

Personal Practice

Modern Management of Medulloblastoma in Children: An Up-date of Literature Review

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Abstract

Medulloblastoma is one of the most frequent intracranial tumours of children. Advances in the surgical and adjuvant management have significantly improved the outcome of children with medulloblastoma. The 5-year survival rate of 30% in 1960s has risen to 70% now. Modern management of medulloblastoma emphasises: 1) aggressive surgery for tumour resection and release of hydrocephalus; 2) postoperative intensive adjuvant therapy. Chemotherapy is the choice for young children while radiotherapy is delayed until they reach three years of age or disease progress. Chemotherapy is used in conjunction with standard-dose radiotherapy for high-risk children, and with reduced-dose for average-risk children. The treatment of patients with recurrent disease remains a major challenge. Studies are still ongoing for further improving the survival rate while minimising treatment-induced morbidity.

Key words

Medulloblastoma; Primitive neuroectodermal tumour

Introduction

Medulloblastoma is a primitive neuroectodermal tumour arising in the posterior fossa. It is one of the most frequent intracranial tumours in children. During the last 25 years, there have been great advances in the management of the disease. The overall all 5-year survival rates of 30% in the

1960s has now risen to 70%. Studies are still ongoing for not only further improving the survival rate but also minimising treatment-induced morbidity. More data now are available on the outcome of long-term survivors. In this paper, based on the previous reviews by other authors,¹⁻⁴ we take a critical look into the up-to-date literature on the management of medulloblastoma together with a brief account of our experience.

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Terminology

Bailey and Cushing⁵ first used the term "medulloblastoma" in 1925 to describe a pluripotential embryonal tumour that arose in the cerebellum in the belief that these tumours was derived from a multipotential medulloblast. The term "primitive neuroectodermal tumours (PNETs)" was proposed by Hart and Earle⁶ in 1973 to include medulloblastoma and similarly appearing central nervous system neoplasms. Histopathologically, both the medulloblastoma and PNETs are composed of round, poorly differentiated cells with sparse cytoplasm and hyperchromatic nuclei. However, the incidence and prognosis of supratentorial and infratentorial PNET are different. The terms "medulloblastoma" and "infratentorial

PNET" are now used interchangeably. In this paper, "medulloblastoma" is the same as "infratentorial PNET", i.e. PNET that originate in the posterior fossa.

Histopathology and Clinical Outcome Correlation

Prediction of outcome may help to avoid both under-treatment and over-treatment. There is increasing evidence that clinical outcome may, to some extent, depend on the histological type of medulloblastoma. The large cell/anaplastic types and the extensive nodularity/desmoplastic types were associated with a worse and better outcome respectively.⁷⁻¹⁰ Among 330 patients evaluated, increasing grade of anaplasia and the extent of anaplasia were associated strongly with progressively worse clinical outcome. No increasing degree of nodularity nor desmoplasia were associated with longer survival. A pathological grading with respect to anaplasia has been proposed.¹⁰ On the other hand, age was reported to be more important than histological type in predicting the tumour behaviour.¹¹ In one study, a total of 181 medulloblastoma with respect to clinical and histological and biological characteristics were studied. Lower growth rate parameters (mean MIB-1 labelling index, apoptotic index, ratio of apoptotic to MIB-1 index) were associated with adult as compared to childhood tumour. No difference was noted in any of the parameters when classical and desmoplastic types were compared as a whole.¹¹ In another study, only Calbindin-d(28k), an expression of the Ca(2+)-binding protein, was reported recently to be the only factor significantly associated with recurrence and poor clinical outcome among other biological markers.¹²

Diagnostic Evaluation

Depends on the symptoms and signs, Computed Tomography (CT) or magnetic resonance imaging (MRI) can each be the first choice to establish the diagnosis of a posterior fossa tumour. Based on the initial cranial imaging, we routinely obtain spinal MRI preoperatively whenever possible for two reasons: 1) medulloblastoma has a significant incidence of cerebrospinal fluid (CSF) dissemination; 2) Artifacts as well as meningeal enhancement from blood product may make the interpretation of images difficult during the first few postoperative weeks, which may delay appropriate adjuvant

therapy. Meningeal Gd-DTPA enhancement lasting for two weeks on MRI T1-weighted images was observed in patients undergone posterior fossa tumour surgery but not in patients undergone cranial surgery for cyst resection or fenestration, probably related to bleeding into subarachnoid space during the operation.¹³

