Meningiomas induced by high-dose cranial irradiation

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Although meningiomas are known to be induced by low doses of cranial irradiation, such as those given to treat tinea capitis, little experience has been reported on the induction of meningiomas by high-dose cranial irradiation. The authors describe a series of 10 patients with meningiomas and a previous history of high-dose radiation therapy, usually given for a primary brain tumor. Of the 10 patients, eight were female, three had multiple meningiomas, and the majority had other stigmata of previous radiation therapy. Eight meningiomas were examined pathologically and one-half were classified as either aggressive or atypical, or were noted to have a high bromodeoxyuridine labeling index. The average time from radiation therapy to diagnosis of a meningioma was 24 years (range 5 to 40 years), a shorter interval than that previously reported for meningiomas induced by lower doses of irradiation. Within this series, patient age at irradiation was significantly correlated with tumor latency; individuals who were younger at the time of radiation therapy had a shorter time to meningioma formation. The latency of meningioma formation is therefore influenced by both the radiation dose and the age of the patient at irradiation.

KEY WORDS: meningioma · radiation-induced tumor · radiation therapy · epidemiological study · carcinogenesis

In 1953, Mann, et al., reported the first case of a suspected radiation-induced meningioma in a 4-year-old girl who had received 6500 cGy of irradiation to the orbit for the treatment of an optic nerve glioma. Four years later, she developed a meningioma in the irradiated field; the tumor became recurrent and eventually malignant. A causal relationship between radiation therapy and meningioma formation was first demonstrated in 1974 by Modan, et al., in a review of the medical records of nearly 11,000 Israelis who had received low doses of scalp irradiation for tinea capitis as children. This epidemiological study showed a fourfold increase in the incidence of meningiomas in this population. More recent epidemiological studies by Preston-Martin, et al., substantiated the relationship between low-dose irradiation and increased risk for development of meningiomas. Their analysis of all meningiomas diagnosed in Los Angeles County during the 1970's showed that exposure to diagnostic head, neck, and dental x-ray studies increased the risk of tumor development. The risk was greatly increased in patients whose first full-mouth dental x-ray films had been obtained before 20 years of age; in these patients, the relative risk was 4.0 for women and 7.0 for men.

The literature on radiation-induced meningiomas has traditionally divided them into tumors caused by low, moderate, or high doses of radiation exposure. Those caused by low doses of radiation, arbitrarily defined as less than 10 Gy, represent the majority of experience with radiation-induced meningiomas. Such low doses of radiation were used primarily for the treatment of tinea capitis between 1909 and 1959, according to a technique first described by Adamson (the KA technique). This treatment delivered approximately 850 cGy to the scalp, 150 cGy to the surface of the brain, and 70 cGy to the base of the brain. Moderate doses of radiation, defined as 10 to 20 Gy, are delivered primarily to the scalp for the treatment of vascular nevi or are obtained incidentally through exposure during thorium dioxide myelography, ventriculography, and head and neck irradiation of local tumors. High-dose irradiation, defined as greater than 20 Gy, is used mostly for the treatment of primary and metastatic brain tumors. Since the survival rate of patients with malignant brain tumors is low, there are only scattered reports of these patients eventually developing radiation-induced meningiomas. Therefore, we retrospectively reviewed the medical records of patients treated for a meningioma, and further evaluated those among them with a prior history of high-dose radiation therapy.

Clinical Material and Methods

The medical records of all patients with meningiomas managed by one of the authors (C.B.W.) were
Radiation-induced meningiomas

