

A 11-year experience of radiation therapy for Medulloblastoma at King Chulalongkorn Memorial Hospital

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Shotelersuk K, Rojpornpradit P, Khorprasert C, Lertsanguansinchai P, Asavametha N.
A 11-year experience of radiation therapy for Medulloblastoma at King Chulalongkorn
Memorial Hospital. Chula Med J 2001 Sep; 45(9): 755 - 65

- Objective** : *To evaluate the treatment outcome of medulloblastoma patients following radiation therapy.*
- Design** : *Retrospective review*
- Patients** : *Medulloblastoma patients who were registered at the Radiation Oncology Division, King Chulalongkorn Memorial Hospital between January 1987 and December 1997.*
- Method** : *Patient's medical records were reviewed. Patient's characteristics, type of treatment and survival were analyzed.*
- Results** : *There were 43 medulloblastoma patients treated with postoperative radiation therapy between 1987 and 1997. The median age was 9 years at the time of diagnosis. The male to female ratio was 1.4:1. The cerebellar vermis was the most common location of the primary tumor. The majority of the patients presented with ataxia and symptoms and signs of increased intracranial pressure. Spinal metastasis at the first presentation was diagnosed in only 2*

cases. Total or near total tumor removal was noted in 34.9%. The median radiation dose of whole brain and primary tumor were 4,000 cGy and 5,315 cGy, respectively. The median spinal dose was 2,965 cGy. The 5-year overall and disease-free survival were 57.9% and 32.16%, respectively.

Conclusion : *Postoperative radiation therapy in our medulloblastoma patients achieved comparable survival rate to previous reports.*

Key words : *Medulloblastoma, Radiation therapy.*

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Received for publication. April 20, 2001.

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สินชัย, นพดล อัสวเมธา. รังสีรักษาใน Medulloblastoma ในโรงพยาบาลจุฬาลงกรณ์.
จุฬาลงกรณ์เวชสาร 2544 ก.ย; 45(9): 755 - 65

- วัตถุประสงค์** : เพื่อศึกษาผลของการรักษา Medulloblastoma
- รูปแบบการวิจัย** : การศึกษาย้อนหลัง
- ผู้ป่วยที่ทำการศึกษา** : ผู้ป่วย Medulloblastoma ที่ได้รับรังสีรักษาหลังการผ่าตัดที่สาขารังสีรักษา
โรงพยาบาลจุฬาลงกรณ์ ระหว่าง มกราคม 2530 ถึงธันวาคม 2540
- วิธีการ** : ศึกษาเพิ่มประวัติผู้ป่วย Medulloblastoma เก็บข้อมูลและวิเคราะห์ ลักษณะ
ผู้ป่วยการรักษาที่ได้รับ และ อัตราการรอดชีวิต
- ผลการวิจัย** : มีผู้ป่วยทั้งหมด 43 ราย อายุเฉลี่ยเมื่อได้รับการวินิจฉัยโรค 9 ปี อัตราส่วน
เพศชาย ต่อเพศหญิงเท่ากับ 1.4:1 cerebellar vermis เป็นตำแหน่งที่พบ
บ่อยที่สุด ผู้ป่วยส่วนใหญ่มาพบแพทย์ด้วยอาการเดินเซ และอาการของการ
เพิ่มขึ้นของความดันในสมอง มีผู้ป่วยเพียง 2 ราย ที่ตรวจพบการแพร่
กระจายของโรคไปน้ำไขสันหลังเมื่อเริ่มวินิจฉัยโรค การผ่าตัดสามารถเอา
เนื้องอกในสมองออกได้หมดหรือเกือบหมด 34.9% ปริมาณรังสีเฉลี่ยที่ให้
ทั้งสมองเท่ากับ 4,000 cGy ในขณะที่ก่อนเนื้องอกปฐมภูมิในสมองส่วน
หลังได้รับ 5,315 cGy ปริมาณรังสีเฉลี่ยที่บริเวณไขสันหลังเท่ากับ
2,965 cGy อัตราการรอดชีวิตที่ 5 ปี เท่ากับ 57.9% และอัตราการปลอด
โรคที่ 5 ปีเท่ากับ 32.16%
- สรุป** : การรักษา Medulloblastoma ด้วยการผ่าตัด และการฉายรังสีใน
โรงพยาบาลจุฬาลงกรณ์ให้อัตราการรอดชีวิตใกล้เคียงกับที่มีรายงาน
- คำสำคัญ** : Medulloblastoma, รังสีรักษา

