Long-Term Survival of Children with Brain Tumors

Outcome is described for 1,034 children who received radiation treatment in the management of a brain tumor at the University of Toronto Institutions from 1958 to 1995. The 5-, 10-, 20-, and 30-year relapse-free (or

Introduction

Potentially curative radiation treatment of children with brain tumors resulted from the introduction of megavoltage irradiation nearly 50 years ago, and initially carried out principally with cobalt gamma rays. Common childhood brain tumors are infrequently cured with radiation doses below 5,000 cGy in 180 cGy fractions. The practical level of radiation tolerance of the brain is 5,500 cGy. Megavoltage irradiation allowed such doses to be delivered without major short-term toxicity. Thus, adults may now be seen who were cured of a childhood brain tumor many years ago.

In practice, curative radiation treatment was introduced slowly, principally during the 1950s and '60s, so that it is still uncommon to see a survivor treated more than 30 years ago. However, enough years have passed that it is now possible to evaluate factors that are predictive of long-term survival in children with brain tumors and to estimate some of the risks associated with having a brain tumor eradicated by surgical and radiation treatment. This analysis updates and expands on a previous publication focusing on these issues [1].

Study Population and Methods

A University of Toronto database exists for children who underwent irradiation for brain tumors diagnosed from 1958 to 1995. A total of 1,034 children up to and including the age of 16 years received radiation treatment for a brain tumor during that 38-year period. With only rare exceptions, initial investigation and surgical management took place at the Hospital for Sick Children and subsequent radiation treatment was carried out at either the Princess Margaret Hospital (1958 to 1986) or Toronto-Sunnybrook Regional Cancer Centre (1986 to 1995). Long-term follow-up was provided at the Hospital for Sick Children until the children were 18 years of age and thereafter at either the Princess Margaret Hospital or Toronto-Sunnybrook Regional Cancer Centre. Radiation treatment was commonly administered postoperatively as a component of primary treatment (87%), rather than at the time of progression or relapse. This patient series is essentially population-based for the greater metropolitan Toronto region and northern Ontario.

Results

Overall Survival
The 5-, 10-, 20-, and 30-year survival rates for all 1,034 patients were 52%, 44%, 38%, and 30%, respectively (Figure 1). One in three of the patients who were alive at 10 years was dead at 30 years. Relapse- or progression-free survival rates at 5, 10, 20, and 30 years were 47%, 45%, 44%, and 44%, respectively.

Age and Gender
Age at diagnosis was not a prognostic factor. The 20-year survival rate was 36% for children less than 4 years old at diagnosis (N = 225), 39% for those 4 to 8 years old (N = 384), and 38% for those 8 to 16 years old (N = 419).

Also, there was no overall difference in survival by gender. As shown in Figure 2, the 20-year survival rate was 37% for boys (N = 582) and 40% for girls (N = 449). However, after 20 years, a greater number of deaths occurred in girls.

Surgical Treatment
For the 607 patients for whom adequate surgical data were available, total resection (N = 143) resulted in a 20-year survival rate of 64% and less than total resection (N = 464), a rate of 36% (P <
Radiation Treatment
The median radiation dose was 5,086 cGy, but the range was narrow. The 10th percentile was 4,000 cGy and the 90th percentile, 5,400 cGy. No significant survival difference was noted when patients who received a radiation dose above the median (5,086 cGy) were compared with those who received a lower dose (4,000 to 5,086 cGy). Respective 20-year survival rates for the two groups were 38% and 43%.

Year of Diagnosis
Overall, no significant improvement in survival occurred for patients treated in 1975 or afterward (N = 562), compared to those treated before 1975 (N = 464). The respective 20-year survival rates for the two groups were 42% and 36% (P = .11; Figure 4).

Tumor Histology
Table 1 summarizes 10- and 20-year survival rates by tumor histology. (Patients with brainstem tumors, optic nerve gliomas, and basal ganglia tumors include those with and without a tissue diagnosis.) The survival curves for patients with low- and high-grade astrocytomas are shown in Figure 5.

