Radiation therapy for neoplasms of the brain

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The effectiveness and complications of radiation therapy for brain neoplasms are reviewed. While the available data suggest a favorable influence and outcome, randomized studies are needed to further optimize radiation therapy techniques and to integrate new therapeutic modalities.

KEY WORDS: brain tumor, radiation therapy, glioblastoma multiforme, astrocytoma, ependymoma, medulloblastoma, germinoma

Radiation therapy is an effective adjunct to surgery in the treatment of incompletely resected primary neoplasms of the brain. Except for recent prospective studies in patients with anaplastic astrocytomas and glioblastoma multiforme, the efficacy of radiation therapy has been based on retrospective analyses of patients treated in single institutions. These patients have usually been collected over a long period of time and have been treated using a variety of techniques. These studies are limited by a lack of uniform criteria for selection of patients for radiation therapy and by the absence of adequate control groups of comparable non-irradiated patients.

This review will detail the rationale and results of radiation therapy in the treatment of patients with the diagnoses of astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, oligodendroglioma, ependymoma, medulloblastoma, suprasellar germinoma, pineal tumors, primary lymphoma, and cerebral neuroblastoma. A discussion of the brain volume to be irradiated and the radiation dose as commonly employed in the treatment of each histological type will be included. The volume of the brain encompassed in the radiation field is based on the biology of the tumor and patterns of recurrence observed following treatment with surgery alone or surgery and radiation therapy combined. The selection of dose is based to some degree on histology, but is limited by the tolerance of the normal brain to irradiation. This summary will therefore begin with a review of the adverse effects of therapeutic irradiation that may occur during and following irradiation for primary brain tumors.

Brain Tolerance to Therapeutic Irradiation

There is an extensive literature on the effects of ionizing radiation on the central nervous system (CNS) of experimental animals; however, most of it is of little use to the clinician. Often the radiation doses were far below those utilized in treatment of CNS neoplasms and were primarily for studies of neurophysiology. At the other extreme, unlike the fractionated doses of clinical radiation therapy, large single doses have been utilized. For many years, the human brain was considered relatively resistant to therapeutic doses of radiation. More recently, it has become necessary to modify this concept as it is now established that dose-fractionation schemes within the clinical range can produce functional changes and, occasionally, even necrosis. It is convenient, as well as prognostically and clinically useful, to consider CNS reactions to irradiation according to time of appearance: 1) acute reactions (that is, those that occur during a course of irradiation); 2) early delayed reactions that appear from a few weeks to 2 or 3 months after completion of radiation therapy; and 3) late delayed reactions that typically appear from several months to many years later.
Definitions of Abbreviations

- BTSG = Brain Tumor Study Group
- CCG = Children’s Cancer Study Group
- CSA = craniospinal axis
- ECOG = Eastern Cooperative Oncology Group
- ED = equivalent dose
- LET = linear energy transfer
- MRE = megavoltage rad equivalent
- NCOG = Northern California Oncology Group
- ret = rad equivalent therapy
- RTOG = Radiation Therapy Oncology Group
- SIOP = International Society for Pediatric Oncology
- UCSF = University of California, San Francisco

Acute Reactions

With conventional fractionation (180 to 200 rads/day given five times per week) to a total dose of 6000 rads, acute reactions are generally of little consequence. When they occur, they usually are manifested by evidence of increased intracranial pressure or an exacerbation of the symptoms or signs caused by the lesion being treated; these reactions probably are due to edema and usually respond to corticosteroid therapy. Using conventional fractionation together with prophylactic dexamethasone (Decadron), Salazar, et al.,134 gave total doses as high as 8000 rads to limited volumes without encountering acute complications.

The United States Radiation Therapy Oncology Group (RTOG)79 conducted a randomized trial which compared several dose-fractionation schemes in more than 1000 patients with brain metastases. Corticosteroid therapy was given as clinically indicated. Some patients received 10 fractions of 300 rads each in 2 weeks while others received five fractions of 400 rads in 1 week, or two fractions of 600 rads in 2 days. The various treatment regimens did equally well, indicating that, insofar as acute reactions are concerned, the larger daily fractions are acceptable, provided that total dose is reduced commensurate with increase in fraction size and that steroid therapy is allowed. Another RTOG study112 utilized 600-rad fractions given twice weekly with misonidazole to a total of 3000 rads. This regimen was also well tolerated. However, when Young, et al.,170 gave two increments of 750 rads to the whole brain they encountered an acute complication rate of 49%. The complications included headaches, nausea, vomiting, temperature elevation, and even cerebral herniation. Hindo, et al.,99 published their results with a single 1000-rad dose given to 54 patients, and reported four deaths within 48 hours and a fifth within 7 days without beneficial effects from steroid therapy. The severe and fatal complications found by both Young and Hindo occurred in the patients who had the most severe pretreatment neurological deficits, and the role of irradiation is not entirely clear.

In summary, with daily fractions of around 200 rads, total doses up to 6000 rads to the whole brain or even higher doses to limited volumes are usually tolerated without clinically significant acute reaction. With commensurate reduction of the total dose, fractions as high as 600 rads are tolerated, but larger fractions should be given with caution. Corticosteroid therapy may be of value in preventing or ameliorating symptoms, if they do occur, but there is no evidence of long-term benefit.

Early Delayed Reactions

The early delayed reaction appears from a few weeks to a few months postirradiation and is usually transient, disappearing without therapy. Probably the first description of an early delayed reaction was by Druckmann35 who, in 1929, reported that 3% of children irradiated for ringworm of the scalp developed temporary somnolence. This observation was overlooked until 1973 when Freeman, et al.,44 reported transient somnolence and lethargy in nearly 80% of children given prophylactic irradiation to the CNS for acute lymphoblastic leukemia. While these children had received only 2400 rads of whole-brain irradiation in 10 fractions over 4 weeks, they also had aggressive systemic chemotherapy and either prophylactic spinal irradiation or intrathecal methotrexate.

In 1963, Rider122 reported two patients who had received about 5500 rads in 16 or 27 fractions, and 10 weeks after radiation therapy, developed nausea, vomiting, dysarthria, dysphagia, cerebellar ataxia, nystagmus, and a positive Romberg’s sign. Recovery began after 4 weeks and was complete in 6 to 8 weeks. Boldrey and Sheline4 described adverse signs and symptoms after partial-brain radiation therapy for low-grade gliomas, menigiomas, or pituitary adenomas. The peak incidence occurred in the 2nd month after irradiation, too soon to have been a result of growth of such lesions. Furthermore, the symptoms usually disappeared within another 6 weeks without therapy.

Hoffman, et al.,76 reported a group of malignant glioma patients treated with radiation therapy plus BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) at the University of California, San Francisco (UCSF). These patients received 6000 rads with 180-rad daily fractions. Within 18 weeks after irradiation, 49% had deteriorated sufficiently to suggest that tumor progression had occurred. However, nearly 30% improved spontaneously without change of therapy. Although generally transient,49 the early delayed syndrome is occasionally progressive. Lampert, et al.,81,82 described two patients who died of brain damage 3 months after irradiation for an extracranial lesion. One patient had received 5400 rads from a cobalt-60 source in 20 fractions over 29 days while the other received 6160 megavoltage-equivalent rads in 32 days. Postmortem examination showed patchy demyelination with central necrosis and petechial hemorrhages.

The importance of recognizing the early delayed syndrome resides in the fact that generally it is transient, and the appearance of new symptoms at this time does

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not necessarily indicate treatment failure nor the need for a change in therapy.

Late Delayed Reactions

For late reactions the latent interval from irradiation to appearance of signs or symptoms varies from a few months to several years. These reactions generally are irreversible and frequently progressive. Clinical findings depend on the area and volume of brain irradiated and range from mild impairment of function to death. White matter is more radiosensitive than is gray matter. The lesion may present with loss of volume due to cerebral atrophy, as a glial reaction masquerading as an intracranial tumor, or as a low-density enhancing or mineralized area on a computerized tomography (CT) scan.

There is an extensive literature on radiation-induced brain necrosis.41,73,90,95,148 However, nearly all studies have failed to relate the number of such injuries to the population at risk, so it usually is impossible to calculate incidence as a function of dose, number of fractions, or treatment time. In 1968, Kramer35 reviewed the world literature for the preceding 37 years and found 57 cases qualifying as radiation necrosis of the brain. Kramer concluded that the normal brain will "ordinarily tolerate a tissue dose of 6500 to 7000 rads in 6 to 8 weeks delivered by 5 daily fractions per week using supravoltage techniques." He noted that such doses occasionally produced brain necrosis.

Sheline, et al.,148 presented another review, based on 80 patients, of therapeutic irradiation and brain injury. In 68 patients, the diagnosis of necrosis had been confirmed by tissue analysis. Of the other 12 patients, four had been irradiated for an extracranial lesion and in eight the brain injury was sufficiently distant from the brain tumor that the injury could not be explained by the presence of the tumor itself. All reported doses were converted to megavoltage rad equivalents (MRE's) and a log-log diagram was constructed in which MRE was plotted against number of fractions. A line was drawn such that most of the points were either on or above it. In essence, this line represents the approximate threshold at which brain necrosis had been reported but, as with other such analyses, this method gives no indication as to the incidence of necrosis with a given dose-fractionation schedule. The threshold doses, as obtained from this plot, were approximately 4500 rads for 10 fractions, 5600 rads for 35 fractions, and 7000 rads for 60 fractions. The slope of the line was 0.44. Utilizing an isoeffect formula similar in form to the NSD* formula of Ellis,38 the slope should equal the sum of the exponents for N (number of fractions) and T (total time in days). If, as suggested by other studies,111 the T exponent is approximately 0.03, then our review would indicate an exponent of 0.41 for N. Thus, the isoeffective dose appears related to the total dose x N -0.41 x T -0.03; or, the isoeffective dose is D x N -0.41 x T -0.03. Whether this formula is applicable at very small or very large numbers of fractions or very short or long overall times remains to be seen, but it does appear to be appropriate over the usual clinically used fraction numbers and times.

A review by Marks, et al.,95 of 139 consecutive patients irradiated for brain tumors with total doses of at least 4500 rads (180 to 200 rads/day; five fractions/week; one field/day) disclosed seven instances of proven brain necrosis. They utilized the formula, equivalent dose (ED) = D x N -0.377 x T -0.038, for calculating ED's. With an ED of 1250 or less there was no necrosis in 51 patients; with an ED between 1251 and 1330 there were two cases of necrosis among 60 patients. The incidence of necrosis in the ED range of 1331 to 1460 was five among 28 patients. If one assumes a daily dose of 180 rads given five times per week, these ED values can be converted into total dose (in rads) for such a treatment regimen. The results of such a calculation are shown in Table 1.