Surgical Management

Preoperative Management and Timing of Operation

Hydrocephalus is usually the key factor to determine how fast that we should move on to surgery. Patients with hydrocephalus presented with headache, vomiting and neck stiffness are at high risk of sudden deterioration due to tonsil herniation. They may suddenly develop apnea after an episode of vomiting. CSF shunting was advocated as a temporising measure before resection of a midline posterior fossa tumour with associated hydrocephalus.^{14,15} However, on one hand definitive internal CSF shunting may be needed in as low as 5-8% of all the patient with medulloblastoma;² on the other hand there are risks associated with shunting including upward tentorial herniation,¹⁶ bleeding into tumour.¹⁷ The modern management for hydrocephalus due to medulloblastoma is external ventricular drainage prior to or together with tumour excision.^{2,3} We usually complete craniospinal MRI and perform external ventricular drainage together tumour excision within one to two days of admission. If a patient is presented with alarming hydrocephalus, we will perform an external ventricular drainage first, then complete the necessary investigations and proceed to tumour excision the next day.

Operation

An external ventricular drainage is placed for relief of hydrocephalus to facilitate tumour resection intra-operatively, and for intracranial pressure (ICP) monitoring post-operatively. Most of the surgeons prefer, as we do a modified prone position (concorde) for a posterior fossa midline tumour.¹⁸ Care must be taken to avoid over-flexion of the neck.¹⁹ A posterior fossa craniectomy or craniotomy (our preference) is performed. The foramen magnum is routinely opened. Whether C1 laminectomy is required depends on how inferior the tumour is located. Typically, the tumour is approached from midline through the vermis. After tumour debulking by coring out the tumour from the center, the floor of 4th ventricle is identified through the foramen of Megandie. Working rostrally the aqueduct comes into view. Although a tumour capsule is never

present, a clear demarcation between tumour and normal brain is often apparent. Following the plane between the tumour and the cerebellum, the tumour is resected along both sides. The foramen of Lusk on both sides of the 4th ventricle should be examined to look for tumour extension. Areas where the tumour invades the cerebellar peduncles and brain stem are left for last. To minimise the risk of postoperative neurological deficit, resecting the tumour flushing these surfaces without violating them is recommended because microscopic residual disease does not appear to adversely affect prognosis.³

Neurophysiological intraoperative monitoring or mapping can be useful adjunct of the surgery to facilitate radical excision while minimise neurological deficit. These include somatosensory brain stem auditory evoked potentials and intraoperative electrical stimulation in conjunction with lower cranial nerve electromyography.^{3,20} Depending on the predominant direction of tumour growth, such as brainstem invasion or cerebropontine angle extension, the sixth, seventh, ninth, tenth, and twelfth cranial nerves are all can be monitored.

Postoperative Management

Majority of our patients extubated after the surgery and observed in the Intensive Care Unit with ICP monitoring. In children who fail to wake up promptly after anaesthesia, or whose ICP is high, an urgent CT scan should be obtained to rule out intracranial haemorrhage. Otherwise, a postoperative MRI is performed during the first 48 hours after surgery to look for residual tumour for two reasons: 1) to look for any residual tumour, its size and see if still resectable; 2) distinguish of postoperative change from residual tumour will be difficult on a late image, and thus delayed the decision for surgery or adjuvant therapy, which affects the outcome. If a residual tumour is found more than 1.5 ml and is still resectable, early re-operation will be carried out with the aim to complete tumour resection or to reduce its volume to below 1.5 ml. Hydrocephalus may persist in the initial postoperative days but with the subsiding of brain oedema and re-opening of the 4th ventricle, the extraventricular drainage can be removed in many of the patients. Persistent high ICP with high CSF output or the development of a large pseudomeningocele signify unresolved hydrocephalus. Third ventriculostomy has been performed increasingly to avoid an internal shunt.² The chance of systemic metastasis via a internal shunt is small but exists.^{14,21-24} The addition of millipore filters to the shunt system to prevent dissemination has been

associated with a high rate of shunt failure,²⁵ and is not routinely recommended.

Surgical Complications

Neurological complications ranged from minor to severe have been reported in late 1980s and early 1990s approximately 25-40% of patients.^{18,26} but have decreased now.² A potentially serious problem is lower cranial nerve and brain stem dysfunction which may require a prolonged period of intubation and possibly tracheostomy and gastrostomy. Mutism has been reported from rare² to 10% of the children.²⁷⁻³⁰

The operative mortality rate (death within one month of surgery) is approaching zero now but remain important for infants.²⁸ It is mainly related to cerebellar haemorrhage, brain stem swelling or ischaemia.³¹

