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Postoperative External Beam Radiotherapy for Medulloblastoma

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Purpose : This study was performed to evaluate the effectiveness and tolerance of craniospinal irradiation for patients with medulloblastoma and to define the optimal radiotherapeutic regimen.

Materials and Methods : We retrospectively analyzed the records of 43 patients with medulloblastoma who were treated with external beam craniospinal radiotherapy at our institution between May, 1984 and April, 1998. Median follow up period was 47 months with range of 18 to 86 months. Twenty seven patients were male and sixteen patients were female, a male to female ratio of 1.7 : 1. Surgery consisted of biopsy alone in 5 patients, subtotal excision in 24 patients, and gross total excision in 14 patients. All of the patients were treated with craniospinal irradiation. All of the patients except four received at least 5,000 cGy to the posterior fossa and forty patients received more than 3,000 cGy to the spinal cord.

Results : The overall survival rates at 5 and 7 years for entire group of patients were 67% and 56%, respectively. Corresponding disease free survival rates were 60% and 51%, respectively. The rates of disease control in the posterior fossa were 77% and 67% at 5 and 7 years. Gross total excision and subtotal excision resulted in 5 year overall survival rates of 76% and 66%, respectively. In contrast, those patients who had biopsy alone had a 5 year survival rate of only 40%. Posterior fossa was a component of failure in 11 of the 18 recurrences. Seven recurrences were isolated to the posterior fossa. Four patients had neuraxis recurrences, three had distant metastasis alone and four had multiple sites of failure, all involving the primary site.

Conclusion : Craniospinal irradiation for patients with medulloblastoma is an effective adjuvant treatment without significant treatment related toxicities. There is room for improvement in terms of posterior fossa control, especially in biopsy alone patients. The advances in radiotherapy including hyperfractionation, stereotactic radiosurgery and 3D conformal radiotherapy would be evolved to improve the tumor control rate at primary site.

Key Words : Medulloblastoma, Radiotherapy

INTRODUCTION

Medulloblastoma is the most common posterior fossa tumor of childhood, and accounts for approximately 25% of all pediatric brain tumors. The chance of surviving five years with medulloblastoma has significantly improved over the past four decades, partly because of the use of chemotherapy, advances in surgical techniques, and better imaging and staging.[1~6] Medullublastoma remains one of the most intriguing tumors studied and treated by the multidisciplinary oncology team because of its unique clinical and pathological characteristics and apparent radiocurability. Standard therapy consists of maximal resection compatible with good neurological outcome and postoperative craniospinal radiation therapy with a boost to the primary site of disease in the posterior fossa using conventional fractionation schemes.[7, 8]

Although the treatment volumes and doses have changed little during the past 40 years, the treatment of medulloblastoma continues to evolve. Radiation doses are altered based on the age of the patient and the perceived risk of recurrence. Likewise, chemotherapy is used based on the age of the patient and the presence of factors prognostic for high risk of failure. The specific role of chemotherapy and

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optimal regimen remain unclear.[9]

We have retrospectively analyzed the records of the patients with medulloblastoma treated in our Department between May, 1984 and March, 1998. Also, we compared the results following radiotherapy with other studies and tried to define possible treatment related toxicites to evaluate the effectiveness and tolerance of external beam radiotherapy. Although treatment policy for medulloblastoma was relatively unique in our instituion, we evaluated the results including survival in terms of extent of surgery to define the optimal radiotherapeutic regimen.

MATERIALS AND METHODS

We retrospectively analyzed the records of 43 patients with medulloblastoma who were treated with postopreative external beam radiotherapy with curative intent at our institution between May, 1984 and March, 1998. Median follow up was 47 months with range of 18 to 86 months. Two patients were lost to follow up at 4 and 5 years from date of diagnosis and were censored from analysis at the date of last follow up. Median patient age was 7 years with range of 3 to 37 years. Twenty seven patients were male and sixteen patients were female with male to female ratio of 1.7 : 1.

