

Clinical Study

Intracranial ependymoma long term outcome, patterns of failure

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Key words: intracranial ependymoma, radiation therapy, surgery

Abstract

We analyzed 31 patients with intracranial ependymoma, all verified by secondary neuropathology review. There were 12 patients with ependymomas and 19 patients with anaplastic ependymoma by the WHO classification. Eight patients received craniospinal irradiation, 22 patients received cranial irradiation alone, and one patient was treated with chemotherapy alone. The median follow-up time was 11 years. The 5- and 10-year progression-free survivals (PFS) were 60% and 48%. Those with anaplastic tumors had a decreased 10 year PFS over those with low grade lesions: 26% vs. 55% ($p = 0.02$). Delivering spinal irradiation in addition to cranial irradiation did not improve outcome. There were relapses in 16 patients. All patients relapsed at the primary intracranial sites with no spinal failures. Patients treated with whole brain irradiation had decreased 10 year PFS over those treated with local fields: 19% vs. 64% ($p = 0.006$). Those patients treated to ≥ 50 Gy had an improved long-term PFS ($p = 0.04$). Multivariate analysis was undertaken with the following variables: extent of cranial irradiation, pathology, anatomic site of ependymoma, cranial irradiation dose, extent of surgery, and whether spinal irradiation was given. With PFS as the endpoint, only extent of cranial irradiation (favoring local fields) and pathology (favoring low grade ependymoma) were significant prognosticators. We conclude that carefully outlined local field irradiation is the therapy of choice, and elective spinal irradiation is of questionable benefit.

Introduction

Intracranial ependymomas arise from the ependymal lining of the ventricular system. Occasionally, these lesions occur anatomically remote from the ventricles. In this case they originate from ependymal cells arising from the subependymal glia which, during the development of the cerebrum, may migrate as bands into the substance of the hemisphere [1]. Most lesions are infratentorial in association with the fourth ventricle. These tumors occur primarily in children with the majority diagnosed by age 5 years [2].

Postoperative irradiation has doubled the 5-year survival over that obtained with surgery alone from 20–30% to 40–60% [3, 4]. The volume of tissue to be irradiated remains controversial. There are proponents of local field cranial irradiation, whole brain cranial irradiation, and cranial-spinal irradiation [5, 6, 7].

This is a retrospective review of patients with intracranial ependymoma treated primarily with surgery and postoperative irradiation. We focus on various prognosticators linking them to outcome and patterns of failure in an attempt to make therapeutic recommendations.

Materials and methods

Inpatient hospital records and radiation therapy charts of 68 consecutively treated patients with an initial diagnosis of intracranial ependymoma were reviewed (Table 1). All patients were treated between 1950 and 1988 at the Radiation Oncology Center, Mallinckrodt Institute of Radiology, Washington University Medical Center.

Pathologic review

Neuropathologic review was performed by NF and KAR on all available pathologic material. The neuropathologists were blinded to the anatomic location, clinical features, and outcome of each case. The tissue was classified by the World Health Organization recommendations [8].

We included all primary glial neoplasmas that showed ependymal differentiation as evident by the presence of perivascular pseudorosettes or true rosette formation. If the pattern of ependymal differentiation was dominant (> 50%) we included the tumor in the category of ependymomas, otherwise the tumor was included under mixed gliomas and we specified the different histologic components and the grade of the neoplasm. Tumors with dominant ependymal differentiation were subtyped as well differentiated ependymomas, ependymomas with focal anaplasia or anaplastic ependymomas if anaplastic areas were the dominant pattern (> 50%). Anaplastic areas were defined by the presence of either 1) an *undifferentiated pattern* characterized by high nuclear/cytoplasmic ratio, short perivascular processes, absence of true

rosette formation and high mitotic activity (> 5 per 10 high power field), or 2) at least two of the following three criteria: a) coagulative necrosis b) endothelial proliferation or c) nuclear anaplasia.