Postoperative Staging and Clinical Prognostic Factors

Accurate postoperative staging is essential for the prognosis and subsequent oncological management. The Chang system,³² a preoperative staging system, has been widely used based on tumour size and extent (T-stage) and the presence and location of metastases (M-stage). The presence of metastases has consistently been shown to be an adverse prognostic factor. The 5-year survival rate of patient without metastasis was more than twice that of patients with metastasis,³³ irrespective of the extent of surgical resection and the tumour volume. However, studies have shown that the extent of residual disease correlates better with outcome than the T-stage (tumour size) assessed preoperatively.³⁴⁻³⁹ In the Children's Cancer Group study (CCG-921),⁴⁰ patients older than 3 years of age, without metastases, and having a residual tumour bulk less than 1.5 cm² had a better 5-year progression-free survival than patients with more than 1.5 cm² of residual tumour (78% vs 54%, p=0.023). Nevertheless, resection of 100% vs 90% of the volume of the tumour did not change the survival rate.

Currently, the recommended postoperative staging guidelines are:^{2,3} 1) a postoperative cranial MRI or CT, with and without contrast within 48 hours of operation, to determine the volume of residual tumour; 2) spinal MRI, preferably preoperatively, or two weeks postoperatively, to identify drop metastases; and 3) Lumbar CSF cytology obtained either immediately after the craniotomy or 15 to 20 days after surgery, to rule out dissemination in the absence of radiologically apparent spread. In a study,⁴¹ 34 patients with medulloblastoma were diagnosed with

leptomeningeal spread based on CSF cytology, spinal MRI, or both. There were 21 discordant results. With the use of either CSF cytology or spinal MRI alone, leptomeningeal spread would be missed in up to 14% to 18%. Thus, both CSF cytology and spinal MRI are recommended for the staging. Because extra-neural dissemination is rarely observed at initial diagnosis, a systemic staging evaluation is not routinely performed.

Age younger than 3 or 4 years is associated with a worse prognosis compared with older patients in many reported series.^{35-38,40} This may be related to the fact that young children are more likely to present with advanced disease that is less amenable to radical resection or with disease dissemination and that these patients often receive reduced doses of radiotherapy.^{34,35,40} It is also possible that the biology of an infantile medulloblastoma is different.¹¹ On the other hand, Di Rocco and coworkers in 1997 showed in a series of 19 cases younger than 3 years old that the prognosis could be good if total resection was achieved followed by chemotherapy.

Currently, patients are categorised as "average-risk" if they have less than 1.5 cm² of residual tumour after operation, and have no evidence of dissemination. Age older than 3 years is also considered one of the factors to be average-risk. Patients with any adverse factor are considered to be "high-risk". These two risk categories have formed the basis for current approaches to treatment stratification in children with medulloblastoma. From the surgical points of view, the implication of these criteria is that extensive tumour resection is strongly advocated. But it will not confer measurable benefit by resecting a small amount of tumour within the brainstem.

Radiotherapy (RT)

Medulloblastoma has a strong tendency of local recurrence and CSF metastases. RT has been an essential part of the standard treatment since 1950s.

Standard-dose Radiotherapy

Standard RT give craniospinal radiation at a dose of 30 to 35 Gy with a posterior fossa boost up to 50 to 55 Gy delivered in 1.8 Gy daily fractions.⁴² The total course typically provided over 6 to 7-week. Local control of the disease is dependent on the posterior fossa dose, which must be greater than 50 Gy.^{40,43,44} With such a regime, the long-term event free survival is about 60-65% of patients. Long-

term sequelae of this treatment include neurocognitive delay, growth failure, endocrinopathy, and secondary oncogenesis. The decline in IQ can be below 80% by 5 years and below 75% by 10 years after treatment.⁴⁵ Attempts have been made to reduce the morbidity by: 1) hyperfractionation; 2) reduction of the craniospinal radiation dosage.

Theoretically, on one hand, hyperfractionation can reduce the side effect of radiation with the same total dosage. On the other hand, it can be used to increase the total dosage for better disease control without increase the morbidity. The feasibility of such approach was confirmed⁴⁶ and its efficacy on high-risk disease patient was suggested in a small series.⁴⁷ Studies on a large scale are planned for patients with average risk disease.⁴

Reduced-dose RT

To avoid the morbidity of irradiation, reduced-dose craniospinal RT has been one of the approaches. In the cooperative study by the Children Cancer Group and Paediatric Oncology Group, average-risk patients were randomised to receive either 36 Gy or 23.4 Gy craniospinal radiation. Both groups received posterior fossa 54 Gy total dose radiation.⁴⁸ The study was terminated at 16 months due to significant increased number of relapse. The event-free survival rate at 5-year were 67% in the standard-dose group and 52% in the reduce-dose group (p=0.080). At 8 years,⁴⁹ the respective event-free survival proportions remained unchanged (67% vs 52% p=0.141). On the other hand, Neuropsychological analyses of the children 6-9 ears after treatment showed that less severe neuropsychologic toxicity in the reduce-dose group, older children experienced less toxicity than children who were younger at the time of radiation.⁵⁰ Reduce-dose RT was established later with the combination of chemotherapy in patients with average-risk disease as review later.