The incidence of childhood cancer is low, and in Thailand are 77.9 per million in boys and 61.0 per million in girls. CNS tumors are the second most common childhood tumor (after leukemia). The age standardized incidence of brain and spinal neoplasms in Thailand was 9.8 per million between 1988 and 1994.⁽¹⁾ Medulloblastoma (MB) represents the most common infratentorial brain tumor in pediatric patients.⁽²⁾ The average incidence in King Chulalongkorn Memorial hospital is 4.8 new cases per year.⁽³⁾ The standard treatment includes surgery, radiation therapy and, in some cases, chemotherapy. A risk group classification has been put into practice to evaluate the prognosis and treatment modality of these patients. Reported survival for medulloblastoma has improved over the last few decades. Recently, the role of chemotherapy has been explored in our hospital. We retrospectively reviewed our eleven-year experience in radiation therapy of medulloblastoma patients who were treated in King Chulalongkorn Memorial Hospital.

Materials and Methods

Records of histopathologically proven medulloblastoma patients who were registered at the Radiation Oncology Division, King Chulalongkorn Memorial Hospital between January 1987 and December 1997 were retrospectively reviewed. Patient characteristics, type of treatment and survival were analyzed. Staging classification was not assessed because of inadequate information. Most of the patients had not undergone MRI spine for disease staging. All patients had undergone suboccipital craniotomy with tumor removal but the extent of surgery was not available for assessment in every case.

Overall survival (OS) time was defined as the duration from surgical date to the date of last follow up or death. Disease free survival (DFS) time was measured from surgical date to the date of diagnosis of recurrent disease. Survival analysis was calculated using the method of Kaplan and Meier.⁽⁴⁾ The analyses were performed using the SPSS v. 9.05 software.

Results

Fifty-seven patients were diagnosed with histopathologically confirmed medulloblastoma between 1987 and 1997. There were forty-three patients referred for postoperative radiation therapy. The median age of the patients at the time of diagnosis was 9 years with a range from 9 months to 39 years of age. Seven cases (16.3 %) were older than 15 years old. Patient characteristics are summarized in table 1.

The tumor was located in the cerebellar vermis in 81.4%. The majority of the patients presented with ataxia and symptoms and signs of increased intracranial pressure. MRI spine was performed for staging in only 3 of 43 cases (7.5 %). Two cases were diagnosed with spinal metastasis at the first diagnosis. Tumor staging was not classified. Details of tumor size and direct tumor invasion were not available. All pathological reports revealed medulloblastoma of the cerebellum. In addition, glial cell differentiation was displayed in nine cases (20.9 %), 5 of which had prominent ependymal differentiation. Desmoplastic MB was recorded in 2 cases.

Treatment

Suboccipital craniotomy with tumor removal was performed in all cases. The extent of surgery was available for assessment in 23 cases (53.5 %). Total

Table 1. Characteristics of medulloblastoma patients treated with radiation therapy.

Characteristics		
Age	: Median (Range)	9 years (9 months-39 years)
Sex	: Male	25 cases (58.14 %)
	: Female	18 cases (41.86 %)
Tumor location		
	: Vermis	76.7 %
	: Vermis & Hemisphere	4.7 %
	: CP angle	2.3 %
	: No record	16.3 %
Clinical presentations		
	: Ataxia	62.5 %
	: Headache	70 %
	: Nausea/vomiting	50 %
	: Diplopia	7.5 %
	: Cranial nerve VII palsy	5 %
	: Weight loss	5 %

or near total tumor removal was noted in 15 cases (34.9 %) of the 43 patients treated with radiation therapy (RT). Subtotal and partial tumor removal was recorded in 2 (4.7 %) and 6 (13.9 %), respectively. Radiation treatment was completed as planned only in 36 cases (83.7 %). Whole craniospinal axis irradiation (CSI) was accomplished in 32 patients. The other four cases received only whole brain radiation with primary tumor boost; 1 of these 4 also received intrathecal chemotherapy. For the seven patients who did not complete radiation treatment, 5 did not complete either cranial or spinal radiation whereas the other 2 completed the brain radiation but not the spine RT.