There was no archival tissue available for analysis in 19 patients. In 18 further cases, the patient did not have an ependymoma. Table 2 outlines the true histology in the misdiagnosed patients. Ten of these eighteen patients were given a different diagnosis initially. Nine of these ten patients were seen before 1972. The eight remaining patients without ependymoma were mistakenly in this data base and have been purged.

The remaining 31 patients, all of who had documented intracranial ependymoma, form the basis of this report. Twelve patients had ependymoma, twelve had anaplastic ependymoma, four had mixed ependymoma-glioma (all with anaplasia), and three patients had ependymoma with atypia.

Clinical evaluation

Patients were seen by both a neurosurgeon and radiation oncologist. Preoperative evaluation consisted of history, physical examination, and radiographic studies. Radiographic studies included skull films, pneumoencephalography, carotid arteriography, and more recently, CT and MR scanning.

There were 14 males and 17 females. Age at diagnosis ranged from 1–56 years (median: 9 years). Presenting symptoms included nausea and vomiting in 26 (84%), headache in 21 (68%), gait

Table 1. Cases reviewed

Total	68
Excluded	37
No archival tissue	19
Other than ependymoma (Table 2)	18
Analyzed	31
Well differentiated	12
Anaplastic	12
Mixed	4
Atypia	3

Table 2. Eighteen patients originally thought to have ependymoma. Histopathologic diagnosis on pathologic review

Pathology on review	Patients
Astrocytoma	5
PNET (NOS)	4
Glioblastoma	3
Oligodendroglioma	2
Medulloblastoma	1
Medulloblastoma	1
Choroid Plexus Papilloma	1
Pineal Tumor	1

disturbance in 17 (55%), diplopia in 11 (36%), lethargy in 6 (19%), weakness in 4 (13%), meningismus in 2 (7%), and a seizure in one patient. Presenting signs were ataxia in 16 (52%), cranial nerve palsy in 15 (48%), papilledema in 13 (42%), dysmetria in 8 (26%), nystagmus in 8 (26%), paresis in 4 (13%), and a bulging fontanel in one patient. The median symptom duration prior to seeking medical attention was two months (range: one week to two years).

Size of the lesion was documented in 25 patients for which the median largest dimension was 4 cm (range: 2–10 cm). The location was infratentorial in 26 patients and supratentorial in five patients (Table 3).

CSF cytology was obtained in nine patients and none showed evidence of malignancy. The remaining 22 patients did not have their CSF evaluated. Therefore, none had any overt signs of spinal involvement.

Treatment

The initial therapy was surgical in all cases. Four patients underwent a total resection. A subtotal resection leaving gross tumor *in situ* was performed in 27 (87%) patients.

Thirty patients received postoperative cranial irradiation (Table 4). Eight patients received elective spinal irradiation at the discretion of the attending radiation oncologist and was not based on site or histology. The total minimal tumor dose for the cranial irradiation ranged from 1806–6180 cGy (median 5029 cGy). The patient who received 1806 cGy was the only one in the study who also received intrathecal gold on two occasions (total of 20 mCi). The median dose per fraction was

Table 3. Histopathology and presenting site

	Supratentorial	Infratentorial
Well Differentiated	0	12
Anaplastic	3	9
Mixed	2	2
Atypia	0	3

170 cGy. Patients were treated over a range of 31–52 elapsed days (median 42 days). The technique used was generally with parallel opposed beams. Beam energies were as follows: cobalt – 10 patients, 4 MV – four patients, 6 MV – five patients, ≥ 18 MV – 11 patients. Thirteen patients received whole brain irradiation followed by a boost, while 17 received local field irradiation from the start with or without a boost.

The eight patients that were given elective spinal irradiation received a median dose of 3485 cGy (range: 1950–3920 cGy) in 150 cGy fractions. All patients were treated with posterior-anterior (PA) fields. These fields were not expanded in the lumbosacral area. Low energy megavoltage beams were employed (≤ 6 MV).

One patient did not receive postoperative irradiation because she was 14 months old at diagnosis and had ependymoma with atypia. She was treated with cyclophosphamide, cisplatin, vincristine, and procarbazine. This patient died with persistent disease 10 months after initiating chemotherapy.

