Radiation treatment for medulloblastoma

A 21-year review

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One hundred and twenty-two patients with medulloblastoma received postoperative irradiation at the Princess Margaret Hospital, Toronto, from 1958 to 1978, inclusive. The surgical procedure in these patients was total resection (44 patients), subtotal resection (66 patients), or biopsy alone (12 patients). Twenty-five patients received adjuvant chemotherapy.

Overall 5- and 10-year survival rates were 56% and 43%, respectively. Improved survival rates were associated with an increased degree of resection and with posterior fossa radiation doses of 5200 rads or more. The posterior fossa was the common site of first relapse (in 56 patients, 46%), and were associated with the use of ventriculosystemic shunts. Millipore filters did not prevent systemic relapse in shunted patients.

A subset of 15 patients who received a posterior fossa dose of 5200 rads or more after a total resection had a 5-year survival rate of 77%, which remained constant to 10 years. This result is considered to be the upper limit that can be achieved by current treatment methods.

KEY WORDS • medulloblastoma • postoperative radiation therapy

The probability of cure for the patient with medulloblastoma with combined surgical and radiation treatment currently approaches 50%. A positive quantum jump in this probability is likely only if studies of adjuvant chemotherapy and/or modulators of the radiation effect prove successful. Nevertheless, there remain several outstanding issues with regard to “conventional” surgical and radiation treatment which we wished to examine.

Generally, neurosurgeons agree that the primary tumor should be resected completely whenever this is practical, but the value of surgical control of increased intracranial pressure (ICP) by shunting prior to resection is controversial, since the incidence of systemic metastatic disease may thereby be increased. Postoperative radiation treatment of the whole brain, spinal cord, and associated meninges became standard practice following the demonstration by Patterson and Farr that this was a necessary treatment component for cure. A number of techniques for irradiating the neuraxis with reasonable homogeneity have subsequently been described. Because relapse at the primary site has been an important failure mechanism and the radiation tolerance of the neuraxis is limited, most authors advocate “boosting” the primary site, usually the posterior fossa, to the maximum tolerated radiation dose. The shape of the dose-response curve for radiation control at the primary site is poorly understood, although, generally, retrospective reviews indicate higher control rates with increasing radiation dose. Deleterious radiation late effects, especially in brain or bone, are important and have a direct bearing on the cost-effectiveness of radiation dose.

Recently, the introduction of screening myelograms has made it clear that an appreciable fraction of patients with medulloblastoma have gross occult spinal metastases at diagnosis. An incidence as high as 43% (seven of 16 patients) has been described in Pittsburgh. Optimal craniospinal radiation dose may well be dependent on the presence of gross metastases.

Summary of Cases

Patient Population

One hundred and forty-three consecutive patients with a diagnosis of medulloblastoma or cerebellar
sarcoma were registered at the Princess Margaret Hospital, Toronto, from 1958 to 1978, inclusive. Twenty-one of these patients were excluded from analysis: 13 patients had received surgical and radiation treatment elsewhere and were referred for follow-up purposes or with relapse; in three patients the initial histological diagnosis was incorrect, and this led to local irradiation only; two patients were irradiated for relapse following previous surgical treatment only; two were diagnosed on the basis of spinal fluid cytology alone; and one patient was in such poor condition that no attempt at histological diagnosis was made. All the remaining 122 patients had initial histological proof of diagnosis and were referred for radiation treatment following a primary surgical procedure. These patients comprise a selected group in the sense that all survived the initial surgical treatment. Since the Princess Margaret Hospital was the only referral center for radiation therapy in the metropolitan Toronto region during these years, and our neurosurgical colleagues uniformly accepted the need for postoperative irradiation in these patients, we believe this series is otherwise unselected and representative of this disease in our geographic region.

Age and Sex. There were 78 males and 44 females, a ratio of 1.8:1. The age range was from 1 to 47 years and the median age was 7 years (25 patients were aged under 5 years, 52 patients 5 to 9 years, 21 patients 10 to 14 years, one patient 15 to 19 years, and 23 patients were aged 20 years or more).

Stage of Tumor. Patients were retrospectively classified according to the clinicopathological operative staging system proposed by Chang, et al.:5

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* For definition see text.

rebellar or cerebral subarachnoid space, or third or lateral ventricles
M3: Gross nodular seeding in the spinal subarachnoid space; metastases outside the cerebellar axis.

When the data were inadequate, the classification "Tx" or "Mx" was used. No patient had an elective myelogram (Table 1).

Site of Tumor. A posterior fossa tumor was demonstrated in all but two patients who had disease in the middle cranial fossa.

