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CLINICAL–PATIENT STUDIES

Long term outcome with post-operative radiation therapy for spinal canal ependymoma

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Abstract
Purpose A retrospective study was performed to evaluate the long term efficacy and safety of post-operative radiation therapy in the management of spinal canal ependymoma at our institution.
Methods and materials Between 1954 and 1997, 22 patients with spinal canal ependymoma were treated with post-operative radiotherapy at our institution. The median age at diagnosis was 34.7 years (range 9.8–56.1 years). All patients underwent open biopsy with histologic diagnosis: 13 patients (59%) had ependymoma (WHO Grade II) and 9 patients (41%) had myxopapillary ependymoma (WHO Grade I). The median tumor size was 4.0 cm (range 1.5–15.0 cm). Twenty patients received subtotal resection and 2 patients received gross-total resection. Median radiation dose was 45.0 Gy.
Results The median follow up for surviving patients was 11.4 years (range 0.6–37.0 years). An 80% progression-free-survival (PFS) was observed for all patients at 5-, 10- and 15-year endpoints. All recurrences were within 3 years of treatment. The 5-, 10- and 15-year overall-survivals (OS) for all patients were 85%, 78% and 64%, respectively. Patients with tumors larger than 6.0 cm at time of presentation demonstrated 5- and 10-year PFS of 58.3% compared to 92.3% for patients with tumors 6.0 cm or smaller ($P = 0.047$). There was no significant correlation between tumor size and OS.
Conclusions Post-operative radiation after subtotal resection is safe and offers durable tumor control and long term patient survival.

Keywords Ependymoma · Radiation · Spinal canal · Spinal cord

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Introduction

Primary spinal canal tumors comprise approximately 15% of all primary central nervous system (CNS) tumors [1]. Ependymomas are the most common neuroepithelial neoplasm in the spinal canal, comprising 50–60% of spinal gliomas [2]. Spinal canal ependymomas have long been characterized as slow-growing tumors with a predominantly local growth pattern, a high rate of local recurrence and a favorable long term survival. Ependymomas are classified by histologic grade as subependymoma (WHO Grade I), myxopapillary ependymoma (WHO Grade I), ependymoma (WHO Grade II); and anaplastic ependymoma (WHO Grade III) [3].

Without prospective randomized trials on this rare tumor, management of primary spinal canal ependymomas is largely based on single institution historical data. Surgery is generally the first line of therapy, and serves the dual purpose of tissue diagnosis and gross tumor excision. The use of adjuvant therapy varies by institution due to uncertainty with regard to the need

for radiation after gross total resection, the influence of histology on recurrence patterns, the optimal radiation dose, and the role of chemotherapy. A retrospective study was performed to evaluate the long term efficacy and safety of post-operative radiation therapy in the management of spinal canal ependymoma at our institution.

Methods and materials

This retrospective study was conducted with approval from the Human Studies Committee of the Washington University School of Medicine. Between 1954 and 1997, 22 patients with spinal canal ependymoma were treated with post-operative radiation therapy at our institution.

The median age at diagnosis was 34.7 years (range 9.8–56.1 years). There were 8 (36%) male and 16 (64%) female patients. Duration of symptoms ranged from 1 to 48 months, with a median of 10 months. Common symptoms included back pain (91%), numbness (55%), gait disturbance (32%), radiculopathy (32%), paresthesias (27%) and urinary retention (27%). Common clinical signs included paresis (77%) and hyperreflexia (36%).

Diagnostic evaluation included conventional myelogram only (12 patients), conventional and CT myelogram (7 patients), myelogram and MRI (3 patients) and MRI alone (2 patients). CSF evaluation was negative in 9 patients and not performed in 13 patients. All patients underwent open biopsy with histologic diagnosis: 13 patients (59%) had ependymoma (WHO Grade II) and 9 patients (41%) had myxopapillary ependymoma (WHO Grade I) [3]. The median tumor size was 4.0 cm (range 1.5–15.0 cm). The tumor locations and characteristics are listed in Table 1. Twenty patients (90%) received subtotal resection (STR) and 2 patients (10%) received gross-total resection (GTR). Twenty patients (91%) received radiation therapy after surgical treatment. Two patients (9%) received salvage radiation therapy for recurrence after treatment with surgery alone (GTR in one case and STR in the other). Median dose of radiation prescribed was 45.0 Gy (range 30.0–54.0 Gy). Median daily fraction size was 1.8 Gy (range 1.5–2.5 Gy). Radiation treatment parameters are listed in Table 2. None of the patients received chemotherapy as part of initial management.