All of the patients had either Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) to evaluate primary tumor. Thirty two patients had CT alone and 7 patients had MRI alone. The remaining 4 patients underwent both CT and MRI. Spine was evaluated by MRI in 5 patients and CT myelogram in 3 patients. Cerebrospinal Fluid cytology was examined in only 12 patients and one patient was positive for cytology. Histologic confirmation of medulloblastoma was obtained in all patients. If both the operative report and postoperative imaging indicated complete removal of visible tumor, the resection was considered to be gross total removal. Surgery consisted of biopsy alone in 5 patients (12%), subtotal excision in 24 patients (56%), and gross total excision in 14 patients (33%). Distribution of patients according to extent of surgery is shown in Table 1.

All patients received radiation therapy to the craniospinal axis and a boost to the posterior fossa except one patient. Most patients were treated in prone position with custom designed mold. Unitl 1987, Cobalt 60 teletherapy Unit was employed to treat the patients and 6 MeV Linear Accelerator was employed thereafter. Parallel opposed lateral fields were used to treat whole brain and single posterior field was used to treat spinal cord to the level of S2. If the single posterior spine field was not able to cover the entire spine, two separate posterior fields were employed with appropriate gap between two spinal fields. The gap was calculated to match the cranial fields and spinal field and gap was moved once a week with 1 cm up and down. The posterior fossa boost treatment was delivered through lateral parallel opposed fields after completing of the cranial fields.

Tumor doses were calculated to midplane of the central axis for both cranial and posterior fossa fields. Because off-axis calculation for the cranial field was not available, the dose to the posterior fossa represents the sum of the midplane central axis doses for the cranial and posterior fossa fields. The spinal dose was prescribed at 3 cm or 5 cm depth depending on thickness of the patient in CT or MRI imaging. All of the patients were treated with conventional fractionation scheme. Total of 3,600 cGy was delivered to whole brain with 180 cGy daily fraction, 5 times a week. Simultaneously spinal cord was treated with 180 cGy daily fraction with gap. After completion of whole brain, posterior fossa was boosted with cone down fields. Table 2 showed distribution of the patients according to dose to primary site and spinal cord. Majority of patients received 5,400 cGy to primary site. One patient received only 3,600 cGy to whole brain and was not able to receive boost

Table 1. Patients Distribution According to Extent of Surgery

Extent of surgery	Number of patients
Biopsy alone	5 (12%)
Subtotal excision	24 (56%)
Gross total excision	14 (33%)
Total	43 (100%)

Table 2. Distribution of Patients According to Dose to Spinal Cord and Posterior Fossa

Dose	Spinal cord	Posterior fossa
< 30 Gy	3	
30~35 Gy	27	
35~40 Gy	13	
< 45 Gy		1
45~50 Gy		3
50~55 Gy		36
55~60 Gy		3
Total	43	43

because of poor tolerance. Also most of patients received 3,240 cGy to the spinal cord although majority of patients treated in 1980s received 3,600 cGy to the spinal cord. Only 3 patients received less than 3,000 cGy to the spinal cord.

Nine patients received adjuvant chemotherapy. Six patients were treated with adjuvant chemotherapy after radiotherapy and three patients before and after radiotherapy. Because criteria for chemotherapy had not been standardized during the study period, analysis of the impact of chemotherapy was not made at this report. Site of recurrence was evaluated in most of the relapsed patients although there was difficulty in reviewing the records because of inadequate follow up. Of five patients who underwent biopsy alone, response to radiotherapy was evaluated with follow up CT or MRI in only 3 patients. Survival rates were obtained with Kaplan-Meier method. Statistical comparisons were made using Chi square test.

RESULTS

The overall survival rates at 5 and 7 years for the entire group of 43 patients were 67% and 56%, respectively (Fig. 1). Corresponding disease-free survival rates were 60% and 51%, respectively (Fig. 2). The rates of disease control in the posterior fossa were 77% and 67% at 5 and 7 years (Fig. 3).