The extent to which chemotherapeutic agents influence the production of radiation necrosis is poorly documented; however, there is evidence suggesting that certain agents do play a significant role. For example, children with acute lymphoblastic leukemia treated with aggressive chemotherapy, both intravenous and intrathecal, plus prophylactic brain irradiation have developed brain damage with doses as low as 2400 rads in 150- to 200-rad fractions which, without chemotherapy, are thought to be far below tolerance levels. Burger, et al.,17 reported five cases of radiation necrosis of the brain or brain stem after administration of 6000 rads in 180- to 200-rad fractions. Four of these five patients had received seven to 10 courses of BCNU, procarbazine, or dibromodulcitol. Pratt, et al.,114 reported a case of fatal cerebral necrosis after administration of 3000 rads in 10 fractions plus multi-agent chemotherapy;

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<th>Equivalent Dose (ED)*</th>
<th>Dose (rad)‡</th>
<th>Incidence of Necrosis‡</th>
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<tr>
<td>≤ 1250</td>
<td>≤ 5760</td>
<td>0/51</td>
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<tr>
<td>1251-1330</td>
<td>5761-6480</td>
<td>2/60</td>
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<tr>
<td>1331-1460</td>
<td>6481-7560</td>
<td>5/28</td>
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* NSD = D x N -0.24 x T -0.11 where D = total radiation dose in rads, N = number of treatment fractions, and T = total time of treatment in days. The NSD is expressed in "ret" (rad equivalent therapy). Such formulas are used in an effort to compare the biological effectiveness of different dose-fractionation schemes.
again, this was a dose that one would expect to be tolerated. Edwards and Wilson reviewed the literature on treatment of radiation necrosis of the brain and concluded that resection of focal necrosis is often efficacious and may be life-saving. They also found that administration of corticosteroids was an effective adjunct to surgical therapy and, in some instances, was effective as primary treatment. Of the 80 patients reviewed by Sheline, et al., 35 had some type of surgical procedure for their necrosis. Nineteen patients reportedly benefited from the surgical intervention; nine of the 19 had superficial necrosis and were among the 11 patients irradiated for skin cancer. With the reduction in morbidity associated with modern neurosurgical techniques, more patients would probably benefit from resection of surgically accessible necrotic lesions.

**Astrocytoma and Glioblastoma Multiforme**

**Classification**

In the initial United States Armed Forces Institute of Pathology fascicle on tumors of the CNS, published in 1952, Kernohan and Sayre stated that “prior to 1926 there was great confusion in the classification and nomenclature of gliomas.” Unfortunately, the confusion remains. In 1926, Bailey and Cushing had proposed a classification system for gliomas; this system, based on presumed histogenesis, became widely accepted. It recognized entities such as astrocytoma, astroblastoma, spongioblastoma polare, and glioblastoma multiforme. In 1949, Kernohan, et al. proposed a new classification system based on the assumption that the gliomas were derived from astrocytes, ependymal cells, or oligodendrogliocytes and that prognostic differences within each cell type were related to the degree of anaplasia. In their opinion, an astrocytoma or a glioblastoma multiforme represented different degrees of astrocytic dedifferentiation. In the Kernohan system the term “astrocytoma,” as used in prior classification systems, was replaced by astrocytoma grade 1; astroblastoma became astrocytoma grade 2; and glioblastoma multiforme became astrocytoma grade 3 or 4. Evaluation of anaplasia was based on the extent of pleomorphism, hyperchromatism, and number of mitotic figures. A similar approach to grading was advocated for ependymomas and oligodendrogliomas. The grading system was introduced into the first Armed Forces Institute of Pathology fascicle on CNS tumors, edited by Kernohan and Sayre. Thus, by the early 1950’s, two distinctly different classification systems were in use. To further complicate matters, some authors have used the Bailey-Cushing concept of glioblastoma multiforme to be synonymous with the Kernohan grade 4 astrocytoma, while others have (as advocated by Kernohan and Sayre) lumped grades 3 and 4 under this term. In practice, the grading system, as generally applied, has correlated poorly with prognosis: in some reported studies grade 1 is associated with a better survival rate than is grade 2, whereas the reverse is true in other studies. Furthermore, survival rate does not correlate with grade 3 compared with 4 in any of the recent randomized trials of malignant gliomas. However, as will be seen, histological features are of prognostic significance.

**Astrocytoma**

There has been no randomized clinical trial evaluating radiation therapy for treatment of astrocytoma. Some authors have reported survival rates for patients who received radiotherapy, but have not included a comparable non-irradiated control group. Others have presented results for selected groups of irradiated or non-irradiated patients. The records of 122 consecutive patients with astrocytoma treated at UCSF were reviewed. In 14 of these patients, predominantly with cerebellar astrocytoma in childhood, the tumors were thought to have been completely excised. Of the 108 patients with incompletely resected tumors, 71 received postoperative radiotherapy whereas the other 37 did not. A number of reviews have shown that, apart from the question of the role of radiotherapy, the important prognostic variables for astrocytomas are: age (younger patients do better); performance status; extent of resection; and histological diagnosis. Performance status could not be detailed in this retrospective review. Extent of resection was similar in the groups that did or did not receive radiotherapy. Twenty-two percent of the group with surgery only and 30% of the group with surgery plus radiotherapy were less than 20 years of age. The usual planned tumor dose was 5000 to 5500 rads given in 180-rad fractions, five fractions per week. The overall 5-year recurrence-free survival rate for incomplete resection alone was 19% versus 46% for incomplete resection plus radiotherapy. The 10-year survival rates were 11% and 35%, respectively. For adults, the 5-year actuarial survival rates were 10% (three of 29) for surgery alone versus 32% (16 of 50) when radiotherapy was added. One histological subgroup, namely gemistocytic astrocytoma, had a particularly poor prognosis, with only one of the seven irradiated patients and none of the four non-irradiated patients surviving 5 years. When the grading system was applied retrospectively (Table 2), patients with astrocytoma grade 1 did better than those with grade 2, and in each

<table>
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<tr>
<th>Astrocytoma Grade</th>
<th>No. of Cases</th>
<th>With Radiotherapy</th>
<th>Without Radiotherapy</th>
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<tr>
<td>1</td>
<td>80</td>
<td>58%</td>
<td>25%</td>
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<tr>
<td>2</td>
<td>28</td>
<td>25%</td>
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* Retrospective analysis of 108 cases treated at the University of California, San Francisco, between 1942 and 1967: 71 patients received radiation therapy and 37 did not.
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grade the irradiated patients had better 5-year survival rates than the non-irradiated groups.

Marsa, et al.\(^\text{96}\) described a 41% actuarial 5-year survival rate in a group of 40 patients, mostly adults, with irradiated hemispheric astrocytomas. Fazekas\(^\text{86}\) compared a group of 32 patients who had had incomplete excision plus adjuvant irradiation with a group of 15 who had had complete excision alone. The actuarial 5-year survival rate was 41% with radiation therapy versus 13% without; some of these patients were children. Based on the Kernohan grading system,\(^\text{69,70}\) the 5-year survival rates were 20% for grade 1 versus 53% for grade 2, Bloom\(^\text{11}\) reported on 120 adult patients with irradiated supratentorial low-grade astrocytoma treated at the Royal Marsden Hospital, in whom the 5-year survival rates were 33% for grade 1 and 21% for grade 2.\(^\text{69,70}\) Survival rates decreased to 16% and 6%, respectively, at 10 years. For patients (including children) with low-grade supratentorial astrocytoma, Laws, et al.\(^\text{85}\) recorded 5-year survival rates of 49% for patients receiving at least 4000 rads compared with 34% for those with less or no irradiation (\(p = 0.05\)). They found that “radiation therapy was of clear benefit, primarily in older patients with incompletely removed tumors.”

Although a prospective randomized trial evaluating radiotherapy for low-grade astrocytomas has not been performed, the available data suggest that for incompletely resected lesions, postoperative radiotherapy improves 5- and 10-year survival rates. However, even with radiation therapy, current survival rates leave much to be desired. Nevertheless, with these potentially fatal but rather slowly progressive lesions, Bloom\(^\text{1}\) correctly cautions against high-dose and large-volume brain irradiation “because of the possible risk of serious brain injury occurring before tumor recurrence.”

Anaplastic Astrocytoma and Glioblastoma Multiforme

A distinction should be made between anaplastic astrocytoma and glioblastoma multiforme. As will be seen, if the distinction is properly made there is a difference in prognosis for the two entities. The difference, however, is lost when these lesions are classified according to the grading system.

A retrospective study at UCSF showed a 5-year recurrence-free survival rate of 18% for patients with postoperatively irradiated anaplastic astrocytoma (malignant astrocytoma) versus 0% for those with glioblastoma multiforme.\(^\text{144}\) Marsa, et al.\(^\text{96}\) had a similar experience, reporting a mean survival time of 20 months for malignant astrocytoma versus 9 months for glioblastoma multiforme and 5-year actuarial survival rates of 19% and 0%, respectively. Kramer\(^\text{77}\) reported a 22% 5-year survival rate for patients with anaplastic astrocytoma. These lesions were reported as astrocytoma grade 3. However, Kramer believes the reason his results are similar to those at UCSF, those at Stanford, and those to be described for the RTOG trial is that the pathologist at his institution actually applied the histological criteria of anaplastic astrocytoma rather than those enumerated by Kernohan for the grading system (S Kramer, personal communication, 1983).

The joint randomized trial of the RTOG and the Eastern Cooperative Oncology Group (ECOG), detailed later,\(^\text{22}\) found an improved survival rate for patients with astrocytoma with anaplastic features compared with that for glioblastoma multiforme, but failed to find a difference in survival when the tumors were classified according to the Kernohan grading system.\(^\text{107}\) Interestingly, a recent review from the Mayo clinic\(^\text{138}\) found no difference in survival rates for patients with astrocytoma grade 3 or 4. It appears that, as a prognostic indicator, the grading system is less effective than some form of histogenetic classification.

In 1969, the United States Brain Tumor Study Group (BTSG)\(^\text{162}\) initiated a postoperative prospective randomized clinical trial for patients with malignant gliomas. The four arms of the study were: 1) supportive therapy only; 2) BCNU, 80 mg/sq m intravenously on 3 successive days, repeated every 6 to 8 weeks; 3) whole-brain radiotherapy with 170 to 200 rads/day, 5 days/week to a total of 5000 to 6000 rads; and 4) BCNU plus radiotherapy. Two hundred and twenty-two patients were entered into the study; 90% were classified as having glioblastoma multiforme and 9% as having anaplastic astrocytoma. The approximate median survival times in weeks were: supportive care, 14; BCNU, 19; radiotherapy, 36; and BCNU plus radiotherapy, 35. The difference in survival time between radiotherapy and either supportive care or BCNU was significant (\(p = 0.001\)). Thus, for the first time in a randomized trial, it was shown that radiotherapy significantly increased the median survival time for patients with glioblastoma multiforme. The 12-month survival rates were 3%, 12%, 24%, and 32%, respectively.

