Radiation-induced intracranial malignant gliomas

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The authors present seven cases of malignant gliomas that occurred after radiation therapy administered for diseases different from the subsequent glial tumor. Included among these seven are three patients who were treated with interstitial brachytherapy. Previously reported cases of radiation-induced glioma are reviewed and analyzed for common characteristics. Children receiving central nervous system irradiation appear particularly susceptible to induction of malignant gliomas by radiation. Interstitial brachytherapy may be used successfully instead of external beam radiotherapy in previously irradiated, tumor-free brain, and thus may reduce the risk of radiation necrosis.

KEY WORDS • glioblastoma • malignant glioma • radiation-induced neoplasm • interstitial brachytherapy • brain tumor

Radiation induction of neoplasia has been documented in experimental animal models and in patients. In monkeys (Macaca mulatta), radiation has been shown to induce malignant glial neoplasms that are histologically very similar to the human glioblastoma multiforme. Since 1970, the number of case reports documenting radiation-induced malignant gliomas in humans has risen sharply (Table 1). The two most common scenarios are: 1) the tumors occurred in patients who had received radiation therapy for pituitary and parasellar lesions and subsequently developed malignant gliomas in the irradiated field of brain; and 2) they occurred in children with acute leukemias who received prophylactic central nervous system (CNS) irradiation in addition to chemotherapy and who subsequently developed malignant gliomas within the irradiated field of brain.

Patients with radiation-induced malignant gliomas have received treatment ranging from biopsy only to surgery, irradiation, and/or chemotherapy. Additional external beam radiotherapy has not been considered for the majority of patients with radiation-induced malignant gliomas, presumably for fear of causing cerebral radionecrosis, or the dosage was reduced to nontherapeutic levels to avoid radionecrosis. These radiation-induced malignant gliomas appear to behave as aggressively as malignant gliomas not induced by radiation. It has been well documented that multimodality therapy with surgery, radiation therapy, and chemotherapy has the best chance for achieving long-term survival in patients with malignant gliomas. In this paper, seven cases of presumed radiation-induced malignant glioma are presented, including three in which the patients were treated with interstitial radiotherapy. The literature on this increasingly more common problem is reviewed.

Case Reports

Case 1

This 49-year-old man presented initially in 1965, at the age of 27 years, with headaches and a bitemporal hemianopsia. The workup revealed an enlarged sella with a suprasellar mass. He underwent a right frontal craniotomy for subtotal resection of a chromophobe pituitary adenoma and subsequently received 4500 rads of radiotherapy via 5 x 5-cm opposed lateral portals. His bitemporal field reduction resolved and he did well until 1977, when he presented again at age 39 years with headaches and recurrent bitemporal hemianopsia. Workup revealed recurrence of his pituitary adenoma. He underwent another subtotal resection via a right frontal craniotomy and subsequently received an additional 5000 rads via anterior oblique portals. Following treatment, his visual field deficits resolved once again.

The patient did well until February 9, 1987, when he presented at 49 years of age with seizures that started focally in his right leg and then became generalized. On examination his vision and fundi were normal. He had a mild right central seventh cranial nerve palsy, a mild right hemiparesis, and mild dysphasia even though he was able to carry on a conversation. Computerized tomography (CT) scanning revealed a left temporal ring-enhancing cystic lesion in the field covered by his
prior radiation treatment (Fig. 1 left). On February 12, 1987, he underwent a left frontotemporal craniotomy for cyst drainage and subtotal resection without complication. The frozen and permanent sections were interpreted as glioblastoma multiforme. A postoperative contrast-enhanced CT scan obtained on February 1987, he underwent a left frontotemporal craniotomy (Fig. 1 center), showed no change in the tumor as compared to the scan of February 16. The seeds were left in place for 7 days (duration based on dosimetry calculations and desired dosage). This gave a final dose of 6600 rads to the entire calculated volume of enhancing tumor. The seeds were removed without complications and no effort was made to aspirate the tumor cyst contents. Follow-up CT scanning in April, 1987, revealed that the tumor was smaller, with less edema and mass effect (Fig. 1 right). While surgery alone can reduce the size of tumor cysts on the CT scan (Fig. 1 left and center), radiographic reduction of the tumor itself is usually reflected fairly soon after the surgery. It is likely that the interstitial brachytherapy contributed to local tumor control and further cyst reduction (Fig. 1 right). At 17 months postoperatively, the patient is ambulatory, with no increase in his dysasia, hemiparesis, or facial palsy. He is receiving Dilantin (phenytoin) and is seizure-free.