Follow-up

No patient was lost to follow-up. The minimum and median follow-up times for those patients alive at the time of last follow-up were 2 and 11 years, respectively.

Statistical methods

Statistical calculations were performed with BMDP statistical software [9]. Overall and progression-free survivals were determined by the actuarial life-table method of Cutler and Ederer [10].

Table 4. Irradiation fields/doses

Total	30	Mean cGy	Range cGy
Generous Local Field (LF)	17	4758	1806–5477
Whole Brain + LF	13	5084	3976–6180
Spinal*	8	3485	1950–3920

* One patient received intrathecal gold-198.

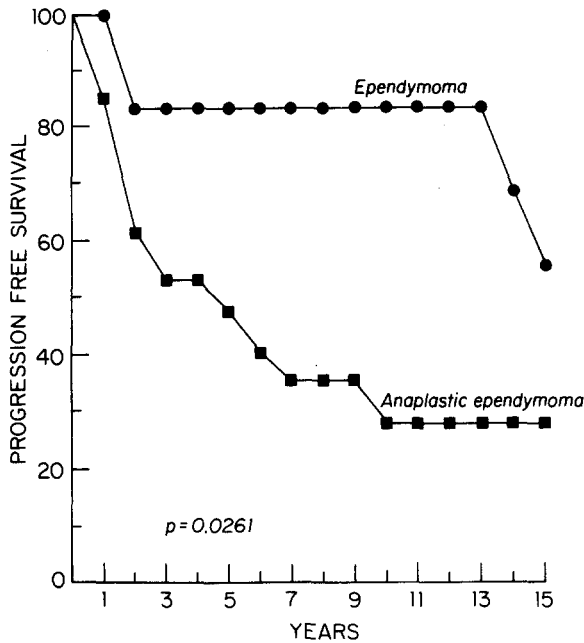


Fig. 1. PFS by histology by the WHO classification.

Survival times were calculated from the time of irradiation. Mantel-Cox statistics were used to test the equality of survival curves [11]. Multivariate analysis was performed by the method of Cox [12].

Results

Survival

The 5 and 10-year overall actuarial survivals for all patients were 66% and 52%. The 5 and 10-year progression-free survivals (PFS) for all patients were 60% and 48%. None died from intercurrent disease.

The histologies were then grouped strictly by the WHO classification [8], placing the mixed glioma and anaplastic ependymoma patients as well as the ependymoma with atypia patients with the anaplastic ependymoma patients. This group was compared to the ependymoma (low grade) patients (Fig. 1). The anaplastic group fared worse with a 26% 10-year PFS vs. 55% 10-year PFS in the ependymoma patients ($p = 0.02$).

Patients with infratentorial ependymomas had

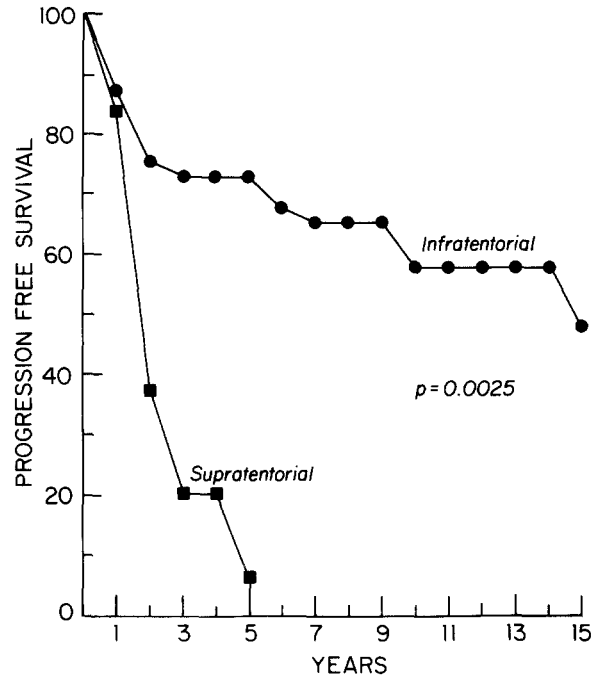


Fig. 2. PFS by anatomic location.

an increased 10-year PFS when compared to supratentorial lesions (48% vs. 0%, $p = 0.00$) (Fig. 2). However, all five patients with supratentorial lesions had high grade tumors; three were anaplastic ependymomas and two were mixed glioma-anaplastic ependymoma.