A subsequent BTSG randomized trial\(^\text{163}\) compared semustine (methyl-1-(2-chloroethyl)-1-nitrosourea: MeCCNU), radiotherapy, BCNU plus radiotherapy, and MeCCNU plus radiotherapy in 467 patients (84% with glioblastoma multiforme, 11% with malignant or anaplastic astrocytoma, and 5% with miscellaneous malignant gliomas). Median survival times were 31, 37, 49, and 43 weeks, respectively. Two-year survival rates were 17%, 14%, 19%, and 19%, respectively. The group receiving BCNU plus radiotherapy had the best survival data, but the difference between this therapy and either radiotherapy alone or radiotherapy plus MeCCNU was not statistically significant. Another BTSG study\(^\text{81}\) randomized 609 patients (87% with glioblastoma multiforme, 11% with malignant astrocytoma, and 2% with miscellaneous malignant gliomas) to receive postoperative radiotherapy plus either BCNU, procarbazine, high-dose methylprednisolone, or BCNU plus methylprednisolone. The survival data of the groups receiving radiotherapy plus either procarbazine or BCNU was significantly better (\(p \leq 0.05\)) than that of the group receiving radiotherapy plus methylprednisolone. The
survival curves of the groups treated with procarbazine and BCNU were virtually identical; the median survival times for the valid study group were 50 weeks for BCNU versus 47 weeks for procarbazine. The addition of methylprednisolone to BCNU did not improve the results of BCNU alone. Assuming that the effect of radiotherapy plus methylprednisolone was similar to that of radiotherapy alone (that is, methylprednisolone did not influence the results) and combining data from these studies, it was concluded that BCNU, when added to radiotherapy, gave an additional modest improvement in survival times.21

While the BTSG trials were being conducted, a joint study of the RTOG and ECOG was underway.22 Between 1975 and 1979, this study randomly assigned 626 patients with malignant gliomas to one of the following treatment options: 1) 6000 rads/6 to 7 weeks administered to the whole brain; 2) 6000 rads given to the whole brain plus a boost of 1000 rads in 1 week directed to the tumor volume; 3) 6000 rads given to the whole brain plus BCNU; and 4) 6000 rads given to the whole brain plus MeCCNU and dacarbazine (DTIC). The radiation dose of 7000 rads yielded essentially the same survival times as did the lower dose of 6000 rads. The survival curves for patients receiving either radiation and BCNU or radiotherapy, DTIC, and MeCCNU were better than those for radiation alone. However, the only significant difference occurred in the 40- to 60-year age range, where the patients treated with BCNU plus radiotherapy had a significantly increased (p = 0.01) survival time compared with patients who received irradiation alone. The 40- to 60-year-old patients receiving MeCCNU plus DTIC and radiotherapy also did better (p = 0.04) than the similar age group treated with irradiation alone, but this protocol was considerably more toxic than BCNU. Neither chemotherapy regimen improved survival time for patients younger than 40 or older than 60 years of age.

Levin, et al.,19 reported a randomized clinical trial of the Northern California Oncology Group (NCOG) in which radiation therapy plus BCNU was compared to radiation therapy plus BCNU and hydroxyurea. The radiation therapy was conventionally fractionated (170 to 200 rads/day). The whole brain received 5000 rads and the tumor volume an additional 1000-rad boost. For patients with glioblastoma multiforme, the median time to tumor progression was 41 weeks for those receiving hydroxyurea versus 31 weeks for those without (p = 0.03).

Prognostic Variables

In addition to establishing the value of radiotherapy and certain chemotherapeutic regimens, these randomized trials disclosed several important prognostic variables. The RTOG/ECOG study identified age as an important prognostic factor. For patients of less than 40, 40 to 60, or greater than 60 years of age, the 18-month survival rates were 64%, 20%, and 8%, respectively.22 The combined BTSG studies also identified an age effect.18 Patients aged less than 45, 45 to 54, 55 to 64, or 65 years or older had relative death rates of 1, 1.75, 2.5, and 3.5, respectively. A multivariate analysis, with adjustment for duration of symptoms, performance status, and histological tumor type as well as other identified prognostic variables, showed "the effect of age is so strong that it adds important prognostic information not explained by the other variables."

Another important variable was the functional performance status. In the RTOG/ECOG study, patients with a Karnofsky performance scale score of 70 to 100 had a median survival time of 12 weeks, and 34% survived 18 months; with a rating of 40 to 60, the median survival was only 6 weeks, and 13% survived 18 months.22 Review of the BTSG trials showed that for Karnofsky ratings of 90 to 100, 70 to 80, 50 to 60, and 10 to 40 the relative death rates were 1, 1.4, 2.0, and 2.9.18

The third important variable was histological diagnosis. In the BTSG trials18 the death rate for patients with glioblastoma multiforme was 1.5 to 2.0 times higher than for those with other malignant gliomas (the ratio varied from BTSG study to study). Nelson, et al.,10 reviewed biopsy material from 503 patients in the RTOG/ECOG trial. When the grading system was applied, the median survival times for astrocytoma grade 3 (10 months) and grade 4 (9 months) were virtually identical. When these patients were separated into groups of astrocytoma with anaplastic foci versus glioblastoma multiforme, marked differences in both median survival times and 18-month survival rates were found. The median survival time for anaplastic astrocytoma was 28 months versus 8 months for glioblastoma multiforme. Survival rates at 18 months were 62% and 15%, respectively. In this review, the feature used to distinguish astrocytoma with anaplastic features from glioblastoma multiforme was the presence in the latter of foci of coagulation necrosis involving astrocytic tumor cells.

In summary, although other factors such as a history of seizures, duration of symptoms, and occurrence of neurological abnormalities may correlate to some extent with prognosis, it is clear that age, performance status, and histological category are strong prognostic variables. When comparing results within or between randomized studies, it is important either to insure that the subsets being compared are in fact comparable, or that, utilizing information about prognostic factors, an adjustment for differences in composition of the subsets has been made. This is, of course, even more important when using data from non-randomized studies.

Hypoxia

It has been established that hypoxia protects cells against irradiation and it is thought that malignant gliomas contain areas of hypoxic but viable tumor cells. Various methods to circumvent the presumed protective effects of hypoxia have been studied. These studies include irradiation under hyperbaric oxygen condi-
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... high linear energy transfer (LET) irradiation, and hypoxic cell radiosensitizers. To date, none of these approaches has improved the survival results of radiotherapy alone.

The fact that, for cell kill, high LET radiations such as fast neutrons and some heavy ions are less dependent on oxygen tension than low LET photon radiation has led to clinical trials with such beams. Neutron irradiation, in doses thought biologically equivalent to those used in conventional photon radiotherapy, did increase local tumor control rate; however, many patients died of brain damage and survival rates were not improved. Similarly, preliminary trials with heavy ion radiotherapy have not proved efficacious.

Certain electron-affinic chemicals serve as substitutes for oxygen in fixing DNA damage caused by radiation. These compounds, which have the advantage over oxygen of not being metabolized while diffusing through tissue, increase the radiosensitivity of hypoxic cells without a corresponding sensitization of euoxic cells. To date, results for two electron-affinic radiosensitizers have been reported. These include a 5-nitroimidazole (metronidazole) and a 2-nitroimidazole (misonidazole). So far, these agents have failed to improve the results of radiation therapy alone. If radiosensitizers are to be useful for malignant gliomas, either a different scheme of utilization or a more effective agent is necessary.

**Unconventional Fractionation**

Several clinical trials have been conducted with unconventional radiation fractionation regimens. The BTSG tried 110 rads twice a day, 5 days a week to a total of 6600 rads in 6 weeks without improving the results obtained with 6000 rads given at 180 to 200 rads once a day. In a randomized trial of 134 patients with glioblastoma multiforme (grades 3 and 4), Simpson and Platts compared protocols with 8- versus 24-hour intervals between treatments. Treatment extended over either 7 or 21 days and total doses were either 3000 or 4000 rads. There was no difference in survival times between patients receiving the thrice-daily versus the once-daily fractionation schedules. However, the number of patients in each of the nine subgroups was small, ranging from seven to 28 patients, and total doses were low; thus, conclusions from this study are questionable.

Payne, et al., carried out a prospective randomized trial of 157 patients with malignant astrocytoma (grade 3 and 4). Patients were stratified according to sex, age, extent of surgery, tumor site, and performance status. All patients received CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) and hydroxyurea. One group received 5000 rads in 25 fractions over 5 weeks. The second group received 3600 to 4000 rads in 36 to 40 fractions of 100 rads each given four times per day for 2 weeks. There was neither a survival nor a toxicity difference between the two groups.

Douglas and Worth treated 30 patients with astrocytoma grade 3, astrocytoma grade 4, or glioblastoma multiforme with three 100-rad fractions per day. Survival with the hyperfractionated radiotherapy was significantly longer than that for a conventionally fractionated historical control group. However, the small number of patients, use of historical controls, and failure to control prognostic variables renders this trial uninterpretable. Shin, et al., randomly assigned 69 patients with grade 3 and 4 astrocytoma to receive either hyperfractionated or conventionally fractionated radiotherapy. Each group received a total of 5000 rads. The hyperfractionated group received 50 fractions in 4 weeks. The 1-year actuarial survival rate was 54% versus 32%, and the median survival time was 13 months versus 9 months for the hyperfractionated versus the conventionally fractionated groups, respectively. The difference between the two groups, however, was not significant (p = 0.05) and could be accounted for by small numbers and an imbalance in age, performance status, and tumor grade. Fulton, et al., recently reported a study suggesting that hyperfractionation plus acceleration (reduction of overall treatment time) may make a difference in survival data. They compared a regimen of 89 rads three times per day (with or without misonidazole) to a total of 6140 rads (over 4½ weeks) to a course of 193 rads once per day to a total of 5800 rads (over 6 weeks). They found median survival times of 29 weeks for conventional fractionation versus 45 and 50 weeks for the multiple daily fractionation; the difference was significant (p = 0.002). Even though the survival time for patients receiving conventional fractionation was unusually low, this is the most convincing study of the value of hyperfractionation. However, since other studies have been negative or the differences have not been statistically significant, these results require confirmation.