Site of relapse in recurred patients is shown in Table 3. The posterior fossa was a component of failure in 11 of the 18 recurrences (61%). Seven recurrences were isolated to the posterior fossa. The median time to failure in the posterior fossa was 27 months and all failures occured within Collins' risk period that is age at the time of presentation plus 9 months. Four patients had neuraxis recurrences, three had distant metastasis alone and four had multiple sites of failure, all involving the primary site. One patient developed distant metastasis at various sites of bone including femur, tibia and ribs which were treated with several courses of palliative radiotherapy and she is alive at the time of

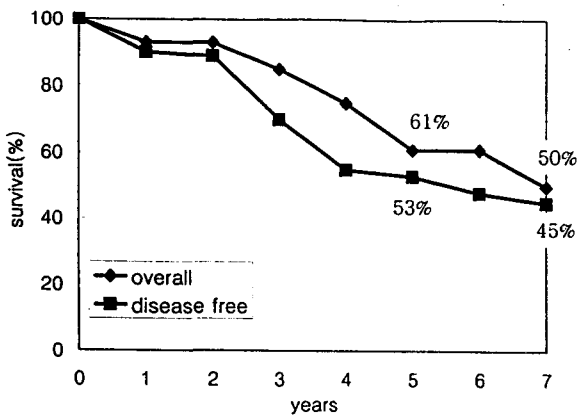

Fig 1. Overall survival rates for entire group of patients.

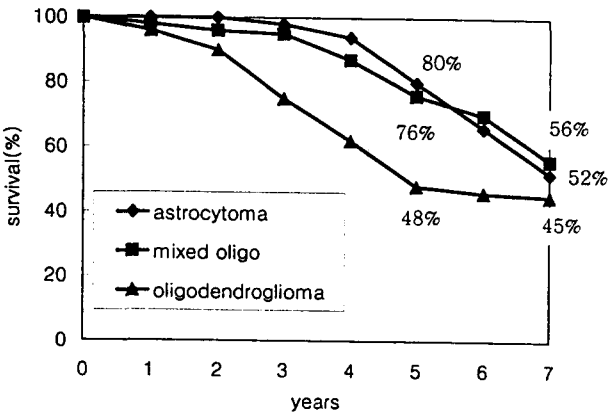

Fig 2. Disease free survival rates for entire group of patients.

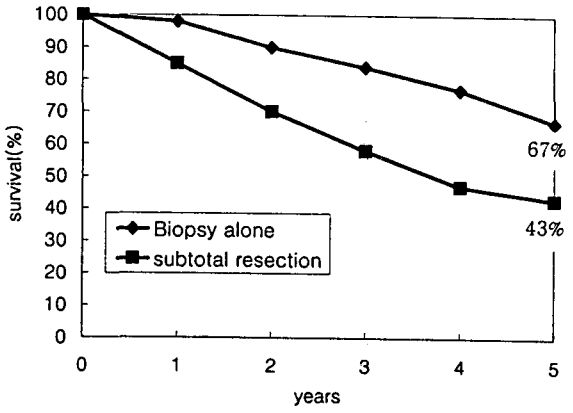

Fig 3. Rate of freedom from posterior fossa recurrence for all patients.

Table 3. Site of Relapse in Recurred Patients

Site	Number of patients
Primary site	7
Neuraxis alone	4
Distant metastasis	3
Primary site and other	4
Total	18

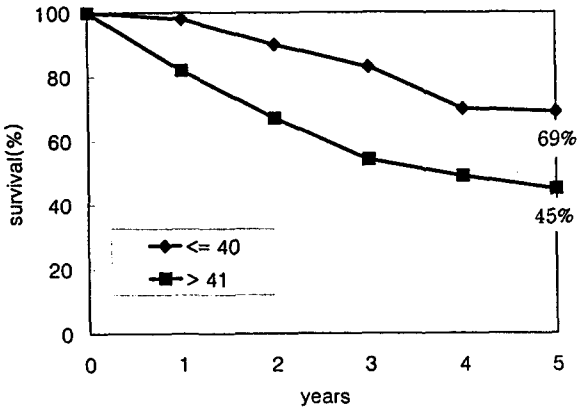

Fig 4. Overall survival rates according to extent of surgery.

analysis.