On March 3, a follow-up CT scan with contrast enhancement (Fig. 1 center) showed no change in the tumor as compared to the scan of February 16. The seeds were left in place for 7 days (duration based on dosimetry calculations and desired dosage). This gave a final dose of 6600 rads to the entire calculated volume of enhancing tumor. The seeds were removed without complications and no effort was made to aspirate the tumor cyst contents. Follow-up CT scanning in April, 1987, revealed that the tumor was smaller, with less edema and mass effect (Fig. 1 right). While surgery alone can reduce the size of tumor cysts on the CT scan (Fig. 1 left and center), radiographic reduction of the tumor itself is usually reflected fairly soon after the surgery. It is likely that the interstitial brachytherapy contributed to local tumor control and further cyst reduction (Fig. 1 right). At 17 months postoperatively, the patient is ambulatory, with no increase in his dysasia, hemiparesis, or facial palsy. He is receiving Dilantin (phenytoin) and is seizure-free.

Summary of 37 reports of radiation-induced malignant gliomas reported in the literature

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Initial Tumor</th>
<th>Age (yrs), Sex</th>
<th>Radiation Dose (rads)</th>
<th>Latency (yrs)</th>
<th>Second Tumor</th>
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* S = surgery; R = radiation; C = chemotherapy; B = biopsy.

TABLE 1

Summary of 37 reports of radiation-induced malignant gliomas reported in the literature
Radiation-induced intracranial malignant gliomas

Case 2
This 10-year-old boy had been diagnosed as having acute lymphoblastic leukemia at the age of 3 years. In the course of his treatment he received 2400 rads of whole-brain irradiation and did well until 9 years of age, when recurrent leukemia was diagnosed via bone marrow biopsy. He received a second dose of combination chemotherapy and an additional 2400 rads of whole-brain irradiation. At 10 years of age he presented with seizures and a progressive left hemiparesis. A CT scan of the head showed a large left frontal ring-enhancing cystic lesion. He underwent a craniectomy, open biopsy, reservoir placement, and cyst drainage at that time without complications. Further external beam irradiation was not considered because of his prior dose and age. It was elected to place radioactive $^{32}$P into the cyst via the reservoir. Therefore, 10 days postoperatively 5 mCi of $^{32}$P was injected, followed 7 days later by an additional 3.6 mCi. The patient tolerated the injections well. Follow-up CT scanning showed a reduction in the size of the cyst.

The boy did well for 7 months and then presented with increasing hemiparesis and dysarthria which did not respond to steroids and tapping of the reservoir. Computerized tomography scanning at that time showed interval enlargement in the tumor cyst. An elective left frontal craniotomy and laser application to the cyst wall was performed without complications. The patient was subsequently treated with intravenous vincristine and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU). His hemiparesis improved and he was able to walk at the time of discharge. He did well for 4 more months, then deteriorated acutely after a seizure and never regained consciousness. Repeat CT scanning showed interval tumor enlargement with significant edema and brain shift. Cyst aspiration via the reservoir produced no improvement in his condition. He died 2 weeks later, 13 months after diagnosis of his glioma.