**Tissue Volume for Irradiation**

Opinions differ regarding the tissue volume that should be treated for malignant glioma. Concannon, et al., compared the tumor volume identified at post-mortem examination with the volume previously treated by radiotherapy (on the basis of the available radiographic examinations) and found that the treatment volume included the gross tumor plus a 1-cm margin of brain tissue in only 10% of the patients. Kramer subsequently recommended that for malignant gliomas, including grades 2 through 4, the entire intracranial contents should be irradiated. Influenced by such recommendations and because of difficulties in defining tumor volume, many of the major randomized clinical trials (for example, those of the BTSG and the RTOG/ECOG) utilized whole-brain irradiation. However, convincing evidence for the superiority of whole-brain irradiation over “generous volume” irradiation is lacking. Sheline used limited fields and reported a median survival time of 10 months for patients with glioblastoma multiforme, a survival time comparable to that obtained with whole-brain radiotherapy in the BTSG and RTOG/ECOG studies. Fos-
sati, et al.\textsuperscript{43} found a 2-year survival rate of 4% for whole-brain irradiation versus 27% for focal irradiation. Payne, et al.,\textsuperscript{110} treated some patients with whole-brain irradiation and others with fields in the order of 10 × 12 cm and concluded that treating less than the total cranial volume did not compromise the results. Ramsey and Brand\textsuperscript{118} randomly assigned 34 patients to either limited-field or whole-brain irradiation, and found an increase in survival time and tumor-free interval in the limited-field treatment group; they thought the better results were due to the higher dose being possible because of the ability to avoid radiosensitive brain-stem structures. The clinical trials of Urtasun, et al.,\textsuperscript{159} Bleehen, et al.,\textsuperscript{10} and the MRC Working Party\textsuperscript{104} used large volumes (about two-thirds of the brain) but not whole-brain treatment. The survival data from these studies are similar to those from groups using whole-brain fields. At least until control of the primary tumor has improved, there seems no compelling reason to treat the whole brain.

Hochberg and Pruitt\textsuperscript{58} compared information from CT scans performed within 2 months before death with postmortem findings. The CT scans defined both the gross and microscopic tumor extent within a 2-cm margin in 80% of patients. Only one of 35 autopsied patients showed microscopic infiltration more than 2 cm beyond the tumor margin indicated on the CT scan. The major source of error was subependymal spread, which occurred in 15% of cases. Multicentricity occurred in 4% to 6% of patients, and in each case was identified by CT scanning. Serial CT scans in 42 patients showed that recurrences were within a 2-cm margin of the primary site in 90% of patients. Hochberg and Pruitt thought that current precision of CT scanning might permit smaller-field higher-dose radiotherapy. Recently both the RTOG and NCOG have adopted clinical trial protocols using less than whole-brain radiotherapy. Patients at UCSF are being treated with generous margins, in the order of 2 to 3 cm around the enhancing lesion seen on the CT scan. Limiting the irradiated volume is important if, without missing tumor, it permits avoidance of tissues that if injured may cause significant morbidity, loss of function, or death. We believe that, with radiation doses currently in use, especially in conjunction with chemotherapy, patients often experience a loss of intellectual capacity and occasionally sustain more overt injury such as brain-stem necrosis.

**Radiation Dose**

Selection of the proper radiation dose for malignant gliomas has been as controversial as selection of the appropriate volume. In a retrospective review of Mayo Clinic data, Scanlon and Taylor\textsuperscript{138} found that patients receiving less than 1400 rads did as well as those receiving higher doses. In a small series treated at the Royal Marsden Hospital, survival times appeared to decrease with an increase in dose from 5000 rads in 5 weeks to 7500 rads in 6 weeks.\textsuperscript{11} On the other hand, Salazar, et al.,\textsuperscript{133} found an increase in survival time as the total dose was increased from a median of 5000 to 6000 rads and to 7500 rads. For patients with grade 4 gliomas the median survival times for the three dose groups were 30, 42, and 56 weeks, respectively. The corresponding survival times for patients with grade 3 tumors were 43, 82, and 204 weeks, respectively. These data, however, must be accepted with caution for the following reasons: 1) the number of patients in each group is very small; 2) the groups were treated chronologically not concurrently; 3) there was no consideration of distribution of prognostic variables among the three dose groups; and 4) approximately one-fifth of the patients in the series did not complete radiotherapy and were excluded from the analysis. Furthermore, doses in the 7000- to 8000-rad range (conventionally fractionated) may well yield more damage than benefit unless carefully restricted to a limited volume. Salazar, et al., did note peritumoral radionecrosis and that quality of life in their high-dose group, as indicated by performance status, declined steadily after radiotherapy. Also, general debilitation was evident by 18 to 24 months postirradiation in their patients who received the high dose.

Two studies, one by the BTSG and the other by the RTOG/ECOG, examined the question of optimum dose in large prospective randomized clinical trials. In these trials the single daily dose was 180 to 200 rads, given five times per week, to a total of 4500 to 7000 rads. The BTSG analyzed the data from 621 patients treated between 1966 and 1975.\textsuperscript{164} These patients were divided into three groups with median doses of 5000, 5500, and 6000 rads. The median survival times were 28, 36, and 42 weeks, respectively. The difference in survival times for doses of 5000 and 6000 rads was significant (p = 0.004). Patient population characteristics (sex, age, percent of patients with glioblastoma multiforme, interval from first symptom to treatment, initial performance status, and percent of patients who received chemotherapy) were comparable in the three dose groups. Since nearly 90% of the patients in the BTSG study had glioblastoma multiforme, this dose response applies to glioblastoma multiforme but not necessarily to other malignant gliomas. As described earlier, the RTOG/ECOG study compared 6000-rad whole-brain irradiation to a 6000-rad whole-brain regimen plus a booster dose of 1000 rads to the tumor volume.\textsuperscript{22} Survival data with the 7000-rad dose were not significantly better than with the lower dose. Combining the results of the BTSG and the RTOG/ECOG trials indicates that, with single daily fractions of 180 to 200 rads, given five times per week, the optimum dose for glioblastoma multiforme is about 6000 rads. Presumably the optimum dose for anaplastic astrocytoma is similar, but this is yet to be proven.

**Interstitial Irradiation**

During the last 5 years, interstitial brachytherapy has been employed at UCSF\textsuperscript{52,86} for the treatment of recurrent malignant brain tumors. Computerized tomogra-
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Phy has been used both to determine the volume for treatment and to develop coordinates for the stereotactic placement of removable afterloaded catheters. High-activity (30 to 50 mCi) iodine-125 ($^{125}$I) sources are implanted into the tumor via up to four catheters, depending on the size of the lesion. Forty-one patients with gliomas who developed recurrence following radiation therapy with or without chemotherapy have undergone implantation and have been followed for a minimum of 1 year. These patients received a minimum tumor dose of 8000 to 12,000 rads, calculated at the periphery of the contrast-enhancing volume. Twenty-one patients had a favorable clinical or CT-documented response lasting from 5 to 53 months. Stabilization of disease was achieved in six patients for 4 to 48 months. In 14 patients the lesion continued to enlarge. However, many of the latter patients were found at reoperation to have radiation necrosis, and it would appear that standard clinical and CT response criteria fail to distinguish necrosis from tumor growth.

The median survival time of patients with recurrent glioblastoma multiforme selected for implantation was 35 weeks. The median survival time of patients with anaplastic astrocytoma has not been reached, and the 3-year survival rate is 65%. Encouraged by these results, a prospective study has been initiated for previously untreated patients with malignant gliomas. Patients receive 6000 rads (180 to 200 rads/day) of external radiation in combination with hydroxyurea. This is followed by a $^{125}$I implant to deliver an additional 6000 rads over 4 to 6 days to the periphery of the contrast-enhancing volume. Subsequently, these patients receive multi-agent chemotherapy in the form of procarbazine, cyclophosphamide, and vincristine. About one-third of patients develop symptomatic radiation necrosis requiring surgical debulking of necrotic tissue. Results of this study are too preliminary for presentation at this time.

Oligodendroglioma

There has been no randomized clinical trial evaluating radiotherapy for oligodendrogliomas. The available studies include small numbers and are retrospective, non-controlled, and contradictory. We reported a retrospective review of 32 patients with oligodendrogliomas who survived the immediate postoperative period. Sixteen received postoperative irradiation, whereas 16 did not. The records disclosed no recognizable selection factors; specifically, there was no correlation between the use of irradiation and tumor location, completeness of resection, histological diagnosis, patients' age, duration of symptoms, or presence of tumor calcification. The 5- and 10-year survival rates were 85% (11 of 13 patients) and 55% (six of 11 patients) with radiation therapy, and 31% (four of 13 patients) and 25% (two of eight patients) without. The difference at 5 years was statistically significant ($p = 0.02$). The survival differences together with the absence of discernible bias in treatment selection led us to believe that radiation therapy at least extended survival times.

Neumann, et al.,$^{108}$ reviewed the experience with oligodendrogliomas at the University of Bonn and concluded that radiation therapy is useless. This report, however, failed to specify radiation dose or technique. It is also unclear as to the characteristics of the irradiated versus non-irradiated patients and tumors. In their Group I patients, the average survival time after irradiation was 3.5 years versus 5 years for those not irradiated. In Group II, survival for radiotherapy was 2 years versus 4 years for no radiotherapy. The fact that the irradiated patients actually did worse than the non-irradiated group suggests that the irradiation technique was faulty or that the patients with the poorer prognoses were selected for irradiation.

A recent paper presenting the Cleveland Clinic experience,$^{120}$ failed to find a difference in survival times for patients who did or did not receive radiotherapy. Although the authors of this report indicated an awareness that certain factors may be of prognostic significance, no effort was made to compare patient characteristics for the two treatment groups.

Chin, et al.,$^{24}$ reported the experience with cerebral oligodendrogliomas at McGill University Hospitals. Again, there is little consideration as to why some patients were selected to receive irradiation except that the majority were said to have been referred because of "incomplete radical resection." The irradiated patients received 5300 to 7000 rads over 7 to 9 weeks. The 5-year survival rate for surgery alone was 82% (nine of 11 patients); however, only 45% (five of the 11) were recurrence-free. For the 24 patients receiving irradiation, the 5-year survival rate was 100%, and 79% were recurrence-free. Chin, et al., concluded that postoperative radiotherapy is indicated in most cases.

A prospective randomized trial looking at the role of radiation therapy for treatment of oligodendrogliomas would be useful. However, there is no indication that such a study will be conducted in the near future. In the meantime, based on our experience fortified by that from the Montreal group,$^{24}$ it is our practice to give postoperative radiotherapy to these patients. Our approach uses generous but less than whole-brain target volumes, giving approximately 180 rads/day, treating all radiation fields at each treatment session, and going to a total dose of about 5500 rads in 6 weeks.