After completion of treatment, patients were followed at 3 month intervals for the first 2 years, then every 6–12 months for 5 years and sporadically thereafter. Evaluations at the time of follow-up consisted of a history and physical examination. Computed tomography (CT) scans or magnetic resonance imaging (MRI) of the spinal canal were only conducted if indicated by patient symptoms or signs. Patients were considered to have local failure if there were clinical, radiographic, or histologic evidence of recurrence. Duration for endpoints was calculated from the date of completion of radiation therapy.

StatView software (SAS Institute, Cary, NC) was used to calculate survival rates based on the Kaplan–Meier method. Univariate analyses were conducted by the log-rank test. A P value of ≤ 0.05 was considered statistically significant.

Table 1 Subsites of involved disease

Spinal subsite	Number of patients (percent of total)	WHO grade (percent within subsite)	Range of tumor size (cm)
Cauda Equina	6 (27.3)	Grade I: 4 (66.6) Grade II-2 (33.3)	2.0–8.0 (mean 5.2)
Cervical	4 (18.2)	Grade I-1 (25.0) Grade II-3 (75.0)	1.5–15.0 (mean 9.0)
Lumbar	3 (13.6)	Grade I-3 (100.0)	2.5–12.0 (mean 8.5)
Filum Terminale	3 (13.6)	Grade II-3 (100.0)	2.0–4.0 (mean 3.0)
Thoracic	2 (9.1)	Grade II-2 (100.0)	3.0–10.0 (mean 6.5)
Conus Medullaris	2 (9.1)	Grade I-1 (50.0) Grade II-1 (50.0)	3.0
Cerivcomedullary	1 (4.5)	Grade II-1 (100.0)	4.0
Deposits ≥ 1 Subsite	1 (4.5)	Grade II-1 (100.0)	2.5 (largest deposit)

Table 2 Radiation treatment parameters

	Number of patients (Percent)
Radiation field	
Local field	13 (59.1)
Whole spine	6 (27.3)
Craniospinal	3 (13.6)
Energy	
Cobalt	9 (40.9)
>6 MV (including mixed low/high energy)	7 (31.8)
≤6 MV	3 (13.6)
Orthovoltage	3 (13.6)

Results

The median follow up for all patients was 10 years (range 0.4–37.0 years). The median follow up for

surviving patients was 11.4 years (range 0.6–37.0 years). An 80% progression free survival (PFS) was observed for all patients at 5-, 10- and 15-year endpoints (Fig. 1). Of the 4 patients (18.1%) who recurred: 2 patients recurred within the radiation fields 17- and 28-months after treatment; one patient recurred in the spine outside of the treatment field 20 months after treatment; and one patient recurred in the treatment field as well as in the untreated cranium 5 months after treatment. Mean time to recurrence was 17 months. All recurrences were within 3 years of treatment. The 5-, 10- and 15-year overall survivals (OS) for all patients were 85%, 78% and 64%, respectively (Fig. 2). Four patients died of disease, 2 patients died of inter-current disease, and 16 patients were censored at last follow up without evidence of disease.

Six patients (27%) demonstrated long term neurologic deficits after treatment. Symptoms included paresis (2 patients), urinary retention (2 patients), urinary incontinence (1 patient) and arachnoiditis (1 patient). All patients had complaints prior to the start of radiation, suggesting that the symptoms were sequelae of tumor invasion or surgical resection, however contribution from radiation cannot be excluded.