Second Malignant Tumors
The cumulative incidence of second malignant tumors was 13% at 20 years and 19% at 30 years (Figure 6). To date, 31 patients have developed a second malignant tumor and 2 patients, a third malignancy. The most common second malignant tumors were gliomas (9 patients), meningiomas (7), acute leukemia (5), sarcoma (3), and other tumors (7). Survival from the date of diagnosis of a second malignant tumor was 58% at 5 years. None of the five patients who developed acute leukemia and only one of four patients who developed a high-grade astrocytoma survived. In contrast, all seven patients with a meningioma are currently alive. All meningiomas were included in this analysis, regardless of the degree of malignancy.

Cause of Death
Among the 546 patients who died, the cause of death was "disease" in 514 patients (94%), toxicity in 6 (1%), second malignant tumor in 12 (2%), and miscellaneous in 14 (3%). The classification "disease" was used when death was due to uncontrolled tumor, whether progressive or recurrent disease, and also for a very small number of patients who underwent prolonged hospitalization for irreversible neurologic damage and in whom no other cause of death was established.

The distribution of the cause of death varied with time (Table 2). In the first 5 years after diagnosis, disease was the cause of death in 97% of patients. After 20 years, disease was responsible for death in 30% of patients. A second malignant tumor became an increasingly important cause of death beyond 5 years after diagnosis.

10-Year Survivors
At 10 years after diagnosis, 269 patients were alive, 69 of whom had previously suffered a relapse and 209 of whom were relapse free. Survival rates at 25 years (from diagnosis) in the relapsed and relapse-free patients were 49% and 94%, respectively (P < .0001).

Survival After Relapse
Survival, measured from the date of first relapse (or progression) for 533 relapsed patients was 22% at 5 years and 12% at 20 years.

Discussion
Tumor progression (or relapse) in a child with an irradiated brain tumor is uncommon after more than 5 years from diagnosis. In this series, the relapse-free survival rate was 44% at 30 years, compared with a rate of 45% at 5 years. In contrast, overall survival, counting deaths from any cause, continued to decline steadily after 10 years from diagnosis, with 10-, 20-, and 30-year survival rates of 44%, 38%, and 30%, respectively, and with little evidence of plateauing of the survival curve at 30 years. Thus, one in three of the 10-year survivors was destined to die during the next 20 years.

These results are very similar to reports from the Surveillance, Epidemiology and End Results (SEER) program, which gave 5-year survival rates for all brain and central nervous system tumors of 45% (1967 to 1973) and 52% (1973 to 1981) [2]. The results are also similar to those from United Kingdom population-based studies, which reported a 10-year survival rate of 40% (1971 to 1976) and a 5-year survival rate of 75% (1983 to 1985) [3]. However, any series of children irradiated for a brain tumor is unfavorably biased, due to the exclusion of low-grade tumors treated by resection alone, in particular, cystic astrocytomas of the cerebellum. The late attrition of early survivors has
also been reported. A United Kingdom study of 3-year survivors of medulloblastoma and ependymoma gave the subsequent 10-year survival rates as 62% and 73%, respectively [4].

In our population, "disease" was the most common cause of death, accounting for 97% of deaths in the first 5 years after diagnosis, 91% of deaths from 5 to 10 years, 74% from 10 to 20 years, and 30% from 20 to 30 years. Hawkins et al from the United Kingdom reported that 25% of 5-year survivors of medulloblastoma and ependymoma died of recurrent tumor in the subsequent 15 years [5].

**Prognostic Factors**

Relapse--As in all tumors, relapse was a very unfavorable prognostic factor in our study population. For example, of the 269 ten-year survivors, only 49% of those who had previously relapsed (N = 60), were alive at 25 years, compared with 94% of those who were relapse free at 10 years (N = 209) (P < .0001). Death from "disease" subsequently occurred in 14/60 (23%) of the patients who had previously relapsed, compared with 6/209 (3%) of those who were relapse free at 10 years. Overall, there were 533 patients who relapsed or progressed. Long-term survival did occur after relapse. Measured from the date of first relapse, subsequent survival was 22% at 5 years and 12% at 20 years.

We have previously observed that it is the patients with low-grade tumors who suffer late relapse, and that the later the first relapse, the longer is the interval from first relapse to death, if this is to occur [1].

**Age, gender, and year of diagnosis** were not significant prognostic factors in the current analysis. It is surprising that survival did not improve in patients treated after 1975, although we have previously reported improvement in certain subsets, for example, patients with medulloblastoma or germ cell tumors [1].