Treatment

Surgical Treatment. Seventy-one patients had a shunting procedure prior to exploration and three patients had a shunt inserted later. A ventriculoperitoneal shunt was placed in 65 of these patients. A millipore filter was used in the shunt system in 20 patients. The primary tumor resection was total (that is, macroscopically complete) in 44 patients (36%); subtotal in 66 patients (54%); and in 12 patients (10%) a biopsy was performed without any attempt at resection.

Radiation Therapy. A number of craniospinal radiation techniques were used during the 21 years of this study. Before 1966, patients were treated primarily with kilovoltage radiation after the method described by Paterson and Farr.25 In 1966, a standard cobalt-60 (Co60) technique was adopted. Patients were treated in the prone position with a foam rubber-lined plaster cast to support the forehead, shoulders, and chest. The brain and upper cervical cord were irradiated with lateral opposed shaped fields. The posterior fossa was boosted with parallel opposed fields. The spine was treated by one or two direct posterior fields, depending on the length of spine. Field junctions were moved at regular intervals. Treatments were given 5 to 6 days per week, with all fields treated on each day. This technique has been described in detail previously.30

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Three patients were excluded from analysis of radiation treatment data: one patient died before commencing radiation treatment, and two patients died before completing their prescribed treatment. Radiation parameters for the remaining 119 patients were:

Radiation quality: Ninety-two patients were treated with Co\textsuperscript{60} alone, 18 were treated with kilovoltage radiation alone, and nine were treated with a combination of Co\textsuperscript{60} and kilovoltage radiation.

Posterior fossa dose: The median dose was 5000 rads (range 3200 to 5950 rads) (Fig. 1); the median number of fractions was 28 (range 18 to 42 fractions), and the median duration of treatment was 39 days (range 23 to 74 days).

Whole-brain dose (excluding posterior fossa boost): The median dose was 3500 rads (range 1900 to 5500 rads), the median number of fractions was 20 (range 15 to 42 fractions), and the median duration was 28 days (range 17 to 51 days).

Spinal-cord dose: This was calculated at an average depth of the cord from the skin surface and varied with age. The median dose was 3500 rads (range 1900 to 4500 rads), the median number of fractions was 20 (range 10 to 33 fractions), and the median duration was 28 days (range 15 to 55 days).

Systemic Therapy. Adjuvant chemotherapy was given to 25 patients. Three patients received intrathecal methotrexate alone. From 1975, 22 patients were randomized to receive chemotherapy according to a protocol of the Children's Cancer Study Group (CCG-942). The agents used were 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), vincristine, and prednisone which, during maintenance, were given as eight 6-week cycles. The median duration on chemotherapy was 11 months (range 1 to 18 months).

Treatment Results

Survival rates were computed using the life table method. Statistical significance was calculated using the generalized Wilcoxon test. Overall survival from the date of resection or biopsy for 122 patients was 56% at 5 years and 43% at 10 years. Corresponding 5- and 10-year relapse-free rates were 49% and 38% (Fig. 2).

Age and Sex. Survival rates for males and females were similar, with respective 5-year rates of 58% and 53% (p = 0.53). The youngest patients in this study fared worse than older patients (Fig. 3). This difference approached statistical significance for patients aged 5 years and under at diagnosis, compared with patients aged 11 to 30 years (p = 0.06). Seven patients were aged 2 years or under at diagnosis; four had died of their disease at last follow-up review, one was alive with disease, and two were alive and disease-free. Median survival was 21 months (range 4 to 56 months).

Stage of Tumor. The 5-year survival rate was 57% for 50 patients with a T\textsubscript{1} or T\textsubscript{2} tumor and was also...
57% for 63 patients with a T3 or T4 tumor (p = 0.34). Respective 5-year survivals for M0 (100 patients) and M1, M2, or M3 (16 patients) were 58% and 47% (p = 0.19).

Cytology Studies. Cerebrospinal fluid was examined for malignant cells preoperatively in 46 patients; three were positive and three were suspicious. Five of these six patients were alive and in a first remission at last follow-up review and one had died with progressive local disease. Eight patients had symptoms or clinical signs of spinal cord involvement at diagnosis. Three of these patients had CSF cytology studies. None was positive for malignant cells. Four of 15 patients whose first relapse was in the spinal cord or supratentorial region had CSF cytology studies at diagnosis. None was positive for malignant cells.

Survival in Relation to Shunting. The 5-year survival rate for 71 patients who had an initial shunting procedure was 59%, and for 51 patients without a prior shunt it was 54% (p = 0.69).