Intracranial Ependymoma

Intracranial ependymomas occur most frequently in children and young adults, but also later in life.$^{15}$ These neoplasms are derived from ependymal cells and are among the most radiosensitive of the gliomas.$^{146}$ The majority (60% to 74%) of intracranial ependymomas arise below the tentorium,$^{42,80,123,156}$ and most occur in the midline of the fourth ventricle.$^{80}$ One-third of fourth ventricle tumors extend through the foramen

Ependymoma: 5-year survival rates

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>Treatment</th>
<th>Supratent. (%)</th>
<th>Infratent. (%)</th>
<th>All Sites (%)</th>
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<td>35</td>
<td>S</td>
<td>25</td>
<td>17</td>
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<td>S</td>
<td>15</td>
<td>35</td>
<td>27†</td>
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<td>12</td>
<td>S</td>
<td>0</td>
<td>25</td>
<td>17</td>
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<td>28</td>
<td>S + RT</td>
<td>42</td>
<td>69</td>
<td>56</td>
</tr>
<tr>
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<td>15</td>
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<td>90</td>
<td>87</td>
</tr>
<tr>
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<td>16</td>
<td>S + RT</td>
<td>33</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>Kim &amp; Fayos, 1977</td>
<td>32</td>
<td>S + RT</td>
<td>46</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>≥4500 rads</td>
<td></td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>Bouchard, 1980</td>
<td>20</td>
<td>S + RT</td>
<td>65</td>
<td>100</td>
<td>70</td>
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<td>Glanzmann, et al., 1980</td>
<td>24</td>
<td>S + RT</td>
<td>46</td>
<td>72</td>
<td>60</td>
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<tr>
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<td>S + RT</td>
<td>35</td>
<td>59</td>
<td>38</td>
</tr>
<tr>
<td>Chin, et al., 1982</td>
<td>16</td>
<td>S + RT</td>
<td>34</td>
<td>47</td>
<td>37</td>
</tr>
<tr>
<td>Garrett &amp; Simpson, 1983</td>
<td>50</td>
<td>S + RT</td>
<td></td>
<td></td>
<td>43</td>
</tr>
</tbody>
</table>

* Supratent. = supratentorial tumor; infratent. = infratentorial tumor; S = surgery only (operative deaths are excluded in survival figures); S + RT = surgery and radiation therapy; — = data not available.  
† Two of the nine patients surviving at 5 years had evidence of recurrence and died within the following 6 months.

Ependymoma: influence of tumor grade on prognosis

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>5-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-Grade</td>
<td>High-Grade</td>
</tr>
<tr>
<td>Bloom &amp; Walsh, 1975</td>
<td>31</td>
<td>83</td>
</tr>
<tr>
<td>Salazar, et al., 1975</td>
<td>28</td>
<td>63</td>
</tr>
<tr>
<td>Sheline, 1975</td>
<td>14</td>
<td>78</td>
</tr>
<tr>
<td>Kim &amp; Fayos, 1977</td>
<td>32</td>
<td>68</td>
</tr>
<tr>
<td>Chin, et al., 1982</td>
<td>16</td>
<td>71</td>
</tr>
<tr>
<td>Salazar, et al., 1983*</td>
<td>16</td>
<td>67</td>
</tr>
</tbody>
</table>

* Whole-brain irradiation for low-grade tumors, craniospinal irradiation for high-grade tumors.

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47 patients with intracranial ependymomas. In 754 cases collected from the literature, Salazar\(^{129}\) reported a 12% incidence of seeding from intracranial ependymomas. Symptomatic seeding occurred in 3% of all patients compared with an incidence of 30% in autopsy cases.\(^{132}\) The actual incidence, however, is difficult to determine and is subject to the methodology of selection and assessment. Obviously, autopsied patients are a selected group, comprising those who have failed treatment and have undergone a postmortem examination. In a recent review of 20 patients treated at UCSF (80% with ependymoma, 20% with anaplastic ependymoma), the only patient who developed spinal seeding also had tumor at the primary site, and it is uncertain when the metastasis occurred (GE Sheline, \textit{et al.}, unpublished data, 1985). In contrast, Kim and Fayos\(^{71}\) reported clinical and radiographic evidence of subarachnoid seeding in seven of 32 patients treated via small local fields. However, six of the seven had poorly differentiated lesions, five of which were infratentorial in origin. Furthermore, five of the seven patients had simultaneous recurrence at the primary site. The high incidence of seeding in this series may be related to the finding that 21 patients (65%) had poorly differentiated ependymomas.

In an attempt to define patients at high risk of spinal subarachnoid seeding, data from four reports have been grouped according to tumor location and degree of malignancy (Table 5). This analysis indicates that patients with high-grade infratentorial ependymomas have a relatively high risk (26%) of seeding and that those with low-grade supratentorial lesions have a relatively small risk of developing seeding along the spinal cord. Patients with either high-grade supratentorial or low-grade infratentorial tumors had a 4% incidence of spinal cord seeding.

Ependymomas may also spread intracranially through the ventricular system. Thus, for patients with low risk of cord dissemination, the question arises as to whether the irradiated volume should include only the primary tumor site, the ventricular system, or the whole brain. The six patients of Salazar, \textit{et al.},\(^{29}\) who had autopsy evidence of intracranial spread also had locally recurrent or persistent disease. Five had received radiation directed to the primary tumor site only, but one had suffered a recurrence in spite of craniospinal irradiation. Three patients had high-grade tumors. Marks and Adler\(^{84}\) found ventricular spread outside the irradiated volume in three of 14 patients treated with partial-brain irradiation. The grades of the primary tumors were not specified. In each instance of ventricular spread there was failure at the primary tumor site. Autopsies in three of the seven patients who died after partial-brain irradiation at UCSF revealed persistent or recurrent disease within but not outside the treated volumes; obviously, whole-brain irradiation would not have improved their chance of cure (GE Sheline, \textit{et al.}, unpublished data, 1985).

Salazar, \textit{et al.},\(^{131}\) reported a local control rate of 12% with partial-brain irradiation and 78% with whole-brain fields for patients with low-grade tumors. The survival rate at 5 and 10 years was 67% (six of nine) for patients undergoing whole-brain irradiation compared with 12% (one of eight) for those treated with partial-brain irradiation. Glanzmann, \textit{et al.},\(^{47}\) found superior survival data in patients with low-grade tumors who received 3000 rads to the whole brain followed by a boost of at least 1500 rads to the primary site. Sheline, \textit{et al.},\(^{132}\) (unpublished data, 1985) observed actuarial 5- and 10-year survival rates of 67% and 57%, respectively, in patients with low-grade ependymomas. The intracranial recurrence rate for patients treated with partial-brain irradiation was 55% (six of 11 patients) compared with 25% (one of four patients) for whole-brain irradiation (p > 0.1); however, with one exception, all recurrences were limited to the primary site. One patient with cord involvement was found at autopsy to have tumor at the primary site also. Read\(^{119}\) found no significant difference in survival data in patients receiving small fields compared with whole-brain irradiation. With low-grade ependymomas the main cause of treatment failure is inablity to achieve local control; thus, whole-brain irradiation may not be indicated. Most patients reported in the literature were treated prior to the development of CT scanning, and in some instances whole-brain irradiation may have been necessary because of inadequate tumor localization. Recent advances in diagnostic procedures such as CT scanning and magnetic resonance imaging (MRI) provide greater precision in the determination of tumor extent and may be expected to decrease the chance of excluding tumor from the target volume when less than whole-brain irradiation is used.

It is our current policy for low-grade supratentorial ependymomas to use a generous target volume based on operative and radiographic findings. Patients with low-grade posterior fossa lesions receive craniospinal axis (CSA) irradiation only when cerebrospinal fluid (CSF) cytology reveals malignant cells or when a preliminary myelogram shows evidence of seeding. Pretreatment myelograms are not obtained in patients with low-grade supratentorial tumors.

For high-grade tumors, the use of CSA irradiation appears to have been effective in decreasing the inci-

**TABLE 5**

Ependymoma: incidence of clinical spinal subarachnoid seeding in four series\(^{*}\)

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Supratentorial</th>
<th>Infratentorial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-Grade</td>
<td>High-Grade</td>
</tr>
<tr>
<td>Svien, \textit{et al.},1953</td>
<td>0/9</td>
<td>0/12</td>
</tr>
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<td>Bloom &amp; Walsh, 1975</td>
<td></td>
<td>0/2</td>
</tr>
<tr>
<td>Sheline, 1975</td>
<td>0/2</td>
<td>0/3</td>
</tr>
<tr>
<td>Kim &amp; Fayos, 1977</td>
<td>0/3</td>
<td>1/8</td>
</tr>
<tr>
<td>total cases</td>
<td>0/14</td>
<td>1/23</td>
</tr>
</tbody>
</table>

\(^{*}\) Number of cases with seeding/total cases in that group. -- = grade not stated.
idence of spinal metastasis. In a review of patients treated without randomization, Salazar, et al. reported a 5-year survival rate of 47% in patients with high-grade ependymomas treated with CSA irradiation compared with 8% for patients receiving only cranial irradiation (p < 0.05). In a series composed predominantly of patients with malignant ependymomas who received a minimum dose to the primary tumor of 4500 rads, 16 of 30 patients treated with CSA irradiation were alive compared with two of six treated with local irradiation only. Marks and Adler were unable to demonstrate an improvement in survival times between patients treated with CSA irradiation and those with more limited field irradiation. However, their criteria for selecting patients for CSA irradiation are not clear. It is our policy to treat high-grade or anaplastic ependymomas with CSA irradiation. A preliminary myelogram is obtained to identify areas of grossly evident seeding, which are given a "boost" dose.

While improvement in local control and survival has been demonstrated when the radiation dose is increased to above 4500 rads, a dose response has not been demonstrated for higher doses. Currently, adult patients at UCSF receive a dose to the brain of about 5400 rads. However, even with doses in this range, 50% of patients with high-grade or anaplastic ependymomas develop local recurrence. An improvement in local control might be achieved by using higher doses of irradiation, and this possibility should be investigated in a randomized clinical trial. The prophylactic spinal cord dose is about 4000 rads with a boost to 5000 rads for areas of gross involvement. Adjuvant chemotherapy has been employed in a small number of clinical trials, but so far improvement in survival has not been demonstrated.

Medulloblastoma

Medulloblastomas usually arise in the midline of the cerebellum and comprise 15% to 20% of intracranial neoplasms in children. The laterally located cerebellar tumor or "arachnoidal cerebellar sarcoma" of the older age group represents a variant of the classical medulloblastoma. These tumors have a similar biological behavior and are treated in a similar fashion. Prior to the use of radiation therapy, the disease was nearly always fatal. The average length of survival with surgery alone ranged from 5.6 to 13 months. Cushing reported only one patient alive after 3 years among 61 patients undergoing surgery alone.