Case 3
This 11-year-old girl had been diagnosed as having acute lymphoblastic leukemia at 2 years of age. She received multiagent chemotherapy, 2400 rads of prophylactic cranial irradiation, and intrathecal methotrexate. She did well until the age of 11 years when she developed the acute onset of gran mal seizures. Computerized tomography and magnetic resonance imaging revealed bilateral enhancing lesions. A bone marrow aspirate was normal and she was believed to be in remission. The left temporal lobe lesion was biopsied and interpreted as gliosis. Six weeks after the biopsy she deteriorated acutely and CT revealed an increase in the size and number of enhancing lesions. She died 5 days later and an autopsy revealed gliomatosis cerebri.

Case 4
This 11-year-old girl had been diagnosed as having acute lymphoblastic leukemia at 5 years of age. She was treated with the same protocol as the patient in Case 2. She remained in remission and did well until the age of 11 years, when she developed the acute onset of grand mal seizures. Computerized tomography revealed a large ring-enhancing cystic lesion. A craniotomy and gross total tumor resection were performed. The pathological diagnosis was anaplastic astrocytoma. Further treatment included intravenous 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). Despite treatment, the tumor continued to grow and the child died at 12 years of age.

Case 5
This 8-year-old boy had been diagnosed as having acute lymphoblastic leukemia at 4 years of age. He was treated as in Cases 2, 3, and 4 and did well until 8 years of age, when he developed severe headaches. Computerized tomography revealed a large cystic tumor in the left parietal lobe. A CT-directed needle biopsy revealed...
an anaplastic astrocytoma. He received an additional 200 rads of whole-brain irradiation and 1000 rads coned down to the region of the tumor. Computerized tomography scans obtained when the boy was 11 years old showed the tumor to be smaller. He remains alive at age 12 years.

**Case 6**

This 10-year-old girl had been diagnosed as having acute lymphoblastic leukemia at 6 years of age. She was treated similarly to Cases 2 to 5. She did well until the age of 10 years when she developed headaches, seizures, and a left hemiparesis. Computerized tomography revealed a large right temporoparietal enhancing lesion. Subtotal resection via craniotomy revealed glioblastoma multiforme. She subsequently received intravenous BCNU but no additional radiation at the family's request. She died 11 months after surgery.

**Case 7**

This 25-year-old woman presented with bitemporal hemianopsia. Computerized tomography demonstrated a suprasellar mass (Fig. 2 left). Biopsy via a subfrontal approach revealed an optic chiasm astrocytoma. She was irradiated with 6300 rads via two parallel opposing fields measuring 5 × 5 cm. Two years after radiation therapy she experienced severe deterioration in her intellectual capacity, and repeat CT scanning was compatible with radiation leukoencephalopathy. Four years after diagnosis of optic chiasm glioma she deteriorated further and a CT scan showed an enhancing right parietal lesion (Fig. 2 center). Stereotactic biopsy revealed glioblastoma multiforme. She was treated with stereotactic interstitial brachytherapy using $^{125}$I seeds only. Steroids were used during surgery but were not continued postoperatively. The family did not wish to proceed with chemotherapy or additional surgery. Follow-up CT scanning at 6 weeks revealed marked reduction in the size of the enhancing mass (Fig. 2 right).

The patient continued to deteriorate mentally and physically and was placed in a terminal-care facility. She died 8 months after brachytherapy due to pneumonia, and permission to perform an autopsy was not obtained. The tumor in this case may not truly be a radiation-induced glioma but rather may represent a natural malignant degeneration of a glial tumor with multicentric features. The chiasm tumor was slightly smaller at the time of diagnosis of the glioblastoma multiforme, which would suggest this was not the site of malignant change. The radiographic response to brachytherapy in this case remains interesting.