Survival in Relation to Resection Extent. Respective 5-year survival rates were 64% for total resection, 56% for subtotal resection, and 33% for biopsy alone (Fig. 4). The difference in survival rates between gross total removal and biopsy only was significant (p = 0.01), and between subtotal removal and biopsy it approached significance (p = 0.06).

Radiation Treatment. One hundred and nineteen patients who completed radiation treatment were analyzed. For the purpose of comparing radiation treatment data only, survival time was measured from the first day of radiation treatment. Seventy-nine patients started radiation treatment within 10 days of surgical treatment. Radiation treatment was delayed in 40 patients because of postoperative complications (29 patients) or for unknown reasons (11 patients). The median delay beyond 10 days was 18 days (range 2 to 38 days). There was no difference in survival times between patients with or without postoperative delay (p = 0.83).

The 5-year survival rate for the 89 patients treated with our standard Co{	extsuperscript{60}} technique{	extsuperscript{90}} was 64%; all of these patients were treated since 1966. This compared with a rate of 47% for 30 patients treated in earlier years by any other technique (Fig. 5). The 8-year survival rate for the standard technique was 58%.

Survival rates showed no statistically significant difference in relation to posterior fossa radiation dose. Respective 5-year survival rates were 71% for 14 patients with doses greater than 5350 rads, 74% for 34 patients with doses of 5200 to 5350 rads, 51% for 38...
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patients with doses of 5000 to 5100 rads, and 50% for 33 patients with doses less than 5000 rads (Fig. 6). However, when patients in each dose range were evaluated for posterior fossa recurrence only, there was a significant trend toward freedom from recurrence with increased dose (chi-square for trend, p = 0.012). The posterior fossa relapse-free rates for each dose range were 11 of 14 (79%) with doses greater than 5350 rads, 28 of 34 (82%) with 5200 to 5350 rads, 28 of 38 (74%) with 5000 to 5100 rads, and 14 of 33 (42%) with less than 5000 rads.

There was no survival difference between 74 patients who commenced radiation treatment with posterior fossa irradiation followed by craniospinal irradiation compared with 23 patients treated in the reverse sequence (p = 0.26).

Systemic Treatment. The respective 5-year survival rates for 25 patients who received adjuvant chemotherapy and 97 patients without adjuvant chemotherapy were 64% and 56% (p = 0.77); corresponding relapse-free rates were 71% and 46% (p = 0.34). However, in making these overall comparisons we inevitably compared recently treated patients with those treated many years ago, so that improvements in surgical and radiation treatment were weighted unfairly, favoring the subset of patients who received chemotherapy. Within the limits set by our small numbers of patients, we could ask the question “was adjuvant chemotherapy of value?” with less risk of error, when the analysis was restricted to patients treated since 1975, when surgical and radiation treatment was relatively standardized. The 3-year survival rate for 22 patients given elective CCNU, vincristine, and prednisone according to the Children’s Cancer Study Group protocol (CCG-942) was 66%, exactly equal to the survival rate for 26 patients treated with radiation alone (Fig. 7). The treatment choice was random for most of these patients.

Relapse

Patterns of Relapse. Fifty-two patients relapsed following an initial remission, and six patients died of progressive disease. Histological confirmation of first relapse was obtained in 25 patients. The median time to relapse was 14 months (range 3.5 to 110 months). Four patients relapsed more than 5 years from diagnosis; all had had posterior fossa doses of 4000 rads or less, and three had been treated with kilovoltage irradiation.

The sites of first relapse were as follows: the posterior fossa alone (19 patients), the spinal cord alone (one patient), supratentorial region alone (six patients), systemic alone (15 patients), posterior fossa alone (19 patients), and both the posterior fossa and spinal cord (nine patients).
of these patients. The respective rates of systemic relapse for patients with or without a shunt were 15 of 74 (20%) and three of 48 (6%). There was a significant trend relating the presence of a ventriculosystemic shunt to the development of systemic metastases (chi-square for trend, \( p = 0.04 \)). The rate of systemic relapse for patients who received adjuvant chemotherapy (three of 25 or 12%) was not significantly different from those who received no adjuvant chemotherapy (15 of 97 or 15%).

**Treatment of Relapse.** Thirty-nine patients were treated for relapse. Fourteen patients had recurrence in the posterior fossa alone. Two of these patients were explored. One had a subtotal tumor removal and the other died of postoperative bleeding from an unresectable tumor. Thirteen patients were re-irradiated to various volumes (posterior fossa alone, seven patients; whole brain, two patients; and craniospinal, four patients). Nine patients were given chemotherapy with various agents (vincristine, cyclophosphamide, procarbazine, CCNU, or intrathecal methotrexate, alone or in combination).