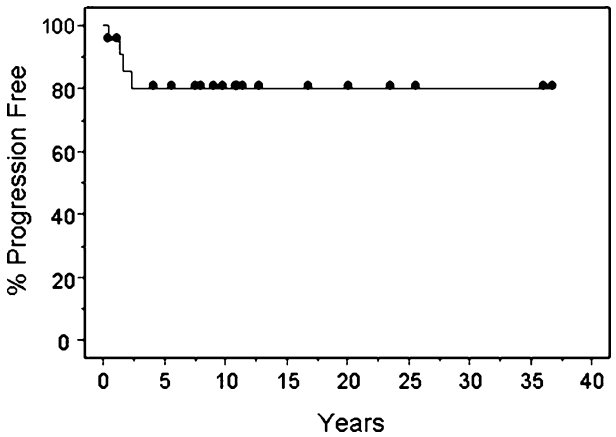

Fig. 1 Progression-free survival for all patients

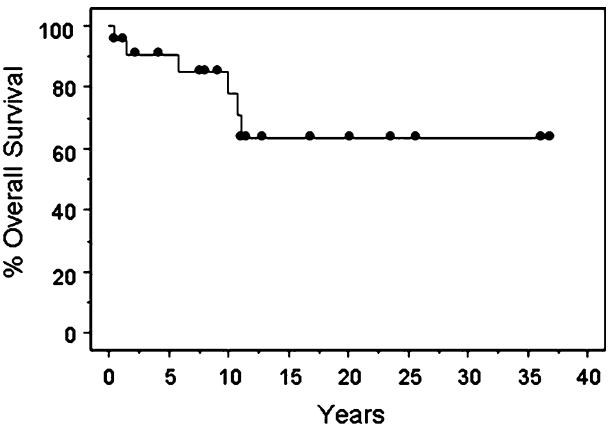

Fig. 2 Overall survival for all patients

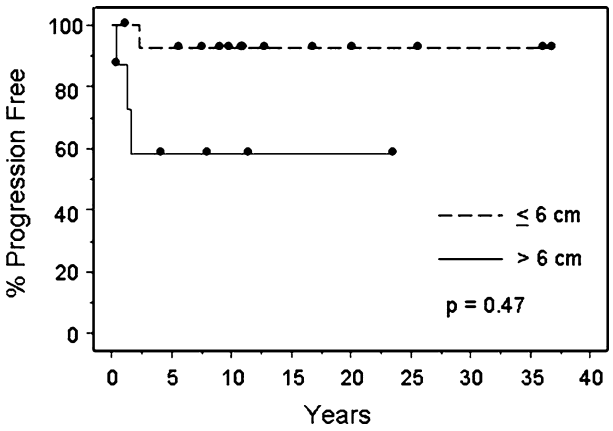

Fig. 3 Progression-free survival for patients with tumors ≤6 cm or >6 cm

Various patient, tumor and treatment factors were examined to determine their influence on prognosis. A worse outcome was observed with larger tumors (Fig. 3). Patients with tumors greater than 6 cm at time of presentation demonstrated 10-year PFS of 58.3% compared to 92.3% for patients with tumors 6 cm or smaller. This difference was statistically significant ($P = 0.047$). There was no significant correlation between tumor size and OS. In this retrospective series, no prognostic value was noted for gender, age, dose prescribed, volume of irradiation, histologic grade, extent of surgery, timing of radiation or era of treatment.

Discussion

Reported survival rates for patients with spinal canal ependymoma after surgery and post-operative radiation range from 68 to 95% at 10 years [4–13]. The median follow up of 11.4 years obtained with this series is quite lengthy with respect to prior studies and provides further evidence of a sustained favorable outcome for these patients.

Institutional reports suggest the potential for excellent control rates with surgery alone for low grade lesions that are completely removed [14–19]. However, progression rates after partial or subtotal tumor removal range from 20 to 50% at 5 years [10, 13, 19–21]. Despite the fact that 90% of the patients in our study

received only subtotal resection, an 80% local control rate was maintained at 15 years with the use of radiation therapy, suggesting that post-operative radiation is effective and should be considered after incomplete resection of tumor. Recurrence rates in series that include high grade tumors (current WHO Grade III) range from 16 to 37% even after documented GTR [9–11], supporting the use of adjuvant radiation for high grade lesions irrespective of the degree of resection.

It is difficult to draw conclusions on the prognostic value of patient, tumor or treatment variables given the small sample size in our series. Our data suggest a PFS advantage with tumors 6 cm or less. Other reports have suggested improved outcome with younger age [13], smaller tumor size [9], distal spinal disease [22], myxopapillary histology [12], low tumor grade [13, 23], gross total resection [8, 10], post-operative radiation [12] and radiation dose above 50 Gy [9].