**Discussion**

Recent reports in the literature have documented 37 cases of malignant gliomas that occurred after radiation therapy (Table 1). These reports delineated criteria for defining a neoplasm as radiation-induced: namely, a long quiescent latent period, a location within the irradiated area, and a tumor distinctly different from the lesion for which the patient was irradiated. Radi- ation-induced gliomas meeting these criteria remain rare. Our Cases 1 and 7 bring the total number of gliomas reported following parasellar irradiation to nine. Case 7 could represent natural malignant degeneration of the patient's chiasmal glioma and subsequent multicentricity. Our Cases 2 to 6 are among 10 reported radiation-induced gliomas following successful treatment of acute leukemia. There are also seven children who were successfully treated for a posterior fossa neoplasm but who were later diagnosed as having a malignant glioma.

The mean age at diagnosis of the patients with radiation-induced glioma was 24 years for the 37 cases. Thirty-three (89%) of the 37 reported patients were less than 50 years of age and 25 (68%) were less than 30 years of age at the time of diagnosis of the malignant glioma. In 24 cases (65%), the patients received cranial

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**FIG. 2.** Computerized tomography scans in Case 7. **Left:** Preoperative scan showing an optic chiasm glioma. **Center:** Scan showing a right parietal enhancing glioblastoma. **Right:** Scan 3 months after interstitial brachytherapy showing a marked reduction in enhancement.
Radiation-induced intracranial malignant gliomas

irradiation for varying reasons when they were children (< 18 years of age). This helps to explain the skewed age distribution toward youth and supports the contention that radiation therapy played some role in inducing tumor formation.

The latency period between cranial irradiation and subsequent glioma diagnosis ranged from 1 to 26 years. There was no obvious difference in the mean latency period for the 24 patients who were younger than 18 years of age when irradiated (8.34 years) versus that for the 13 who were irradiated after 18 years of age (9.92 years). The mean latency period for the seven children with leukemia who developed gliomas (6 years) appears to be shorter than for the other groups, but this difference is not statistically significant.

The tendency toward youth in this group of patients should put the majority into a more favorable prognostic category if aggressive multimodality therapy is administered, as documented by various studies on malignant gliomas.28-29 No statistically significant data about survival after diagnosis of the radiation-induced glioma can be derived from the 37 reported cases. However, their survival rate anecdotally appears to compare unfavorably with survival rates obtained in larger series of nonradiation-induced malignant gliomas in patients of similar age who were treated with surgery, radiation therapy, and chemotherapy.28-29 The most optimistic explanation for the poorer survival rate is a lack of aggressive multimodality therapy. It appears that only eight of the 37 patients were treated with surgery, irradiation, and chemotherapy and they included those who survived the longest (Table 1).

The distribution of these radiation-induced malignant gliomas in the brain is dependent on the area irradiated. Aggressive surgical excision should always be considered when the area of involved brain does not entail a prohibitive risk. Intersitial brachytherapy seems to be of value in treating recurrent, previously irradiated malignant cerebral gliomas,10 and a randomized study is in progress to determine whether brachytherapy is helpful in the first-line treatment of malignant gliomas. Intersitial brachytherapy appears to be a potential alternative to external beam irradiation for this select group of patients and should help to avoid radiation damage/necrosis of functioning brain in previously irradiated fields. Additional external beam therapy can also be used if it is considered to be safe. Dritschilo, et al.,9 have published a series of 32 patients who were treated with multiple courses of radiation therapy to the brain for various tumors. If more than 3 years had elapsed since the patients' initial radiation treatment, they were considered to have recovered radiation tolerance and were re-treated to essentially a full dose (4000 to 5000 rads). The majority of their patients improved functionally after repeat irradiation, and 24% survived more than 5 years. Two had evidence of radiation necrosis at autopsy, and an additional three patients were still alive with severe neurological deterioration attributed to the radiation. Dritschilo, et al., believed that the risk of tumor recurrence outweighed the risk of radiation necrosis.

We think that the number of radiation-induced CNS tumors will increase with time, especially as children with successful treatment to various neoplasms survive to adulthood. Recent reports appear to document this concept.3-8,11,14,16-19,21,22,24-27,30,31

References


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