occupational exposure, increase the risk for acoustic neuroma. In a recent review, Propp et al. did not find adequate evidence to support these associations.

In the clinical setting, an effort should be made to estimate an individual’s risk. Since the present study shows a linear dose-response relation, patients with higher doses are at greater risk. However, it is rarely possible to know the precise dose to the cerebellopontine angle. Another indicator of an increased risk is the prior occurrence of a radiation-related neoplasm. Previously, we observed that of 70 individuals in this cohort with neural tumors, 7 had multiple tumors. We also observed a larger than expected number of individuals with multiple radiation-related neoplasms. Although we initially postulated that this was due to increased susceptibility, it now appears that known factors, including larger radiation doses, account for these findings. Nevertheless, the presence of one tumor (thyroid, parathyroid, salivary, or neural) should be taken as an indicator of an increased risk for another.

The findings in this article raise the question whether asymptomatic irradiated patients should be screened for acoustic neuromas. Screening for hearing loss has been recommended for older individuals in the general population, and in irradiated patients the possibility of an acoustic neuroma should be considered. One approach that has been suggested is that all patients who notice hearing loss should be tested further, and that all elderly patients should be screened with a whispered-voice test. In irradiated patients, hearing loss, particularly if it is asymmetric, and symptoms of vestibular disease should raise the suspicion of an acoustic neuroma. Hearing loss, tinnitus, sensory deficits, and gait disturbances were the symptoms, in decreasing order of frequency, observed among the atomic bomb survivors who developed acoustic neuromas.

Because acoustic neuromas are continuing to occur 50 years after exposure, people who have been exposed to head or neck radiation as children should be both informed and questioned about potential symptoms so they can notify their physicians promptly if they develop any of them.

Acknowledgments

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References