The significance of time to star and duration of RT have been addressed recently.⁵¹⁻⁵³ In an analysis 63 patients with medulloblastoma, the 5- and 10- year progress free survival rate were 67% and 64% respectively for patient with RT treatment duration <50 days, and were 42% and 29% respectively for duration =>50 days. The most common reasons for protracted RT treatment duration were haematologic toxicity and use of <1.6 Gy fractionation size per day.⁵² In the International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 study comparing radiotherapy alone vs preradiotherapy plus chemotherapy,⁵³ multivariate analysis identified that the duration of radiotherapy <= 50 days is a

favourable factor associated significantly with the event free survival rate. The authors recommend that gaps in treatment because of public holidays and machine servicing should be avoided whenever possible. Although no national guideline exist in this area, it might be appropriate to adopt a policy for compensation for gaps in radiotherapy treatment.

Chemotherapy

Medulloblastoma is a chemotherapy-sensitive tumour. The current chemotherapy protocols aim at improving disease control and patient survival, dose reduction of craniospinal irradiation, improving the neuropsychological outcome as well as postponing radiotherapy in patients less than three years of age.

Chemotherapy for Patients With High-risk Disease

Among the three prospective randomised studies in which all-risk patients were randomised to compare treatment with RT alone or RT plus chemotherapy, subgroup analysis in two studies showed that the addition of chemotherapy to RT improved survival for children with high-risk medulloblastoma.^{34,36} In the International Society of Paediatric Oncology study,³⁶ vincristine and lomustine were used. In the Child Cancer Study Group,³⁵ vincristine, lomustine, and prednisone were used. In a later single-arm study with high-risk disease patients received the same regime of chemotherapy plus standard-dose RT, a 85% progression-free survival rate at 5 years was achieved.^{54,55} For eligibility in the study, children had to be at least 3 years old and must have had either subtotal resection, evidence of metastatic disease at the time of diagnosis, or brainstem involvement. Patients with metastatic disease at diagnosis had a 5-year progression-free survival of 67±15%, compared with 90±6% for those with localised disease.

Chemotherapy for Patients With Average-risk Disease

Benefit of chemotherapy was not directly demonstrated for children with average-risk disease until the results of the International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 study was reported recently. In this randomised study, a regime of four cycles of preradiation chemotherapy at 3-week intervals composed of vincristine, etoposide, carboplatin and cyclophosphamide followed by standard-dose RT was compared with RT alone for non-metastatic medulloblastoma.⁵³ The patients were 3 to 16 years-old without metastasis. Event Free Survival was significantly

better for chemotherapy and radiotherapy group ($p=0.0366$), with 78.5% at 3 years and 74.2% at 5 years compared with 64.8% at 3 years and 59.8% at 5 years for RT alone. For patients who had a complete tumour resection, the event-free survival was significantly better with chemotherapy than radiotherapy alone but not for patients who had a less than total resection. There was no significant outcome difference between patients with different time interval from surgery to radiotherapy.

Chemotherapy in Conjunction With Reduced-dose RT

Because of the significant neuropsychological impairment with surgery and standard craniospinal radiotherapy, studies have been carried out to determine the efficacy of treating average-risk children with reduced-dose RT plus chemotherapy. In a nonrandomised prospective phase II study from 1984 to 1989 (CCG-9892),⁵⁶ children between 3 and 10 years of age with non-disseminated medulloblastoma were treated with postoperative, reduced-dose craniospinal RT (23.4 Gy) and 55.8 Gy of posterior fossa radiation. Vincristine was administered during RT, and lomustine, vincristine, and cisplatin chemotherapy were administered during and after radiation. The progression-free survival was 86% at 3 years and 79% at 5 years. These overall survival rates compare favourably to those obtained in studies using standard-dose RT alone or plus chemotherapy. Intellectual analyses⁵⁷ of this study at a median of 2.5 years with maximal 4 years after treatment showed that the estimated rate of decline of IQ from baseline was about 4 points per year. Females were more subject to verbal IQ decline than were males ($p=0.008$), and young children (<7 years of age) were more negatively affected than were older children, with a significant decline in non-verbal IQ ($p=0.016$). The author concluded that intellectual loss was substantial but suggestive of some degree of intellectual preservation compared results of children received standard-dose RT. A phase III study on reduced-dose RT + post-RT chemotherapy (POG&CCG A9961) has been completed in 2000 and the results are pending.⁴