The overall survival rate according to extent of surgery is shown in Fig. 4. An improved survival was noted with gross total or sutotal resection compared to biopsy alone, although it was not statistically significant because of small number of patients in each group of patients. Gross total excision and subtotal excision resulted in 5 year overall survival rates of 76 and 66%, respectively. In contrast, those patients who had biopsy alone had a 5 year survival rate of only 40% and a local control rate of only 40%. This was most likely due to the fact that biopsy alone patients had more advanced disease. Of five patients who underwent biopsy alone, 3 patients had follow up CT or MRI. Two patients were noted to have complete response and one patient was considered to have partial response.

There was no significant treatment related toxicities although six patients had to have a break during the treatment time. Review of the records showed endocrine abnormalities in 3 patients and poor mental capacity in 2 patients. Because of the young age of some patients, all of the possible late complications have not yet developed. No secondary tumors have developed.

DISCUSSION

The improvement in treatment of medulloblastoma over the past 30 years has influenced the survival in medulloblastoma. Once considered universally fatal, improvements in neurosurgical technique, chemotherapy and radiotherapy have increased survival rates to 60~70% at 5 years.[1, 10] Recent studies demonstrated that the extent of surgical resection is important prognostic factor[1, 5, 10~12] and our study showed similar results compared with those studies. A maximal resection should be attempted with avoiding major morbidity, since patients treated with subtotal resection may yield similar survival rates to those treated with total resection.[12, 14] In our study, gross total excision and subtotal excision resulted in 5 year survival rates of 76% and 66%, respectively and this was not statistically significant. Although patients treated with biopsy alone showed poor prognosis, it is important to recognize that these patients usually have more advanced disease at the time of presentation.

There has been progress in the radiotherapy of medulloblastoma over the past decades. Analyzing the treatment factors influencing posterior fossa and spinal tumor control as well as survival, it is clear from other studies that craniospinal irradiation is a necessary part of medulloblastoma treatment.[3, 5, 7, 10, 13, 14] Landberg et al. reported a 5% survival rate in patients receiving only posterior fossa irradiation and 53% survival rate for patients treated with craniospinal irradiation followed by a posterior fossa boost.[2]

The optimal dose of craniospinal irradiation has not been well established, though recent data are relevant. A number of single institution reports suggest that doses of craniospinal irradiation below 30 Gy may be as effective as higher doses.[5, 15~18] However, Deutsch et al.[18] reported different preliminary results of a randomized study by the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) comparing standard (36 Gy) versus lower dose (23.4 Gy) craniospinal irradiation in patients with standard risk disease. In both arm of the study, craniospinal irradiation was followed by a posterior fossa boost to bring the dose to 54.0 Gy. No chemotherapy was given in this study. Patients who received standard dose craniospinal irradiation had a 3 year disease free survival rate of 80%, compared with 56% corresponding survival rate in reduced dose patients.[19] Therefore, dose reduction to 23.4 Gy would not appear safe even in favorable patients. Lower craniospinal irradiation doses appear to be successful for patients treated with chemotherapy as well as radiotherapy,[20, 21] although a POG-CCG trial randomizing standard risk patients between 36.0 Gy versus 23.4 Gy and chemotherapy followed by a posterior fossa boost was aborted because of insufficient accrual.

The dose to primary site to achieve adequate local control has been well established. Berry et al. demonstrated poor local control with doses less than 52 Gy.[22] Also Silverman

and Simpson reported that at least 50 Gy was required to obtain successful posterior fossa control.[6] In our study no dose response conclusion was made because only a few patients received less than 50 Gy to the primary site. Standard therapy should imply the doses of 54 to 55.8 Gy to the posterior fossa.