Our study does not demonstrate a dose response relationship for tumor control. Some investigators have observed a trend towards improvement with doses of 50 Gy or higher and advocate for treatment to 55 Gy, with the last 5 Gy given to a boost volume [9]. A dose range of 45–50 Gy has been used historically as the threshold dose beyond which the incidence of radiation myelopathy is thought to increase significantly. Current models of spinal cord tolerance suggest that up to 55 Gy in conventional fractions (2 Gy or less per day) can be delivered safely with a less than 2% risk of causing radiation myelopathy [24–29]. Nevertheless, in the absence of strong evidence for a dose–response, most institutions remain cautious about escalating dose beyond 50 Gy and continue to recommend doses in the range of 40–50 Gy [11–13, 22, 30–32]. Only 2 patients in our series were treated beyond 50 Gy (both received 54 Gy in 1.8 Gy fractions). Radiation therapy did not seem to cause treatment related late effects within our population, suggesting that the doses used in our study (range 30 Gy–54 Gy; median 45 Gy) can be delivered safely.

Only 1 patient in our series failed outside of the localized treatment field. The vast majority of spinal ependymoma recurrences occur at or near the primary site. Of those patients who fail at distant sites in the CNS, many do so despite the addition of cranio-spinal irradiation (CSI) [13, 30]. Whereas the increased morbidity associated with CSI is well established, there is little evidence in the literature that whole-CNS or whole-spinal irradiation adds tumor control or survival advantage for non-disseminated lesions. The role of large volume irradiation should therefore be limited to patients with disseminated disease.

Chemotherapy has a limited role in the management of spinal ependymomas. There is no data to suggest a benefit for chemotherapy in the initial treatment of adults. Treatment of very young patients is individualized and sometimes utilizes chemotherapy in an attempt to delay radiation. Several prospective randomized trials of chemotherapy in intracranial ependymoma have failed to demonstrate a local control or survival advantage [33–35]. The efficacy of chemotherapy continues to be investigated in clinical trials.

Improvement in both surgical and radiation treatments is expected to have occurred over the time course of this study. Although we did not find a difference in outcome of our patients by year of treatment, other investigators have shown improved outcome with later eras of treatment [13]. Improved microsurgical techniques and earlier diagnosis through CT and MR imaging have contributed to improved chances of GTR at first presentation. The use of three dimensional imaging for radiation treatment planning allows for more conformal radiation delivery in the modern era. New treatment modalities such as intensity modulated radiation therapy, image guided radiation therapy, stereotactic radiosurgery and helical tomotherapy will theoretically allow for improvement in the therapeutic ratio.

Conclusions

Post-operative radiation after subtotal resection is safe and offers durable tumor control and long term patient survival.

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References

1. McCormick PC, Stein BM (1996) Spinal cord tumors in adults. In: Youman JR (ed) Neurological surgery, 4th edn. WB Saunders, Philadelphia, p 3102
2. Schiffer D (1997) Brain tumors. Biology, pathology, and clinical references, 2nd edn. Springer, Berlin
3. Kleihues P, Cavenee WK (2000) World Health Organization classification of tumours: pathology & genetics; tumours of the nervous system. IARC Press, Lyon
4. Chun HC, Schmidt-Ullrich RK, Wolfson A et al (1990) External beam radiotherapy for primary spinal cord tumors. J Neurooncol 9:211–217
5. DiMarco A, Griso C, Pradella R et al (1988) Postoperative management of primary spinal cord ependymomas. Acta Oncol 27:371–375
6. Garcia DM (1985) Primary spinal cord tumors treated with surgery and postoperative irradiation. Int J Radiat Oncol Biol Phys 11:1933–1939