The four patients who underwent a total excision had an improved long-term PFS over those that had a subtotal excision, but the difference was not statistically significant. The 10-year PFS was 75% vs. 36% respectively ($p = 0.37$).

The 10-year PFS in the 17 patients who received at least 50 Gy to the primary tumor was 49% vs. 31% in patients receiving less than 50 Gy ($p = 0.05$). Arbitrary cut offs at 40 Gy or 45 Gy did not show a statistically significant dose response, primarily because of small numbers of patients at the lower dose levels.

Figure 3 displays PFS by whether or not the whole brain was initially treated. Patients treated to the whole brain had a 10-year PFS of 28%. Those who received local field irradiation with or without a boost had 10-year PFS of 75%. These results statistically favored the local field group ($p =$

0.006). Ten of 13 patients in the whole brain group were treated in the pre-CT era compared to 6/17 in the local field subset.

Additionally, primary tumor size, duration of symptoms prior to diagnosis, gender, age and elapsed days of cranial irradiation had no bearing on clinical outcome.

Of the eight patients who underwent spinal irradiation, seven had anaplastic histologies (12/19 with anaplastic histology did not receive spinal irradiation) and two were supratentorial. There was no difference in PFS between those patients who did or did not receive spinal irradiation. Likewise, there was no difference in long-term survival between the nine patients who had negative CSF cytology and the 22 patients in whom this diagnostic test was not performed ($p = 0.95$).

Patterns of failure

All 16 recurrences were at the primary site in the radiation field. There were no spinal failures. Two of the recurrences were salvaged with further surgery and chemotherapy. Both patients are currently without disease.

When grouped pathologically by the WHO classification, 3/12 (25%) patients with ependymoma recurred versus 13/19 (68%) patients with anaplastic ependymoma. The median cranial irradiation dose in the patients who failed was 4832 cGy. The median time from recurrence to death in the 14 patients who succumbed was 106 days (range: 16–422 days).

Table 5. Multivariate analysis with PFS as endpoint

Variable	P-value
Extent cranial XRT	0.002
Pathology	0.052
Anatomic Site	0.206
Cranial XRT Dose*	0.208
Extent Surgery	0.241
Spinal XRT	0.712

* Entered as a continuous variable.

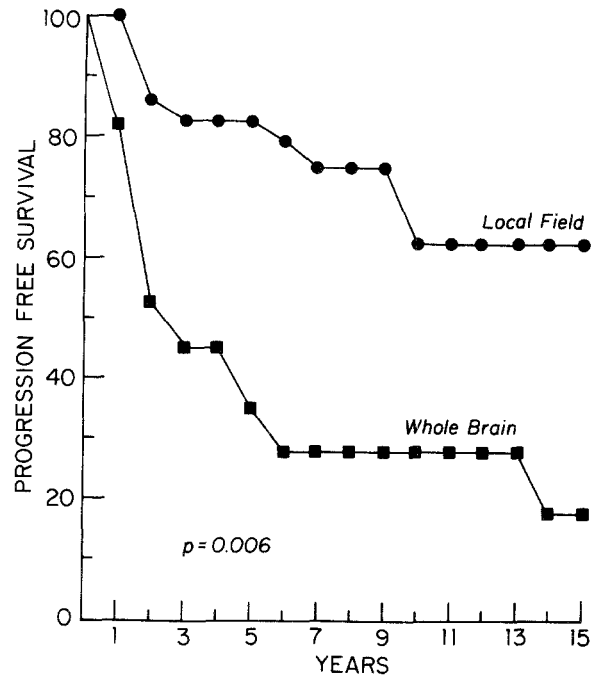


Fig. 3. PFS by cranial volume irradiated.