TABLE 1

<table>
<thead>
<tr>
<th>Age at Irradiation (yrs)</th>
<th>Tumor Latency (yrs)</th>
<th>Dose† (cGy)</th>
<th>Reason for Irradiation</th>
<th>Pathology</th>
<th>Other Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>13, F</td>
<td>19</td>
<td>5250</td>
<td>optic glioma</td>
<td>benign</td>
<td>vascular malformation</td>
</tr>
<tr>
<td>13, F</td>
<td>27</td>
<td>4000</td>
<td>astrocytoma</td>
<td>benign</td>
<td>multiple BCC</td>
</tr>
<tr>
<td>13, F</td>
<td>40</td>
<td>4000</td>
<td>epidermoidoma</td>
<td>benign</td>
<td>second meningioma, vascular malformation</td>
</tr>
<tr>
<td>10, F</td>
<td>30</td>
<td>4000</td>
<td>chronic otitis</td>
<td>benign</td>
<td>acoustic neuroma</td>
</tr>
<tr>
<td>16, F</td>
<td>34</td>
<td>4000</td>
<td>acoustic neuroma</td>
<td>aggressive</td>
<td>thyroid nodule, vascular malformation</td>
</tr>
<tr>
<td>10, M</td>
<td>25</td>
<td>3940</td>
<td>medulloblastoma</td>
<td>aggressive</td>
<td>second meningioma, schwannoma</td>
</tr>
<tr>
<td>14, M</td>
<td>19</td>
<td>3940</td>
<td>medulloblastoma</td>
<td>benign, BUdR labeling index 3%</td>
<td>none</td>
</tr>
<tr>
<td>2, F</td>
<td>5</td>
<td>4825</td>
<td>medulloblastoma</td>
<td>atypical</td>
<td>—</td>
</tr>
<tr>
<td>13, F</td>
<td>5</td>
<td>4680</td>
<td>medulloblastoma</td>
<td>—</td>
<td>multiple BCC</td>
</tr>
<tr>
<td>5, F</td>
<td>10</td>
<td>4000</td>
<td>medulloblastoma</td>
<td>benign</td>
<td>second meningioma, BCC</td>
</tr>
</tbody>
</table>

* UCSF = University of California, San Francisco; BCC = basal cell carcinomas; BUdR = bromodeoxyuridine; — = data not available.
† For a radiation dose listed as “high,” the exact dose was not recorded but the dose was assumed to be high on the basis of the reason for irradiation.

reviewed for a history of radiation therapy. Of 500 patients with meningiomas, eight were found to have had previous radiation therapy at high doses. An additional two patients were obtained from other practicing neurosurgeons within the department. Medical records were reviewed for information regarding the underlying diagnosis, including the reason for irradiation, the age at irradiation, and the dose of radiation therapy. The latter was not always available since decades had often elapsed between radiation therapy and meningioma detection. Medical records were also examined for evidence of other possible radiation-induced diagnoses. Tumors were confirmed pathologically in eight of the 10 patients; in the remaining two patients, the diagnosis of meningioma was made on a clinical and radiographic basis.

To determine whether age at irradiation was significantly correlated with tumor latency, the product-moment correlation coefficient was calculated.

Results

We were able to identify 10 patients with meningiomas who had previously undergone irradiation to the head at doses higher than 2000 cGy (Table 1). Since eight of these patients were obtained from a review of 500 patients with meningiomas, the overall incidence of meningiomas induced by high-dose irradiation in our series is 1.6%. However, our department treats a disproportionately high number of patients with primary brain tumors, so these results may be biased. Based on the method of data collection, the incidence of meningiomas in patients with past exposure to high doses of radiation therapy cannot be determined.

The patients were aged 1.5 to 16 years at the time of irradiation. Radiation therapy was given for a variety of reasons, but the most common underlying diagnosis was medulloblastoma. Eight of the 10 patients were female. Since men and women undergo radiation therapy for brain tumors in equal numbers, women are overrepresented in our series. Eight of the 10 patients had information available in their medical records indicating that other stigmata of irradiation were present, including cryptic vascular malformations of the brain, skin and thyroid tumors, and nerve-sheath tumors. Three patients were noted to have multiple meningiomas.

Meningioma was diagnosed at 24 ± 10 years (mean ± standard deviation) after radiation therapy. Age at irradiation was significantly correlated with tumor latency (r = 0.648, p = 0.043). Two patients received radiation therapy very early in life; in contrast, current practice is that other therapy be tried first and radiation be used only if the first approach is unsuccessful. These two patients had the shortest intervals from irradiation to diagnosis of a meningioma (5 and 15 years).

Eight of the patients were treated by surgical resection and their tumor pathology was reviewed at the University of California, San Francisco. Although no meningioma was found to be malignant, two were classified as aggressive, one as atypical, and one had an unusually high bromodeoxyuridine labeling index (3%), a feature that has been shown to correlate with early tumor regrowth in meningiomas.¹⁴

Discussion

The vast majority of experience with radiation-induced meningiomas is with those occurring after low doses given for the treatment of tinea capitis. Since this treatment was used extensively earlier in this century and since tinea capitis has no impact on length of survival, large populations are available for studying the effects of low doses of brain irradiation on the development of meningiomas. Ron, et al.,¹⁵ performed a comprehensive long-term follow-up study of Israeli children who underwent treatment for tinea capitis by the KA technique between 1948 and 1960. A total of 19 meningiomas (17 benign and two malignant) were found in this cohort of 10,834 individuals. The relative risk for meningioma induction was 9.5 times greater in irradiated individuals than in control subjects. A causal relationship between radiation exposure and tumor induction was further substantiated by a strong dose and dose-averaged dose.
response; the relative risk increased to 20 with doses of radiation greater than 2.0 Gy.