As far as treatment related complication is concerned, all of the patients tolerated radiotherapy well without serious acute toxicities, although six patients had to have a treatment break during the treatment time. The late complications were very difficult to define because of the relatively inadequate follow up. However, review of the records showed 3 patients developed endocrine abnormalities and 2 patients did poor mental capacity. Thus we might commit that craniospinal radiotherapy of medulloblastoma is a safe and effective modality of the treatment.

Also, This study suggest that there is room for improvement in terms of posterior fossa control, especially more advanced disease. The medulloblastoma patients with more advanced disease particularly those with large and unresectable primary tumors may require more aggressive treatment including higher posterior fossa doses. This can be achieved by recent technological advances in radiotherapy. These advances might include hyperfractionation, stereotactic radiosurgery, or 3D conformal radiotherapy.

CONCLUSION

Our study showed patients with medulloblastoma can be effectively treated with craniospinal irradiation without significant treatment related toxicities. There is room for improvement in terms of posterior fossa control. Thus the advances in radiotherapy including hyperfractionation, stereotactic radiosurgery, and 3D conformal radiotherapy can be developed to improve the local control at primary site.

REFERENCES

1. **King GA, Sagerman RH.** Late recurrence in medulloblastoma. Am J Roentgenol Radium Ther Nucl Med 1975; 123: 7-12
2. **Landberg TG, Lindgren ML, Cavallin-Stahl EK, et al.** Improvements in the radiotherapy of medulloblastoma. Cancer 1980; 45:670-678
3. **Paterson E, Farr RF.** Cerebellar medulloblastoma : Treatment by irradiation of the whole central nervous system. Acta Radiol 1953; 39:323-336
4. **Chatty EM, Earle KM.** Medulloblastoma : A report of 201 cases with emphasis on the relationship of histologic variants to survival. Cancer 1971; 28:977-983
5. **Harisiadis L, Chang CH.** Medulloblastoma in children : A correlation between staging and results of treatment. Int J Radiat Oncol Biol Phys 1977; 2:833-841
6. **Silverman CL, Simpson JR.** Cerebellar medulloblastoma : The importance of posterior fossa dose to survival and patterns of failure. Int J Radiat Oncol Biol Phys 1982; 8: 1869-1876
7. **Bloom HJ.** Medulloblastoma in children : Increasing survival rates and further prospects. Int J Radiat Oncol Biol Phys 1982; 8:2023-2027
8. **Tomita T, McLone DG.** Medulloblastoma in childhood : Results of radical resection and low dose neuroaxis radiation therapy. J Neurosurg 1986; 64:238-242
9. **Packer RJ, Sutton LN, Golwein JW, et al.** Improved survival with the use of adjuvant chemotherapy in the treatment of medulloblastoma. J Neurosurg 1991; 74:433-440
10. **Chang CH, Housepian EM, Herbert C Jr.** An operative staging system and a megavoltage radiotherapeutic technique for cerebellar medulloblastoma. Radiology 1969; 93:1351-1359
11. **Norris DG, Bruce DA, Byrd RL, et al.** Improved relapse-free survival in medulloblastoma utilizing modern techniques. Neurosurgery 1981; 9:661-664
12. **Jenkin D, Goddard K, Armstrong D, et al.** Posterior fossa medulloblastoma in childhood : Treatment results and a proposal for a new staging system. Int J Radiat Oncol Biol Phys 1990; 19:265-274
13. **Jenkin RD.** Medulloblastoma in childhood : Radiation therapy. Can Med Assoc J 1969; 100:51-53
14. **Merchant TE, Wang MH, Haida T, et al.** Medulloblastoma : Long-term results for patients treated with definitive radiation therapy during the computed tomography era. Int J Radiat Oncol Biol Phys 1996; 36:29-35
15. **Brand WN, Schneider PA, Tokars RP.** Long-term results of a pilot study of low dose cranial-spinal irradiation for cerebellar medulloblastoma. Int J Radiat Oncol Biol Phys 1987; 13:1641-1645
16. **Duffner PK, Cohen ME, Voorhess ML, et al.** Long-term effects of cranial irradiation on endocrine function in children with brain tumors. A prospective study. Cancer 1985; 56: 2189-2193
17. **Evans AE, Jenkin RD, Sposto R. et al.** The treatment of medulloblastoma. Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. J Neurosurg 1990; 72:572-582
18. **Kun LE, Constine LS.** Medulloblastoma-caution regarding new treatment approaches. Int J Radiat Oncol Biol Phys 1991; 20:897-899
19. **Deutsch M, Thomas P, Boyett J, et al.** Low stage medulloblastoma : A Childrens Cancer Study Group and Pediatric