7. Linstadt DE, Wara WM, Leibel SA et al (1989) Postoperative radiotherapy of primary spinal cord tumors. Int J Radiat Oncol Biol Phys 16:1397–1403
8. Read G (1984) The treatment of ependymoma of the brain or spinal canal by radiotherapy: a report of 79 cases. Clin Radiol 35:163–166
9. Shaw EG, Evans RG, Scheithauer BW et al (1986) Radiotherapeutic management of adult intraspinal ependymomas. Int J Radiat Oncol Biol Phys 12:323–327
10. Sonneland PR, Scheithauer BW, Onofrio BM (1985) Myxopapillary ependymoma. A clinicopathologic and immunocytochemical study of 77 cases. Cancer 56:883–893
11. Waldron JN, Laperriere NJ, Jaakkimainen L et al. (1993) Spinal cord ependymomas: a retrospective analysis of 59 cases. Int J Radiat Oncol Biol Phys 27:223–229
12. Wen BC, Hussey DH, Hitchon PW et al (1991) The role of radiation therapy in the management of ependymomas of the spinal cord. Int J Radiat Oncol Biol Phys 20:781–786
13. Whitaker SJ, Bessell EM, Ashley SE et al (1991) Postoperative radiotherapy in the management of spinal cord ependymoma. J Neurosurg 74:720–728
14. Fischer G, Mansuy L (1980) Total removal of intramedullary ependymomas: follow-up study of 16 cases. Surg Neurol 14:243–249
15. Greenwood J Jr (1963) Intramedullary tumors of the spinal cord. A follow-up study after total surgical removal. J Neurosurg 20:665–668
16. Hanbali F, Fourney DR, Marmor E et al (2002) Spinal cord ependymoma: radical surgical resection and outcome. Neurosurgery 51:1162–1172; discussion 1172–1164
17. McCormick PC, Torres R, Post KD et al (1990) Intramedullary ependymoma of the spinal cord. J Neurosurg 72: 523–532
18. Cooper PR (1989) Outcome after operative treatment of intramedullary spinal cord tumors in adults: intermediate and long-term results in 51 patients. Neurosurgery 25:855–859
19. Guidetti B, Mercuri S, Vagnozzi R (1981) Long-term results of the surgical treatment of 129 intramedullary spinal gliomas. J Neurosurg 54:323–330
20. Asazuma T, Toyama Y, Suzuki N et al (1999) Ependymomas of the spinal cord and cauda equina: an analysis of 26 cases and a review of the literature. Spinal cord 37:753–759
21. Cervoni L, Celli P, Fortuna A et al (1994) Recurrence of spinal ependymoma. Risk factors and long-term survival. Spine 19:2838–2841
22. Marks JE, Adler SJ (1982) A comparative study of ependymomas by site of origin. Int J Radiat Oncol Biol Phys 8:37–43
23. Mork SJ, Loken AC (1977) Ependymoma: a follow-up study of 101 cases. Cancer 40:907–915
24. McCunniff AJ, Liang MJ (1989) Radiation tolerance of the cervical spinal cord. Int J Radiat Oncol Biol Phys 16:675–678
25. Schultheiss TE, Stephens LC, Peters LJ (1986) Survival in radiation myelopathy. Int J Radiat Oncol Biol Phys 12:1765–1769
26. Wara WM, Phillips TL, Sheline GE et al (1975) Radiation tolerance of the spinal cord. Cancer 35:1558–1562
27. Marcus RB Jr, Million RR (1990) The incidence of myelitis after irradiation of the cervical spinal cord. Int J Radiat Oncol Biol Phys 19:3–8
28. Kim YH, Fayos JV (1981) Radiation tolerance of the cervical spinal cord. Radiol 139:473–478
29. van der Kogel AJ (1993) Retreatment tolerance of the spinal cord. Int J Radiat Oncol Biol Phys 26:715–717
30. Garrett PG, Simpson WJ (1983) Ependymomas: results of radiation treatment. Int J Radiat Oncol Biol Phys 9: 1121–1124
31. Kopelson G, Linggood RM, Kleinman GM et al (1980) Management of intramedullary spinal cord tumors. Radiology 135:473–479
32. Peschel RE, Kapp DS, Cardinale F et al (1983) Ependymomas of the spinal cord. Int J Radiat Oncol Biol Phys 9:1093–1096
33. Evans AE, Anderson JR, Lefkowitz-Boudreaux IB et al (1996) Adjuvant chemotherapy of childhood posterior fossa ependymoma: cranio-spinal irradiation with or without adjuvant CCNU, vincristine, and prednisone: a Children's Cancer Group study. Med Pediatr Oncol 27:8–14
34. Timmermann B, Kortmann R, Kuhl J et al (2000) Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: results of the German prospective trials HIT 88/89 and HIT 91. Int J Radiat Oncol Biol Phys 46:287–295
35. Robertson PL, Zeltzer PM, Boyett JM et al (1998) Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: a report of the Children's Cancer Group. J Neurosurg 88:695–703