Concerning radiation doses and treatment time, analysis was performed only for patients who

had completed radiation treatment for that part. All patients were treated using a Co-60 machine with some patients receiving a 10 MV Linac boost to the posterior fossa. The brain was treated with opposing lateral fields. A single daily fraction of 1.8-2 Gy was utilized. A direct posterior spine field was applied down to the level of S2-S3. The dose per fraction to the spine varied from 1 Gy to 2 Gy per day depending upon patient age and performance status. Median whole brain and primary tumor doses in 38 patients were 4000 cGy and 5315 cGy, respectively. Median treatment time for brain irradiation was 46 days (6.5 weeks). Median radiation dose to the spine in the patients who completed spinal irradiation was 2,965 cGy and median treatment time was 44.5 days (6.3 weeks). The radiation doses are summarized in table 2.

Table 2. Radiation treatment techniques.

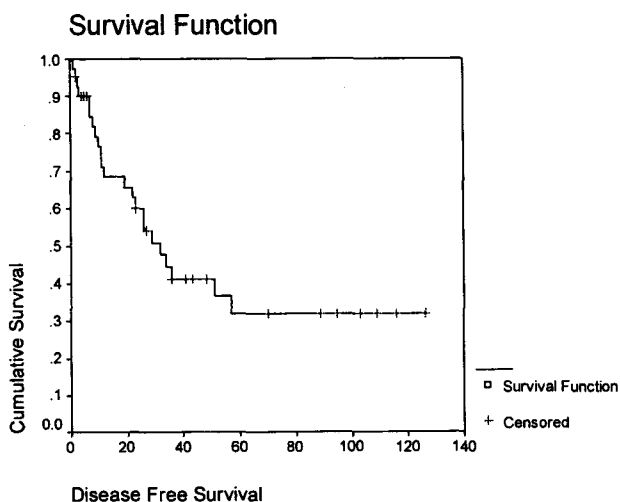
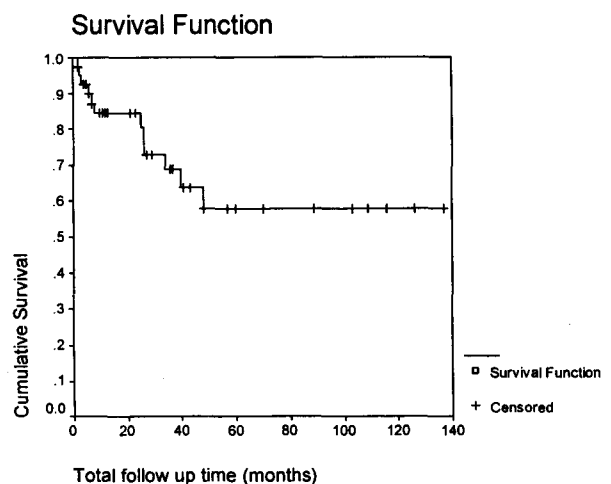
RT techniques	Complete treatment	Median dose (range)	Median treatment time (range)
Whole brain	38 cases	4,000 cGy (3060 - 4750)	
Total tumor dose	38 cases	5315 cGy (3450 - 6000)	46 days (28-71)
Spine radiation	32 cases	2,965 cGy (2,000 - 3,680)	45 days (22-290)

Four cases of the 43 patients (9.3 %) received chemotherapy. One patient aged one year and 8 months, received intrathecal chemotherapy instead of spinal irradiation. Two patients received systemic chemotherapy as adjuvant treatment after complete craniospinal axis irradiation. Pre and post RT chemotherapy was utilized in the other one patient who was 2 years old at the time of diagnosis.