Twelve patients had a relapse in the spinal or supratentorial region, with or without clinical evidence of posterior fossa recurrence. Five of these patients underwent subtotal resection and one total resection. All were re-irradiated to various volumes (local fields only, five patients; craniospinal, five patients; whole brain, one patient; and posterior fossa plus spine, one patient. One patient received miso- nidazole during re-irradiation. Chemotherapy was given to seven patients (vincristine, procarbazine, CCNU, or prednisone, alone or in combination).

Systemic sites of recurrence were found in 13 patients. Five patients were given palliative local irradiation and 12 received chemotherapy (vincristine, cyclophosphamide, procarbazine, CCNU, chlorambucil, or prednisone, alone or in combination).

The response to treatment was assessed on a clinical basis: five patients continued to deteriorate, two were stable, 19 had some improvement, and 13 returned to normal activity. The median survival from relapse for these 39 patients was 11 months (range 4 days to 132+ months). The respective median survival periods for each site of relapse were as follows: posterior fossa alone, 10 months (range 4 days to 92+ months), spine or supratentorial region, 12.5 months (range 5 days to 132+ months), and systemic, 7 months (range 2 to 21).

At last follow-up, three patients were alive with disease and five patients, all of whom relapsed only within the central nervous system (CNS), were alive and disease-free at 3, 9, 17, 92, and 132 months from relapse.
Complications and Toxicity

During the active treatment phase, significant complications and toxicity were seen.

Postoperative Period. Fifty-three patients had acute postoperative complications, which were fatal in four: pulmonary embolism, pneumonia, cerebellar abscess, and one unspecified complication following shunt revision. No residual tumor was found in two of the three of these patients who underwent autopsy.

Non-fatal tumor or surgical complications were as follows: fever and/or sepsis (17 patients), increased ICP requiring shunt insertion or shunt revision (16 patients), respiratory failure (eight patients), deterioration in consciousness (seven patients), intracranial hemorrhage (six patients), brain-stem edema (four patients), hemiparesis (three patients), cardiac complications (two patients), CSF leak (two patients), convulsions (two patients), acute psychotic reaction (one patient), and steroid-induced gastrointestinal bleeding which required vagotomy and partial gastrectomy (one patient).

During Radiation Treatment. The specific complication of radiation treatment which resulted in temporary interruption of treatment was neutropenia and/or thrombocytopenia (eight patients). Moderate depression of blood counts was seen in all patients. A white blood cell count of less than 1000 and/or platelet count of less than 10000 were our usual criteria for interrupting treatment.

More important causes of treatment interruption were fever with or without sepsis (four patients), shunt malfunction (six patients), spinal cord compression (two patients), generalized skin rash (one patient), extradural hematoma (one patient), and extreme agitation (one patient). The median period of interruption was 9 days (range 2 to 70 days).

The 5-year survival rate for 21 patients whose radiation treatment was interrupted was 37% compared with 62% for 98 patients without interruption (p = 0.005). This difference was due entirely to the poor prognosis of patients in whom treatment was interrupted for causes other than radiation-induced myelosuppression.

Chemotherapy. Transient myelosuppression was seen in all 25 patients. Immunosuppression resulted in an increased incidence of infections: herpes zoster (three patients) and Pneumocystis carinii (one patient). None of these infections was fatal (although very recently we have seen fatal varicella). Two patients stopped adjuvant chemotherapy prematurely because of subjective intolerance.

The late effects of brain damage caused by medulloblastoma or its treatment are beyond the scope of this paper, but we noted that, of our 68 survivors, 41 patients had no residual overt neurological deficit and were able to lead normal lives, 19 patients had moderate neurological deficits, and eight patients had major deficits: mental retardation, paraplegia, and blindness. None of these patients had developed second tumors or cataracts.

Discussion

The overall survival rate of our patients, 56% at 5 years and 43% at 10 years, compared favorably with other recent reports. In these studies, the 5-year survival rates ranged from 33% (44 patients) to 73% (nine patients) and the 10-year survival rates from 20% (44 patients) to 31% (59 patients). Survival rates for males and females in this study were similar, although most reports indicate that females have a better prognosis.

In our experience, children aged 5 years or less appeared to have a smaller chance of survival than patients 6 to 30 years old, but this was not a significant observation. Others have reported that adults have a longer average survival time than patients aged less than 16 years, and in a pediatric study the initial survival advantage of children older than 75 months was not maintained.