During the last 20 years, CT and MRI replaced air studies for imaging of brain tumors and provided much more information on tumor anatomic extent. Major improvements in neurosurgical technique led to an increased frequency of grossly complete resection. Also, adjuvant chemotherapy was introduced. It could be that moderate outcome improvements have been masked by the irradiation of an increasingly poor prognostic mix of patients. Certainly, low-grade tumors are irradiated less frequently today than they were in the early years of this report. Moreover, the annual number of patients irradiated has dropped from an average of 29 in 1958 to 1974 to 22 in 1975 to 1995, with no change in the status of pediatric radiation oncology, which was practiced in only one center in the region throughout those years.

**Extent of Resection**--Total resection of a brain tumor is associated with significantly improved outcome, when compared with less extensive surgical procedures. Therefore, in recent years a greater effort has been made to achieve grossly complete resection. In this series, complete resection was achieved in 17% of patients in the 1970s, 24% in the '80s, and 31% in the '90s. However, it remains unclear whether grossly complete resection has a causal relationship with survival, or is only a marker of good prognosis.

When complete resection is achieved in low-grade tumors, especially low-grade astrocytomas, no additional therapy may be indicated. In high-grade tumors the intensity of adjuvant therapy, whether radiation treatment or chemotherapy, may sometimes be decreased after total resection. The attempt to achieve total resection, at acceptable costs, remains the foundation of current practice.

**Radiation Treatment**--Throughout the years of this review, the radiation treatment dose utilized was that regarded as the maximum tolerable, and variations in dose were due mainly to perceived differences in tolerable dose; for example, a reduction of approximately 500 cGy was made in children under 2 years of age. Thus, it is not surprising that there was no significant difference in outcome related to the radiation dose utilized.

The overall 30-year survival rate of 30% must be attributed mainly to the effect of radiation treatment. It is difficult to speculate as to what the survival rate in this series would have been had treatment been limited to the surgical procedure. It is mainly patients with low-grade astrocytomas who have a chance for continued disease-free survival after less than complete resection. When the 201 patients with low-grade astrocytomas were excluded from this series, the 30-year survival rate for the remaining 833 patients was 31%.

In this group of patients with mainly high-grade tumors, the prospect for long-term survival after varying degrees of resection alone can reasonably be assumed to be low, and is likely less than 5%. It is therefore assumed that long-term survival occurred in not less than 25% of patients with high-grade tumors as a consequence of radiation treatment, which, therefore, is an important prognostic factor for long-term survival.

It is not yet possible to quantitate the overall improvement in survival that may occur following the
use of adjuvant systemic treatment. This modality remains experimental for most tumors [1].

**Radiation and Second Malignant Tumors**

Second malignant tumors become an increasingly important cause of death after 5 years from diagnosis, and especially after more than 10 years. In our series, the 30-year cumulative incidence of a second malignant tumor was 19%. With almost half of these tumors resulting in death, this complication is an important cause of the difference in 30-year overall and relapse-free survival rates (30% and 44%, respectively). The distribution of second malignant tumors in 31 patients included 9 gliomas and 7 meningiomas. All of these tumors occurred in or adjacent to the radiation treatment volume and must be assumed to be radiation induced. Four additional patients with basal cell carcinoma, parotid carcinoma, thyroid carcinoma, and sarcoma must also be assumed to have had a radiation-induced second malignant tumor, for a total of 20/31 (64%). At present, there is no alternative to radiation treatment for high-grade tumors and no known way of modulating the oncogenic effect of radiation. Fortunately, this toxicity is delayed for a long period and is only a small concern during the first 10 years of follow-up.

**Summary**

In summary, death after 5 years in a child with a brain tumor is common. Children with such tumors have about a 50-50 chance of dying in the ensuing 25 years, usually due to failure to control a relapsed low-grade tumor. After 15 to 20 years from diagnosis, death from a second malignant tumor, often induced by radiation, becomes more frequent than death as a direct result of the original tumor. A first relapse of a brain tumor more than 5 years after diagnosis is uncommon. At present, relapse-free status at 5 years is the most important prognostic factor for future survival.

**References:**


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