Multivariate analysis

A Cox regression analysis was performed with PFS as the endpoint for the following variables: cranial radiation dose, histology (ependymoma vs. anaplastic ependymoma), anatomic site (supratentorial vs. infratentorial), extent of cranial irradiation (whole brain vs. local field), extent of surgery (total vs. subtotal resection), and spinal irradiation (given or not). Table 5 reveals that volume of cranial irradiation favoring local fields was the most significant variable. Low-grade histology was the only other variable that attained significance.

Complications

There was one surgical complication of a left hemianopsia in a patient with a supratentorial lesion. Four patients had growth retardation following irradiation. One patient had bilateral hearing loss and two patients demonstrated cognitive impairment. The patient who received intrathecal gold

developed arachnoiditis and a neurogenic bladder eventually necessitating an ileal stoma.

Discussion

The importance of secondary neuropathologic review is evident from this study. This is especially true when dealing with tissue that was diagnosed many years ago. Nine of the ten misdiagnosed patients were treated 20 or more years ago – prior to the advent of immuno-histochemistry. Many of these cases were PNETs, medulloblastoma derivatives, choroid plexus tumors or pineal lesions. Any of these can seed the CSF. If these nonependymoma patients were included in the analysis, the spinal failure rate would have been increased thus altering conclusions about the volume to be irradiated.

Overall and progression free survivals are comparable to other series of intracranial ependymoma with secondary neuropathologic review [4, 13, 14]. Tumor histology was strongly prognostic with the anaplastic lesions faring worse. This has been noted by many other investigators [5, 6, 7, 14, 15]. Patients with supratentorial lesions had a uniformly dismal outlook. All five patients died with uncontrolled intracranial tumor. The patients all had anaplastic ependymomas. Chin, et al. [15] also noted a decreased survival as well as an association with high grade histology in the patients presenting with supratentorial lesions. However, Ross and Rubinstein failed to demonstrate a correlation between histological features and survival [16].

Total cranial irradiation doses greater than 50 Gy gave a statistically superior survival on univariate analysis. Others have noted a dose response for this tumor [6, 13, 14, 17]. None of these series have done a multivariate analysis, however, which for our data, revealed that the cranial dose was not significant.

Both the University of Rochester [7] and the Mayo Clinic [14] experiences have shown a higher failure rate in patients treated with local field cranial irradiation versus whole brain. We found the opposite to be true. Most of our patients treated to the whole brain underwent a subsequent local field

boost. Since the majority (77%) of patients treated in this fashion were seen in the pre-CT era, it is conceivable that there were geometric misses in the boost segment of therapy. On the other hand, only 35% of patients treated to a local field only were seen in the pre-CT era. It is unclear to what degree localization errors contributed to the high failure rate in patients treated to the whole brain initially. However, the extent of cranial irradiation was the most significant independent prognostic factors on multivariate analysis, with local fields only being superior.

Intracranial relapse was the only site of relapse in this series despite most patients being treated to the brain alone. The spinal axis was not treated in 23 patients, yet there were no spinal failures. This group included both infratentorial lesions and those with anaplastic histology. Other recent papers have noted that the overwhelming failure pattern is intracranial [4, 13, 14]. Subsequent spinal recurrences may be due to seeding [18] but are very rare as the primary site of recurrence. Given the above pattern of failure and the known toxicities of cranial-spinal irradiation. We do not recommend elective spinal irradiation.

Conclusion

Postoperative radiotherapy improves the survival of patients with intracranial ependymoma over surgery alone yet half the patients still die of disease. Anaplastic histology bodes a poor prognosis. Local field cranial irradiation is recommended with field borders based on MR or CT scans. As this tumor has a dose response on univariate analysis, investigational efforts to improve the clinical outcome might focus on increasing the total dose, possibly by hyperfractionation. Elective spinal irradiation is of questionable value. Secondary neuropathologic review is necessary when analyzing these cases.

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