Oncology Group randomized study of standard vs reduced neuraxis irradiation. Proc Annu Meet Am Soc Clin Oncol 1991; 10:124

20. **Goldwein JW, Radcliffe J, Packer RJ, et al.** Results of a pilot study of low-dose craniospinal radiation therapy plus chemotherapy for children younger than 5 years with primitive neuroectodermal tumors. Cancer 1993; 71:2647-2652
21. **Goldwein JW, Radcliffe J, Johnson J, et al.** Updated results of a pilot study of low dose craniospinal irradiation plus chemotherapy for children under five with cerebellar primitive neuroectodermal tumors (medulloblastoma). Int J Radiat Oncol Biol Phys 1996; 34:899-904
22. **Berry MP, Jenkin RD, Keen CW, Nair BD, Simpson WJ.** Radiation treatment for medulloblastoma. A 21-year review. J Neurosurg 1981; 55:43-51

국문 초록

수아세포종의 수술 후 외부 방사선치료

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전 하 정 · 이 명 자

목 적 : 수아세포종에 대한 수술 후 두개척수 방사선종양학 의학용어집에 따라 방사선치료의 효과를 평가하고 최적의 방사선치료 방법을 알아보고자 함이 본 연구의 목적이다.

대상 및 방법 : 1984년 5월부터 1998년 4월까지 본원 치료방사선과에서 두개척수 외부 방사선치료를 받은 43명의 수아세포종 환자를 후향적으로 분석하였다. 추적기간은 18개월에서 86개월이었으며 중앙추적기간은 47개월이었다. 남자는 27명이었고 여자는 16명으로서 남자와 여자의 비율은 1.7 : 1이었다. 5명의 환자에서는 조직검사만을 시행하였고 14명에서는 육안적 완전절제술, 나머지 24명의 환자에서는 아절제술을 시행하였다. 모든 환자는 두개척수 방사선치료를 받았고, 39명의 환자는 최소 5,000 cGy의 방사선을 원발부위에 조사받았으며 40명의 환자는 최소 3,000 cGy의 방사선을 척수에 조사받았다.

결 과 : 대상환자 43명의 5년 및 7년 생존율은 67% 및 56%이었고, 5년 및 7년 무병생존율은 각각 60% 및 51%이었다. 원발병소의 국소제어율은 5년 및 7년에 각각 77% 및 67%이었다. 육안적 완전절제술 및 아절제술을 시행받은 환자의 5년 생존율은 각각 76% 및 66%이었으며 반면에 조직검사만을 시행받은 환자는 5년 생존율이 40%에 불과하였다. 총 18명의 재발환자 중 11명에서 원발부위가 재발부위이었으며 7명의 환자는 원발병소에서만 재발하였다. 4명의 환자는 척수에서, 3명의 환자는 원격전이만을 보였고 나머지 4명의 환자에서는 원발부위를 포함하여 여러부위에서 재발하는 양상을 나타내었다.

결 론 : 수아세포종의 뇌척추 방사선치료는 유의한 치료 부작용이 없는 효과적인 치료요법이었다. 그러나 원발부위의 국소치료효과를 높이기 위하여 개선하여야 할 점이 있는 것으로 사료되며 이는 다분할조사, 정위적 방사선수술 및 삼차원 입체 조형치료 등 방사선요법의 기술적 발전으로 이루어 질 수 있을 것으로 생각된다.

핵심용어 : 수아세포종, 방사선치료