Disease free survival (DFS) and Overall survival (OS)

Follow up data after radiation was obtained in 41 patients (95.3 %). One of the 2 patients not

included in the analysis of treatment results had completed craniospinal axis irradiation, the other did not complete either cranial or spinal radiation. Median follow up time was 26 months, ranging from 2 to 137 months. Sixteen of 41 cases (39 %) had recurrent disease. Nine patients developed spinal metastasis whereas six had primary tumor relapse, and one had recurrence of both primary tumor and spinal metastasis. The two year disease-free survival was 60.08 % whereas 5 year DFS was 32.16 % (Figure 1). Overall 2 and 5-year survivals were 80.54 % and 57.9 % respectively (Figure 2).

**Figure 1.** Disease free survival rate.**Figure 2.** Overall survival rate.

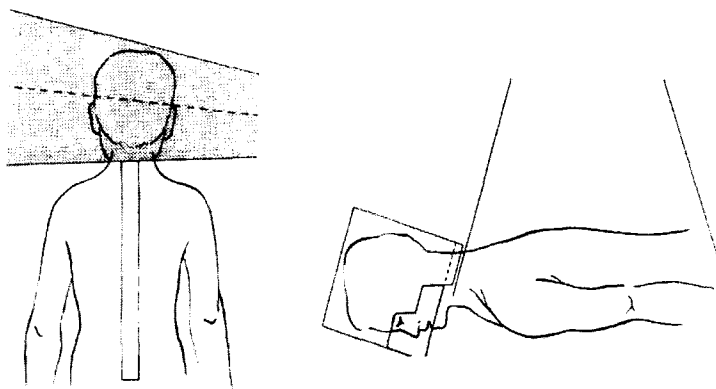


Figure 3. The standard craniospinal axis irradiation techniques.

Discussion

Medulloblastoma represents the most common malignant brain tumor in children. Craniospinal axis irradiation (CSI), combined with surgery and chemotherapy, is currently the mainstay of treatment (Figure 3). Long term survival has been achieved, especially in average-risk patients.⁽⁵⁾ A study from the Pediatric Oncology Group revealed a 67 % 5 year event-free-survival in low stage medulloblastoma receiving standard-dose neuraxis irradiation.⁽⁶⁾

The peak incidence of MB is between 5 to 10 years. Adult cases account for 15 - 20 % of all cases.⁽³⁾ In our study, the results were similar; median age was 9 years with 16 % diagnosed after 15 years old. The disease was a little more common in boys, the male to female ratio being 1.4:1. The typical location for childhood medulloblastoma is in the cerebellar vermis. The disease tends to spread within a craniospinal axis. The incidence of CSF dissemination at diagnosis is as high as 15 - 30 %. CSF dissemination may manifest as positive cytology or gross tumor seeding in the subarachnoid space. Extra CNS metastasis is less common.^(3,5) In our study, cerebellar vermis was the primary tumor location in 81.4 %. However, we found only 2 patients who had spinal metastasis at the first diagnosis. This is because only 3 cases had staging MRI spine and data from CSF cytology

was not available for analysis. At the present time, MRI spine is undertaken in every case with newly diagnosed medulloblastoma to attempt early detection of leptomeningeal disease. Currently, Magnetic Resonance Imaging of the spine is recommended for staging work up in all medulloblastoma patients because leptomeningeal disease significantly affects the prognosis and treatment. Fouladi M et al. reported 20 % discordant results between CSF cytology and spinal MRI. Positive MRI with negative CSF cytology was found in 8.5 % whereas 11.3 % with positive cytology had negative MRIs.⁽⁷⁾ Meyers SP et al. found that spinal MRI had greater diagnostic accuracy than CSF cytologic analysis in the early detection of disseminated medulloblastoma. Moreover, delaying spinal MRI and CSF cytology by more than 2 weeks after surgery can reduce false-positive results.⁽⁸⁾

Medulloblastoma is referred to as primitive neuroectodermal tumor of the cerebellum and then subdivided on the basis of cellular differentiation.⁽⁹⁾ We found 20.9 % cases of glial cell differentiation, 5 of which had prominent ependymal differentiation. Desmoplastic MB was recorded in 2 cases. Correlation of the histopathological reports with treatment results was not attained because of the small number of patients.