Medulloblastomas commonly infiltrate the subarachnoid space and have a striking propensity to spread throughout the cerebrospinal axis. McFarland, et al., found a 33% incidence of metastasis within the CNS in a collected literature series of 430 patients. Six percent of the metastases were supratentorial and 94% occurred within the spine. Since many of these patients had received irradiation to the entire CSA, some had been observed for short intervals of time, and an autopsy was not performed in others, the true incidence of CNS metastasis may be substantially higher. For this reason, radiation therapy for the treatment of these tumors is directed to the entire CSA. This recommendation is supported by the poor prognosis of patients treated to more limited volumes. Landberg, et al., reported a 5% 10-year survival rate in patients with radiation directed to the posterior fossa only compared with a 53% survival rate when CSA irradiation was administered.

Pretreatment myelography has demonstrated that as many as 30% of patients have clinically unsuspected metastases to the cord at the time of diagnosis. Cerebrospinal fluid cytology at the time of diagnosis is an inaccurate predictor of spinal cord involvement in that cytology studies are frequently negative in patients with demonstrable spinal cord metastases and the finding of malignant cells in the CSF does not correlate with subsequent spinal metastasis. The measurement of polyamines, specifically putrescine, in the CSF is useful in monitoring patients with medulloblastoma. Progressive elevation of polyamines or later development of positive CSF cytology may predict the recurrence of disease in advance of other diagnostic studies.

Prior to 1970 the 5- and 10-year survival rates were approximately 35% and 25%, respectively (Table 6). More recent reports show an improvement, with 5-year survival rates ranging from 50% to 60% or higher. The improvement can be ascribed, in part at least, to the use of megavoltage radiation, improved radiation therapy techniques, and delivery of higher doses to the posterior fossa.

The majority of recurrences are diagnosed within 2 to 3 years after treatment, but they may appear even beyond 5 years. The most common site of initial tumor recurrence is the posterior fossa. In a

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>3 Yrs</th>
<th>5 Yrs</th>
<th>10 Yrs</th>
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<td>Aron, 1969</td>
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<td>Kramer, 1969</td>
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<td>Harissidis &amp; Chang, 1977</td>
<td>59</td>
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<td>Cumberlin, et al., 1979</td>
<td>33</td>
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<td>Hirsch, et al., 1979</td>
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<td>Berry, et al., 1981</td>
<td>122</td>
<td>56</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>relapse-free survival</td>
<td></td>
<td>49</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>&gt; 5300 rads to post. fossa</td>
<td>15</td>
<td>77</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Silverman &amp; Simpson, 1982</td>
<td>50</td>
<td>51</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>relapse-free survival</td>
<td></td>
<td>46</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>≥ 5000 rads to post. fossa</td>
<td>21</td>
<td>85*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5000 rads to post. fossa</td>
<td>29</td>
<td>36*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kopelson, et al., 1983</td>
<td>43</td>
<td>56</td>
<td>56</td>
<td></td>
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<tr>
<td>Deutsch, 1984</td>
<td>29</td>
<td>83</td>
<td></td>
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<tr>
<td>myelogram staged</td>
<td></td>
<td>83</td>
<td></td>
<td></td>
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<tr>
<td>relapse-free survival</td>
<td></td>
<td>63</td>
<td></td>
<td></td>
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<tr>
<td>not myelogram staged</td>
<td>32</td>
<td>38</td>
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<tr>
<td>relapse-free survival</td>
<td></td>
<td>28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Differences in survival rates were significant (p = 0.0005).
Radiation therapy for brain tumors

collected series of 159 patients, 75% of recurrences were in the posterior fossa alone, 6% in the posterior fossa and spinal cord, 8% in the spinal cord alone, and 6% in supratentorial sites; 5% of patients had extraneural metastasis.19 Cumberlin, et al.,22 reported that 10 of the 14 tumors initially recurred in the posterior fossa alone. Later, after an average of 7.8 months, six of these 10 patients developed evidence of spinal cord involvement. It was proposed that these spinal cord metastases may be secondary to recurrence in the posterior fossa. Silverman and Simpson150 observed spinal cord recurrence in eight patients, all but one of whom had simultaneous involvement of the posterior fossa.

The frequency of local control of the primary tumor site is related to dose; the local control rate for patients receiving a dose of 5000 rads or more is substantially greater than when a lower dose is employed (Table 7). These higher doses not only result in improved local control but are accompanied by a decrease in the incidence of spinal cord recurrence150 and an improvement in survival.8,27,140

Radiation treatment of the CSA is technically exacting and requires painstaking attention to detail. The patient must be carefully immobilized. At UCSF, the cranial contents and spinal cord are treated concurrently for a portion of the therapy. The whole brain and upper cervical cord are treated via parallel opposed coaxial fields. Individualized shielding blocks protect the eyes and the nasopharynx. Special consideration must be given to the blocking at the base of skull where inadequate coverage of the subfrontal meninges may result in tumor recurrence in the region of the cribiform plate.8,33,53,67,72 The spinal cord is treated with one or two posterior fields depending on its length. The whole-brain field is rotated to produce a junction parallel with the diverging beam of the spinal field. To avoid areas of significant overdosage or underdosage, a calculated gap is established between abutting fields; the gap is moved 0.5 to 1 cm every 1000 rads. For Silverman & Simpson, 38% (11/29) 80% (16/20) 55% (27/49) Berry, 17% (2/12) 86% (6/7) 42% (8/19) Cumberlin, et al., 42% (14/33) 78% (67/86) 68% (81/119) Silverman & Simpson, 38% (11/29) 80% (16/20) 55% (27/49) Kopelson, et al., 50% (7/14) 78% (7/9) 61% (14/25) total 39% (34/88) 79% (96/122) 62% (130/210)

* Numbers in parentheses indicate total number of patients with local treatment/year of study.
† Patients at risk for 5 years.

TABLE 7
Medulloblastoma: relationship of local control to dose to posterior fossa

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>&lt; 5000 Rads</th>
<th>≥ 5000 Rads</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumberlin, et al., 1979†</td>
<td>17% (2/12)</td>
<td>86% (6/7)</td>
<td>42% (8/19)</td>
</tr>
<tr>
<td>Berry, et al., 1981</td>
<td>42% (14/33)</td>
<td>78% (67/86)</td>
<td>68% (81/119)</td>
</tr>
<tr>
<td>Silverman &amp; Simpson, 1982</td>
<td>38% (11/29)</td>
<td>80% (16/20)</td>
<td>55% (27/49)</td>
</tr>
<tr>
<td>Kopelson, et al., 1983</td>
<td>50% (7/14)</td>
<td>78% (7/9)</td>
<td>61% (14/25)</td>
</tr>
<tr>
<td>total</td>
<td>39% (34/88)</td>
<td>79% (96/122)</td>
<td>62% (130/210)</td>
</tr>
</tbody>
</table>

It has been claimed that a better prognosis follows subtotal or gross total tumor resection than with lesser procedures.8,53,109 Berry, et al.,3 observed a statistically significant increase in survival rates in patients undergoing gross total resection compared with those receiving biopsy alone. On the other hand, Kopelson, et al.,73 found no substantial difference in survival rates for patients with small tumors who underwent gross excision compared with lesser procedures. Silverman and Simpson were unable to correlate tumor control and survival times with extent of surgery provided that an adequate dose was delivered to the primary tumor. It is our policy, however, to recommend resection of the tumor to the extent possible within the limits of acceptable morbidity and, if necessary, to reestablish CSF pathways.

Although modern radiotherapy has substantially improved the prognosis for patients with medulloblastoma, the best outcome that can be achieved with conventional radiation therapy alone is limited by CNS tolerance levels and probably has been reached.11 The use of adjuvant chemotherapy is currently under investigation. It is hoped that chemotherapy will increase survival or permit reduction of radiation therapy dose. Multi-institutional randomized trials with adjunctive chemotherapy have been completed by the International Society of Pediatric Oncology (SIOP) and the Children's Cancer Study Group (CCSG); preliminary results are available.2,11 Each study compared radiation therapy plus chemotherapy with radiation therapy alone. The SIOP study used a regimen including weekly injections of vincristine during radiotherapy followed by eight courses of vincristine and CCNU each 6 weeks. Patients in the CCSG study received similar chemotherapy plus prednisone. Each trial demonstrated a marginally significant improvement in disease-free survival time for patients receiving chemotherapy. The 54-month disease-free survival rates in the CCSG and SIOP studies were 59% and 55%, respectively, for radiotherapy plus chemotherapy and 49% and 43%, respectively, for radiotherapy alone. These trials demonstrated that extent of disease (SIOP, CCSG), extent of resection (SIOP), and age (SIOP) were prognostic
factors. The benefit of chemotherapy was primarily in high-risk patients identified as those less than 2 years of age (SIOP, p = 0.04), those having only partial or subtotal tumor excision (SIOP, p = 0.005), and those with larger lesions (CCSG, p = 0.04; SIOP, p = 0.003). Patients with smaller primary tumors did not benefit from chemotherapy. It may be that the improved prognosis with chemotherapy for children less than 2 years of age is due to chemotherapy compensating for the reduced dose of radiation used in this age group.11

As the survival rate of children with medulloblastoma has improved, a greater appreciation of late complications of treatment has developed. Neuropsychological dysfunction,57,116 impaired growth secondary to the direct effects of radiation on the spine,115 pituitary-hypothalamic dysfunction,141 and immunological dysfunction27 have been identified. Although in some studies 70% to 80%,12,57 of surviving patients have been reported to be living an active life with no or minimal disability, other studies have suggested that there may be significant neuropsychological sequelae. Raimondi et al.,57 compared 16 children who were irradiated for medulloblastoma (four of whom also received systemic chemotherapy) with 12 who had surgery only for cerebellar astrocytoma. Five patients with medulloblastoma had an intelligence quotient (IQ) of 80 or less and seven were mentally defective (IQ ≤ 69), whereas only one of the six astrocytoma patients who underwent IQ testing was below the normal range. Hirsch, et al.,57 compared the IQ's of children with medulloblastoma receiving surgery, radiotherapy, and chemotherapy to patients with cerebellar astrocytoma treated with surgery alone. An IQ of less than 70 was found for 31% of patients with medulloblastoma (18%, if patients with brain-stem involvement were excluded) and 19% for those with cerebellar astrocytomas. Academic ability was judged normal in 25% of medulloblastoma patients compared with 73% of astrocytoma patients. Impaired intellectual function has been recognized in children following intensive systemic chemotherapy, intrathecal chemotherapy, and radiation therapy for acute lymphoblastic leukemia.148

Interpretation of these and other studies is confounded by differences in tumor characteristics and location with resulting differences in the surgery utilized and by the variable unknown effects of increased intracranial pressure, reduced school attendance, psychological stress, and the adequacy of rehabilitation.37 Prospective serial studies are needed to quantitate the risk and determine the mechanisms of injury.