In other series of patients treated for meningioma at medical institutions in Israel,14,15 it was found that compared to spontaneously occurring meningiomas, meningiomas induced by exposure to low doses of radiation tended to occur in younger individuals and were more often calvarial in location, malignant in histology, recurrent in course, and multiple in presentation. Many of these features were also seen in our series. Reports by Rubinstein, et al.,13 and Soffer, et al.,15 also concluded that radiation-induced meningiomas were unexpectedly more common in men than in women. However, epidemiological studies of similar patients undergoing scalp irradiation for tinea capitis in the United States have demonstrated a marked preponderance of male patients undergoing this treatment, and Harrison, et al.3 have shown that after correcting for this bias, women are still at greater risk than men for developing meningiomas, even if the tumors are induced by radiation. This finding is supported by our series, in which eight of the 10 tumors occurred in women.

The observation that radiation-induced meningiomas are more likely to be calvarial in location is misleading. When restricting a review to patients who underwent treatment with the KA technique, this finding would be expected because the calvaria is the primary site of exposure. In a more recent epidemiological study of patients with meningiomas in Los Angeles County,60 full-mouth dental x-ray studies were found to be a risk factor for meningiomas, particularly of the skull base and corresponding to the site of exposure. Therefore, there appears to be no propensity for a specific location of radiation-induced meningiomas; rather, the location depends on the site of exposure.

Radiation-induced meningiomas have a strong tendency toward aggressive biological behavior. This feature, more than any other, distinguishes them from spontaneously occurring meningiomas. A higher percentage of radiation-induced meningiomas are frankly malignant.15 Furthermore, even those tumors classified as benign more frequently have increased cellularity, nuclear pleomorphism, giant cells, and mitoses, indicating a potential for rapid growth and biological aggressiveness. These features are consistent with the higher recurrence rate seen in radiation-induced meningiomas after gross total resection. In an evaluation of consecutive meningioma patients, Rubinstein, et al.,13 noted a recurrence rate of 26% among patients with radiation-induced meningiomas compared to 11% in those with spontaneous meningiomas. Soffer, et al.,15 found a recurrence rate of 19% in patients with radiation-induced meningiomas compared to 3% in those with spontaneous meningiomas. In the series reported by Soffer, et al., the mean interval between tumor resection and recurrence was 6.2 years, compared to 10.5 years in the series of Rubinstein, et al. Therefore, radiation-induced meningiomas were more likely to recur and tended to recur earlier than idiopathic tumors. Because a greater number of meningiomas induced by low-dose irradiation are calvarial and therefore more accessible to gross total removal, comparison of the above rates probably underestimates the potential for these tumors to recur.

Our series of patients had a mean interval of 24 years from irradiation to tumor diagnosis. When considered together with the induction times reported for other meningiomas caused by high-dose irradiation,16 the overall average time to tumor induction is 21 years. In comparison, the average time to tumor occurrence is 27 years after moderate doses of irradiation5,6 and 35 years after low doses.3 This indicates an inverse relationship between the dose of radiation exposure and the time to tumor formation.

Conclusions

There are considerable data to support a causal relationship between radiation exposure and the subsequent development of meningiomas. Not only have large epidemiological studies shown an increased incidence of meningiomas in patients undergoing low-dose exposure to radiation, they have also demonstrated a dose-response relationship and an association between the site of exposure and that of tumor development. By comparing patients exposed to high doses of irradiation to those exposed to low doses, it becomes evident that there is an inverse relationship between dose and time to tumor formation. Furthermore, our series has demonstrated that age at irradiation is correlated with tumor latency; individuals who were younger at the time of irradiation had shorter intervals to tumor formation. Like meningiomas induced by lower doses of radiation exposure, those caused by higher doses are more likely to occur in women and to be multiple at presentation and aggressive in nature.

Acknowledgments

The authors thank Cheryl Chrisensen for manuscript preparation and Jeffrey Miller and Pamela Derish for editing the manuscript.

References


J. Neurosurg. / Volume 79 / July, 1993

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Manuscript received April 21, 1992.
Accepted in final form December 31, 1992.
This work was supported by Training Grant CA 09291 from the National Institutes of Health.
Portions of this paper were presented at the Annual Meeting of the American Association of Neurological Surgeons in San Francisco, California, April 11–16, 1992.
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