Surgery, removing as much tumor as possible, and craniospinal axis irradiation has been the standard approach for medulloblastoma for several decades. There is evidence to suggest that more extensive surgical resections are related to an improved survival rate, especially in nondisseminated medulloblastoma.⁽⁹⁻¹¹⁾ However, one report has shown that there is no statistically significant difference in survival between total and subtotal resection.⁽¹²⁾ Residual tumor less than 1.5 cm has been classified as average risk with more than 1.5 cm as poor risk.⁽¹³⁾ We discovered that total, near total or subtotal resection was possible in 39.5 % of our patients. As the extent of surgery was available for assessment only in 23 cases (53.5 %), the survival impact was not evaluated.

Concerning postoperative radiation therapy, the craniospinal dose is typically 3,600 cGy in 20 fractions, and the dose to the posterior fossa 5,400 - 5,580 cGy. These doses are usually reduced in children younger than 2 or 3 years old. Five-year survival rates range from 50 % to 65 % or higher.⁽⁶⁾ Our results were quite comparable with other reports. The 2-year and 5-year survival rates were 80.54 % and 57.9 %, respectively. The 5-year disease free survival was 32.16 %. The majority of recurrences were spinal (62.5 %) and primary tumor (43.75 %). No case of extra-CNS metastasis was demonstrated. The seven patients who did not complete radiation treatment as planned had poor outcomes. Only one case was alive after 5 years. In the patients who received RT as planned, 4 cases did not obtain spinal RT. Three of these had spinal recurrence. Surprisingly, one patient still survived without disease after 10 years.

In this case series, adult medulloblastoma seemed to have favorable prognosis. Four in seven

cases had long term survival (43, 60, 116 and 137 months). A retrospective review of 32 adult MB from MGH showed that 5-year disease free and overall survival rates were 57 % and 83 %, respectively.⁽¹⁴⁾ A greater ability to tolerate and complete treatment in adults might be an explanation for the improvement of outcome. Nonetheless, the median follow up time of our patients was quite limited (26 months). Therefore, any interpretation of long term survival has to be made cautiously.

Craniospinal axis irradiation needs meticulous treatment planning and set up. The literature indicates that inadequate radiation volumes, particularly at the cribiform plate or junction of cranial and spinal field, will increase recurrence risk.^(15,16) Altering fractionation has not demonstrated any survival benefit in MB patients.⁽¹⁷⁾ The role of proton therapy is being investigated.⁽¹⁸⁾ Review of radiation treatment techniques in this study was not done because a number of patients did not have simulation films.

Due to concern of debilitating effects on growth and neurologic development, reduced doses of the craniospinal axis with or without chemotherapy have been extensively studied. Attempts to lower the craniospinal axis to 2,340 cGy in average risk medulloblastoma have resulted in an increased incidence of isolated leptomeningeal relapse and lower 5 year EFS and overall survival than standard dose radiation.^(6,19) There is no definite evidence that adjuvant chemotherapy improves the outcome in average risk medulloblastoma.⁽²⁰⁾ Studies of the role of reduced dose craniospinal radiation with chemotherapy have been ongoing. A recent report from Children Cancer Group Study showed 79 % 5 year progression free survival from reduced dose

CSI with adjuvant chemotherapy in non disseminated medulloblastoma. ⁽²¹⁾ Currently, the outcome of reduced dose craniospinal axis radiation is being explored in our hospital.

Chemotherapy has been shown to be active in recurrent medulloblastoma. Survival benefit has also been demonstrated from adjuvant chemotherapy in poor-risk patients. ^(22 - 24) Additionally, postoperative chemotherapy can be used to delay radiation therapy in children less than three years of age. ⁽²⁵⁾ Our current protocol allows a greater role for chemotherapy. Further studies are needed in this field.

Conclusion

Results of postoperative radiation therapy in our medulloblastoma patients appear comparable to previous reports. However, long-term outcome needs cautious interpretation due to limited median follow-up time. Further study of the role of chemotherapy awaits a long-term follow up.

Acknowledgement

The authors are grateful to Dr. Suree Thitathan and Dr. Prabhatsorn Rajatapiti for good patient care and Ms. Arunee Puangnak for her excellent computergraphic work. This work was supported by Development Grants for New Faculty / Researchers of Chulalongkorn University.

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