Irradiation may affect the growing spine and lead to axial growth retardation. Probert, et al.,115 found that 16 of 22 children who received doses of 4000 rads in 4 weeks to the spine had retarded spinal growth.

Pituitary-hypothalamic dysfunction has been reported in patients receiving radiation therapy for lesions outside the hypothalamic-pituitary axis.135,142 Shalet, et al.,142 reported impaired growth hormone response to provocative stimuli in 10 of 27 children treated with various combinations of surgery, radiation therapy, and chemotherapy. Hirsch, et al.,57 found that 65.5% of patients studied had growth hormone deficiency. Although growth hormone deficiency is most frequent, other pituitary hormone deficiencies have been reported.57,121,136 The site of damage is uncertain, but it may be hypothalamic rather than pituitary.142 The incidence and degree of endocrine dysfunction appears dose-related with a threshold of 2400 to 2900 rads.141,143

Impairment of pituitary function is a gradual process and may not become evident for several years. All children who undergo irradiation to the hypothalamic-pituitary axis should be tested for pituitary function before irradiation and periodically thereafter; early detection of deficiencies is important so that appropriate hormonal replacement therapy can be instituted before irreversible damage has occurred.

Tumors of the Pineal and Suprasellar Regions

Tumors of the pineal and suprasellar regions may be classified into four histogenic groups: 1) tumors of germ-cell origin (germinoma, teratoma, embryonal carcinoma, choriocarcinoma, and endodermal sinus tumor); 2) tumors of pineal parenchymal cell origin (pineocytoma and pineoblastoma); 3) tumors originating from glial or other surrounding tissues (glioma, ganglioglioma, meningioma, hemangiopericytoma, and chemodectoma); and 4) non-neoplastic cysts and vascular lesions.126 Over 50% of the tumors in the pineal region are germinomas.126 Tumors of pineal parenchymal cell origin comprise about 17% of pineal region neoplasms.33,66,135

Complete surgical extirpation of pineal tumors is difficult to achieve because of their location and infiltrative nature.50,171 In the past, a high mortality rate (30% to 50%)130 was associated with biopsy or attempted resection; frequently, this led to the use of radiotherapy without biopsy proof of the nature of the lesion. Decompressive shunting was performed when indicated. Recent neurosurgical advances have substantially reduced the operative mortality.65,153 and many patients, particularly those with suprasellar lesions, now have a histological diagnosis at the time of referral for radiotherapy.

Tumors of germ-cell origin often produce biochemical markers such as alpha-fetoprotein and beta-human chorionic gonadotropin, which are found in the serum and the CSF.11,68,165 Patients with or suspected of having germ-cell tumors should be screened for the presence of these biomarkers prior to treatment. If present, serial determinations provide a sensitive monitor of tumor response to treatment. Furthermore, an increase in biomarker levels may be the first indicator of recurrence.11 The presence of biomarkers together with tumor response to low-dose radiotherapy, as shown by serial CT or MRI, may allow establishment of a diagnosis without biopsy.
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Reported tumor control and survival rates following radiation therapy for tumors of the pineal and suprasellar regions are shown in Table 8. Interpretation of the literature is difficult because of absence of histological diagnosis and the small number of patients in most series. Five-year survival rates have ranged from 44% to 78%, with an average of approximately 64%. In contrast, a literature review by Rubin and Kramer\(^{125}\) failed to identify any long-term survivors in patients with germinomas treated by surgery alone. The incidence of intracranial recurrence ranges from 6% to 40% (average 25%)\(^{1,66,102,156}\) and varies with histological diagnosis as well as radiation therapy technique.

Wara, et al.,\(^ {167}\) reviewed the results of treatment of 118 patients with pineal or suprasellar tumors treated in 12 CCGS institutions. Sixty-five percent of patients were alive after 2 to 15 years. A histological diagnosis had been obtained in 57 patients. Three (21%) of the 14 patients with a pineal parenchymal cell tumor or a malignant teratoma survived compared with 72% (26 of 36 cases) of those with a germinoma. The survival rate of patients with biopsy-proven germinomas was comparable to that of patients treated without biopsy, which was 71% (42 of 59 cases). It is noteworthy that some non-germinomatous tumors have an excellent outcome. Sung, et al.,\(^ {85}\) controlled the disease in four patients with teratoma (follow-up period 6 to 14 years) and two with pineoblastoma (follow-up period 3 to 6 years).

Wara, et al.,\(^ {167}\) also noted a relationship between age and prognosis: 65% of patients under the age of 30 years and 41% of those aged 30 years or over were alive at the time of review. Jenkin, et al.,\(^ {66}\) observed a similar relationship between age and survival: their survival rate was 81% for patients 25 years of age or younger compared with 37% for older patients. Since the pathological diagnoses of many patients in the earlier reports are not known, this may simply indicate that younger patients are more likely to have germinomatous tumors. On the other hand there may be, as with both low- and high-grade gliomas, an age dependence unrelated to histological diagnosis.

Germinomas may infiltrate, spread along the ventricular walls, or seed throughout the leptomeninges. The incidence of cerebrospinal seeding ranges from 7% to 12%\(^ {11,130}\). According to Wara, et al.,\(^ {167}\) nine (8.3%) of 109 patients with pineal or suprasellar tumors who did not receive spinal irradiation developed metastasis. In the absence of a biopsy, the incidence of spinal seeding is low and does not warrant routine spinal irradiation.\(^ {130,146,165}\) With the more widespread use of preredotherapy biopsy there has been an increase in the incidence of seeding of the subarachnoid space (Table 9). Sung, et al.,\(^ {155}\) reported metastasis to the cerebrospinal subarachnoid space in 57% (eight of 14 cases) of histologically verified germinomas. The increased incidence of spinal subarachnoid seeding in patients who have had a biopsy may necessitate CSA irradiation. In 10 patients with biopsy-proven germinoma treated by Jenkin, et al.,\(^ {66}\) none of five patients treated with CSA irradiation developed seeding compared with two of five patients in whom the spine was not treated.

A myelogram should be obtained at the time of diagnosis to ascertain the presence or absence of gross involvement of the spinal cord. Also, CSF cytology should be obtained even though the correlation between CSF cytology and metastasis to the spinal cord is uncertain.\(^ {23,66}\) With millipore-filtered CSF and tissue culture techniques, as many as 60% of patients have viable malignant cells in the CSF at the time of diagnosis.\(^ {137}\) The presence of malignant cells in the CSF, however, does not necessarily indicate the presence or future occurrence of subarachnoid metastases. Furthermore, CSF cytology may be negative in cases of cord involvement. Cytological testing is useful in detecting posttreatment recurrence or metastases.

Because of the infiltrating nature of germinomas, the tendency toward intraventricular spread, and the high rate of intracranial recurrence, the use of fields encompassing at least the entire ventricular system\(^ {16,166}\) or the whole brain\(^ {11,23,66,125,130,146}\) is generally recommended.

<table>
<thead>
<tr>
<th>TABLE 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pineal and suprasellar tumors: 5-year survival rates following radiation therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases*</th>
<th>S-Year Survival</th>
<th>Follow-Up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubin &amp; Kramer, 1965</td>
<td>6/8</td>
<td>50%</td>
<td>&gt; 19 mos</td>
</tr>
<tr>
<td>Bradfield &amp; Perez, 1972</td>
<td>8/16</td>
<td>44%</td>
<td>3-17 yrs</td>
</tr>
<tr>
<td>Mincer, et al., 1976</td>
<td>8/12</td>
<td>75%</td>
<td>4-14 yrs</td>
</tr>
<tr>
<td>Wara, et al., 1977</td>
<td>15/19</td>
<td>69%</td>
<td>2-21 yrs</td>
</tr>
<tr>
<td>Jenkin, et al., 1978</td>
<td>27/47</td>
<td>59%</td>
<td>2 mos-10 yrs</td>
</tr>
<tr>
<td>age &gt; 25 yrs</td>
<td>5/16</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>age ≤ 25 yrs</td>
<td>12/15</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Sung, et al., 1978</td>
<td>44/72</td>
<td>78%</td>
<td>5-23 yrs</td>
</tr>
<tr>
<td>Salazar, et al., 1979</td>
<td>13/22</td>
<td>54%</td>
<td>1-16 yrs</td>
</tr>
<tr>
<td>Wara, et al., 1979</td>
<td>73/118</td>
<td>66%</td>
<td>2-15 yrs</td>
</tr>
<tr>
<td>age &lt; 30 yrs</td>
<td>66/101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age = 30 yrs</td>
<td>7/17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abay, et al., 1981</td>
<td>14/27</td>
<td>70%</td>
<td>2-30 yrs</td>
</tr>
<tr>
<td>Amendola, et al., 1984</td>
<td>13/25</td>
<td>75%</td>
<td>3-30 yrs</td>
</tr>
</tbody>
</table>

* Number of patients alive without recurrence at the time of the report/total cases in the series. The total for all 10 series combined was 221/366 (60%).

<table>
<thead>
<tr>
<th>TABLE 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pineal and suprasellar tumors: incidence of spinal subarachnoid seeding in biopsied vs. unbiopsied tumors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>Spinal Seeding*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unbiopsied Tumors</td>
<td>Biopsied Tumors</td>
</tr>
<tr>
<td>Sung, et al., 1978</td>
<td>72</td>
<td>6% (3/50)</td>
</tr>
<tr>
<td>Wara, et al., 1979</td>
<td>100</td>
<td>1.7% (1/59)</td>
</tr>
<tr>
<td>Chapman &amp; Linggood, 1980</td>
<td>19</td>
<td>8% (1/12)</td>
</tr>
<tr>
<td>total</td>
<td>3% (5/121)</td>
<td>23% (18/79)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses indicate number of patients with seeding/total number of patients.
† Biopsied germinomas comprised 14% of the series (5/36).
With less than whole-brain irradiation there have been local recurrences at the margin of the irradiated volume; the frequency of such marginal recurrence should be less with the widespread availability of CT and MRI for better determination of tumor extent. In a literature review, Salazar, et al., found that patients treated with whole-brain irradiation had a higher survival rate than those with irradiation directed to the ventricular system only or to smaller volumes. The survival rate without evidence of recurrence for patients with whole-brain irradiation was 76% compared with 61% and 51% for those with irradiation directed to the ventricular system or with smaller volumes, respectively.