We were not able to confirm the prognostic value of Chang's T classification, but our data on the anatomical extent of the primary tumor were retrospective, gleaned from a review of operative, radiological, and clinical reports, and thus were not precise. Nor were we able to demonstrate any prognostic value for CSF cytology studies, and were in agreement with Deutsch and Reigel, who, in a screening myelogram program, also found no correlation between cord seeding and positive CSF cytology.

Our data confirmed that an increased degree of resection was associated with favorable outcome, a finding confirmed by most authors but not all. While it appears axiomatic that it is the smaller, favorably located tumors that are amenable to total resection, the contribution of these factors to outcome could not be analyzed in this small retrospective study. We believe that total resection should be the objective of surgical treatment, within the limits set by acceptable morbidity. Harisiadis and Chang reported that subtotal tumor removal with good restoration of CSF flow represented the optimal surgery in their series. At Philadelphia, a more complete surgical removal with the use of the operating microscope resulted in a significantly improved relapse-free rate (21 patients). In contrast, Mealey and Hall found that the
extent of tumor resection had no significant bearing on prognosis.

We analyzed various radiation parameters. Our standard Co\textsuperscript{60} technique\textsuperscript{10} was associated with a favorable outcome, and this remains our current technique. We also obtained evidence that a higher dose to the primary site (5200 rads or more) was associated with a superior survival rate and significantly lower rate of local recurrence. In comparison, at the Columbia-Presbyterian Medical Center, 5-year survival rates were 35% for posterior fossa doses of 4000 to 4700 rads (17 patients); 45% for doses of 4700 to 5200 rads (25 patients); and 48% for doses of more than 5200 rads (13 patients).\textsuperscript{10} Cumberlin, et al.,\textsuperscript{7} reported a posterior fossa tumor recurrence rate of 83% (10 of 12 patients) following irradiation with 5000 rads, and 14% (one of seven patients) for 5500 rads and over. Others have reported favorably on control rates with high radiation doses.\textsuperscript{20}

The subset of 15 patients who received a dose of 5200 rads or more to the posterior fossa following a gross total tumor removal had a 5-year survival rate of 77% which remained constant to 10 years. This result very likely approximates the upper limit that could be achieved by current treatment methods. In practice, the delayed morbidity of high-dose brain irradiation sets a limit of approximately 5500 rads/28 fractions/38 days for moderate-volume irradiation of older patients, with downward modification for younger children, so that exploration of the modulators of radiation effect is of interest in this tumor system.

There was no survival advantage for the 22 patients who received adjuvant chemotherapy in the context of the randomized prospective multi-institutional clinical trial currently being conducted by the investigators of the Children's Cancer Study Group.\textsuperscript{11} Only large trials of this nature can answer the important question of the value of adjuvant chemotherapy, since, as our single-institution data suggest, a positive drug effect, if present, is unlikely to be large.

Subfrontal relapse occurred in a small number of our patients, as reported by others.\textsuperscript{14} It is known that when whole-brain irradiation is delivered with direct lateral radiation fields alone, the eye blocks may result in a lower dose to the subfrontal meninges, particularly in the midline.\textsuperscript{30} It is possible that boosting this region with an anterior radiation field directed between the eyes may decrease this particular form of relapse.

Our incidence of systemic metastases at first relapse, 18 of 52 (35%) patients, was high compared with other reports,\textsuperscript{4,6,9,27} and the majority (15 of 18) occurred in the absence of recurrence in the central nervous system. Our pediatric patients almost routinely underwent ventriculoperitoneal shunting before resection during the last 15 years under review, and this may have been a factor. In a literature review, Kessler, et al.,\textsuperscript{18} found eight documented examples of shunt-related metastases among 53 patients with systemic medulloblastoma metastases. Hoffman, et al.,\textsuperscript{17} previously reported our pediatric experience: four of 41 shunted children metastasized via the shunt and died of systemic disease. Subsequently, millipore filters were inserted into the shunt lines in the hope of blocking tumor dissemination by this route. Our current data indicated that there was no difference between the rates of systemic metastases for patients with (three of 20 or 15%) or without (12 of 54 or 22%) a filter (p = 0.74, two-tailed Fisher's exact test). Similarly, adjuvant chemotherapy did not appear to alter the rate of systemic metastases in shunted patients. We conclude that, whenever possible, systemic shunts should be avoided.

Treatment of patients who had relapsed with additional resection when practical and re-irradiation, with or without systemic treatment, proved to be of good palliative value, and occasionally led to a long second remission. Possible deleterious late effects of treatment, especially with radiation and/or systemic agents, on brain, bone, or endocrine glands, and the risk of second tumor induction are significant and require that minimum effective treatment be defined for each prognostic subset of patients. There is therefore some urgency to the investigation of prognostic factors in this malignancy.

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References

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