The intracranial recurrence rate in patients receiving 5000 rads or higher to the primary tumor site is substantially less than in those receiving less than 5000 rads. Sung, et al., found an intracranial relapse rate of 47% (15 of 32 cases) for patients receiving less than 5000 rads compared with 10% (four of 40 cases) for those receiving 5000 rads or more. In their review, Salazar, et al., observed a median survival time of 4.5 years for patients receiving less than 1500 ret (approximately 5000 rads with conventional fractionation) compared with 9.25 years for those receiving higher doses (p < 0.05). In that series, 90% of patients with elective whole-brain irradiation and a tumor dose of at least 5000 rads survived without evidence of recurrence compared with 33% of patients treated with the same dose directed to smaller fields and with 33% of patients who received less than 5000 rads to the primary site, regardless of field size. Germinomas appear to be similar in radiosensitivity to testicular seminomas and it may be possible to employ a lower dose for tumors with less than whole-brain irradiation or with smaller volumes; the frequency of such marginal recurrences should be less.

Primary Lymphoma of the Central Nervous System

Primary non-Hodgkin's lymphoma, an uncommon neoplasm, occurs most frequently in adults, with a peak incidence in the fourth to fifth decade. Reflecting the historical controversy over their histogenesis, a variety of terms have been applied to these tumors; the appellations "microglioma," "peripheral sarcoma," "perivascular sarcoma," and "reticulum cell sarcoma" have been used because it was thought that the cells of derivation were the microglia, perithelial cells, or reticulum cells of the leptomeninges. More recent studies have shown that these tumors are of lymphoid origin and are similar morphologically to non-Hodgkin's lymphoma arising outside the CNS. The predominant histological types are diffuse histiocytic and diffuse undifferentiated lymphomas (according to the Rappaport system of classification) or immunoblastic, small non-cleaved and large non-cleaved lymphomas (according to the Working Formulation system). The predominant histological types are diffuse histiocytic and diffuse undifferentiated lymphomas (according to the Rappaport system of classification) or immunoblastic, small non-cleaved and large non-cleaved lymphomas (according to the Working Formulation system). These types comprised 77% of the lesions included in the review by Helle, et al., the majority of which would be considered as "high-grade" lymphomas. Several studies confirm that primary CNS lymphomas are predominately of B cell origin. However, at least one case of primary leptomeningeal T cell lymphoma has been reported. In immunosuppressed or immunocompromised patients, primary CNS lymphomas occur with greater frequency and at a younger age than in non-immunologically suppressed individuals. During the last few years there has been a substantial increase in CNS lymphoma, especially in patients with acquired immunodeficiency syndrome.

Primary CNS lymphomas most commonly arise in the supratentorial region but also occur in the cerebellum and brain stem. Multiple lesions have been re-

TABLE 10

Primary central nervous system lymphoma: results of treatment

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Mean Dose (rads)</th>
<th>No. of Cases</th>
<th>No. Dead</th>
<th>Mean Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Litman &amp; Wang, 1975</td>
<td>4300</td>
<td>19</td>
<td>16</td>
<td>34.2</td>
</tr>
<tr>
<td>Rampen, et al., 1980</td>
<td>4100</td>
<td>12</td>
<td>10</td>
<td>17.2</td>
</tr>
<tr>
<td>Berry &amp; Simpson, 1981</td>
<td>4400</td>
<td>19</td>
<td>15</td>
<td>10*</td>
</tr>
<tr>
<td>Letendre, et al., 1982</td>
<td>4100</td>
<td>16</td>
<td>9</td>
<td>31.3</td>
</tr>
<tr>
<td>Gonzalez &amp; Schuster-Uitterhoeve, 1983</td>
<td>4400</td>
<td>15</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Mendenhall, et al., 1983</td>
<td>4800</td>
<td>8</td>
<td>6</td>
<td>21.3</td>
</tr>
<tr>
<td>Sagerman, et al., 1983</td>
<td>4200</td>
<td>10</td>
<td>9</td>
<td>40.8</td>
</tr>
<tr>
<td>Helle, et al., 1984</td>
<td>5400</td>
<td>15</td>
<td>6</td>
<td>21.3†</td>
</tr>
</tbody>
</table>

* Median survival time.
† Patients lost to follow-up with recurrence were assumed to have died of their disease at the time lost.

S. A. Leibel and G. E. Sheline
Radiation therapy for brain tumors

TABLE 11
Primary CNS lymphoma: relationship of treatment volume to outcome*

<table>
<thead>
<tr>
<th>Treatment Volume</th>
<th>No. of Cases</th>
<th>Mean Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>whole brain</td>
<td>71</td>
<td>25.3</td>
</tr>
<tr>
<td>primary tumor only</td>
<td>15</td>
<td>39.6</td>
</tr>
<tr>
<td>craniospinal axis</td>
<td>9</td>
<td>17.8</td>
</tr>
</tbody>
</table>


ported in 16% to 60% of patients. Satellite paraventricular or meningeal nodules may be present and in some cases diffuse leptomeningeal or subependymal spread occurs. Lymphoma of the CNS may be found in association with ocular involvement. Eye involvement often antedates the development of CNS disease; Margolis, et al., observed that eight of nine patients with ocular lymphoma developed fatal intracranial lymphoma at some time during the course of their disease. Extraneural involvement is found at autopsy in 3% to 7% of patients. Radiation therapy has resulted in clinical improvement and prolongation of survival although, as utilized to date, its curative potential has been limited. The results of radiation therapy from eight recent publications are summarized in Table 10. Each of these studies retrospectively reviewed a small number of patients, usually treated with a moderate radiation dose. Mean duration of survival following radiation therapy with doses of 2850 to 6000 rads ranged from 20 to 40.8 months. Berry and Simpson reported a 1-year survival rate of 47% and a 2-year survival rate of 16%. Combining data from the reports included in Table 10 gives a 1-year survival rate of 66%; 2-year survival rate of 43%; 3-year survival rate of 28%; 4-year survival rate of 18%; and a 5-year survival rate (with or without recurrent disease) of 7%. Few patients have survived 5 years or longer without evidence of disease. Littman and Wang reviewed the literature up to 1974 and found five of 131 patients had survived 5 years free of disease. In the literature included in Table 10 there are three additional cases of 5-year survivors, giving a total of eight (3%) among 245 reported patients.

Radiation therapy generally results in prompt clinical and radiographic improvement with the duration of improvement lasting an average of 12 to 24 months. This is usually followed by relapse due to local recurrence. Although the optimum volume to irradiate has not been established, most patients have been treated with whole-brain irradiation (Table 11).

However, some have received radiotherapy only to the region of the tumor plus a "generous" margin. The mean survival time of the latter group was 39.6 months compared to 25.3 months in patients treated with whole-brain irradiation. The longer survival with local-field irradiation probably was due to selection, with patients having smaller unifocal lesions receiving the more limited treatment. Some investigators have advocated treatment of the entire CSA; however, the incidence of seeding of spinal cord is small. Since most patients, including those who develop spinal seeding, fail at the primary site, it is unlikely that prophylactic irradiation of the entire CSA would make a major impact on survival rate. Although craniospinal irradiation may be of benefit in selected patients, criteria for their selection are lacking. Some authors have used CSF cytology as a basis for selection; however, the clinical significance of positive or negative cytology has not been established.

Based on the excellent local control of extraneural lymphomas, the majority of patients have been treated with tumor doses of around 4000 to 4500 rads; however, the high rate of local recurrence of CNS lymphomas with such doses is convincing evidence that they are inadequate. Table 12 presents mean survival time as a function of dose from six reported series of patients. The frequency of long-term survival does not appear to increase with increasing dose; however, only 12 patients received doses of 5500 rads or higher. Although not shown in Table 12, the majority of those surviving at least 3 years received doses of 4000 to 5000 rads. Berry and Simpson found that the median survival period of a subset of patients who received 5000 rads or more to the whole brain was superior to, but not significantly better than, the median survival time of those who received a lower radiation dose or partial-brain irradiation. The RTOG is currently conducting a study in which patients receive 4000 rads to the whole brain followed by a 2000-rad boost to the tumor volume. This study should provide better data on control rates and patterns of failure with such doses.

Reports of the use of chemotherapy have been largely anecdotal. High-dose intravenous methotrexate, intrathecal methotrexate, and corticosteroids have resulted in objective tumor responses. A combination
of cyclophosphamide, doxorubicin, vincristine, and dexamethasone produced complete resolution of the lesion in one case.154

For solitary lesions the current policy at UCSF, admittedly somewhat arbitrary, is to irradiate the entire brain to a dose of 4000 rads and then give an additional 2000 rads to the primary site and surrounding margin of normal tissue. When there are tumor cells in the CSF or the myelogram reveals disease within the spinal canal, the spine is treated to a dose of about 4000 rads and the area of myelographically identified tumor is boosted to 5000 rads. The whole axis is also treated when diffuse brain involvement is present. In patients with ocular involvement, 4000 rads in 4 1/2 weeks (if given prior to extensive retinal damage) results in improvement in visual acuity in about 75% of patients. Frequently, the improvement is maintained until the death of the patient from CNS disease.93

Neuroblastoma

Primary cerebral neuroblastoma is a rare tumor that occurs predominantly in childhood60 and is derived from ganglion-cell precursors.126 Horten and Rubinstein characterized this neoplasm as a clinicopathological entity distinct from primitive neuroectodermal tumors. Unlike peripheral neuroblastoma, elevated catecholamine metabolite levels in CSF, urine, or serum have not been found in patients harboring cerebral neuroblastomas.126 These tumors may present as a large cystic lesion with a peripheral mural nodule or as a solid mass.

Berger, et al.,7 reviewed the results of treatment of 11 patients with cerebral neuroblastoma at UCSF. Six patients presented with cystic tumors and five had solid lesions. All patients underwent craniotomy. Gross total removal was achieved in only two patients with cystic tumors. All patients received postoperative radiation and one patient, with a solid tumor, also received seven cycles of chemotherapy in the form of procarbazine, CCNU, and vincristine. None of the six patients with cystic tumors developed a recurrence, and all were alive 26 to 109 months following treatment. Four of the five solid tumors recurred at the primary site 8 to 31 months following treatment. Four of the five cystic tumors developed a recurrence, and all were alive 26 to 109 months following treatment. Although Horten and Rubinstein found leptomeningeal or ventricular dissemination or both in 38% of their autopsy series, this pattern of disease 52 months following treatment.

At UCSF, we are giving postoperative irradiation to a total dose of 5400 rads, in daily fractions of 180 rads delivered to the involved region with generous margins. Craniospinal irradiation is reserved for patients in whom a myelogram or CSF cytology demonstrates evidence of tumor dissemination. Adjuvant chemotherapy and/or more aggressive local therapy should be considered for patients with subtotally resected solid tumors.

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Summary

The available data suggest that postoperative radiation therapy favorably influences the outcome of patients with primary neoplasms of the brain. These results represent the limits that can be achieved with conventional radiation therapy, at least with conventional fractionation, with acceptable levels of treatment morbidity. Randomized studies are needed both to optimize the radiation therapy technique and to integrate new therapeutic modalities into the management of patients with primary brain tumors.

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