Chemotherapy for Infant

Among patients with malignant brain tumours, infants and very young children have the worst prognosis and the most severe treatment-related neurotoxic effects. One of the most important advances in the modern management of medulloblastoma is that with prolonged postoperative multi-drug chemotherapy protocols lasting from 8 to 24 months, RT can be postponed for 1-2 years or even avoided in young children. With this approach, the disease-free survival ranged from 40% to 70% in patients with average-

risk disease.⁵⁸⁻⁶³ However, for infants with metastatic disease, more effective treatment is needed.

Between 1976 and 1988, 17 children less than 36 months old with medulloblastoma (12) and ependymoma (5) were treated with post-operative MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) chemotherapy. RT was reserved for recurrent disease.⁵⁹ The long-term results were reported in 1997.⁶³ Eight of the 12 medulloblastoma patient survived without evidence of the disease, with median survival time of 10.6 years (range, 6.2 to 15.2 years); Four relapsed were disease free from 7.5 to 13.5 years post relapse after receiving salvage therapy with cisplatin (n=1) or irradiation (n=3). All relapses occurred within 26 months of diagnosis. Data on growth demonstrated height less than the 5th percentile in all children who received cranial irradiation compared to 25 to 95th percentile for nonirradiated children. Intellectual ability for the group who did not require radiation was within normal range (mean IQ 100.1) and stable across annual assessments. Those who required radiation had lower IQs which continued to decline over time (mean IQ 85 at mean age of 5.8 years, declining to 63 at 10 years).

The largest experience has been that of the Paediatric Oncology Group,⁵⁸ in which a four-drug regime of vincristine, cyclophosphamide, cisplatin and etoposide was used repeatedly in 198 children younger than 3 years with malignant brain tumour until 36 months of age or until disease progression. Radiotherapy was given upon completion of chemotherapy. For medulloblastoma patients, the overall 2-year PFS rate was 34±8%; the median time of relapse was 9 months; no patient relapsed beyond 26 months of diagnosis. Children in whom disease was localised and in whom a gross-total resection had progress free survival rate of 74% at 1 year in children less than 24 months of age and 91% at 2 years in those between 24-36 months of age. They noted objective tumour response to patients with residual disease postoperatively. Complete responses to chemotherapy were associated with a progression free survival rate approaching that achieved with gross total resection. In a subsequent analysis⁶⁴ of the 75 surviving children at a median survival time of 6.4 years, five had developed second malignancies, with an accumulative risk of 11.3% at 8 years. These malignancies, including sarcoma (two cases), myelodysplastic syndrome, acute myelogenous leukaemia, and meningioma occurred in both children who did and did not undergo RT. Prolonged use of alkylating agents with accumulative dose was probably responsible for the haematological malignancy. The authors stressed the importance of longitudinal assessment of the long-term effects of combining

chemotherapy and radiotherapy in children with brain tumour in coming years.

It is yet to be answered that: 1) what is the optimal chemotherapy protocol for infant and young children, not only in terms of disease control and short term side effect, but also long term secondary malignancy? 2) to what age such an approach can be extended? 3) in patients with complete response, dose RT or high-dose chemotherapy is required to sustain disease control?

Diagnosis and Management of Recurrent Disease

Although the overall outlook for patients with medulloblastoma has improved dramatically during the last 20 years, as many as 30 to 50% of patients in most series died from tumour "recurrence", which in reality represents progression of residual disease. Most of the recurrence occur in the posterior fossa accounting almost 60% of the cases, spine about 20%, supertentorial about 10% with most in the subfrontal region, and systemic about 5%. Many of the recurrence in the central nervous system are multiple, especially subarachnoid space dissemination.²¹ The average survival from the time of recurrence is between 25-48 months in most of the series.²

Diagnosis

Routine surveillance imaging has been used for identifying disease recurrence or progression at an early stage. This has been the practice in most of the centers, including our own. The benefit of it is controversial.⁶⁵⁻⁶⁸ Longer survival achieved by early detection of recurrence might be a reflection of lead-time and length biases. Surveillance procedure will give more importance as new effective therapeutic options are developed for recurrent medulloblastoma. The period of recurrence may be estimated from the Collins' law,⁶⁹ where the period of risk is the age of the patient at the time of diagnosis plus 9 months. There are many exceptions and it has been observed that medulloblastomas recur more than 8 years after diagnosis.⁷⁰ Therefore, the duration for which a patient must be followed before the disease can be referred to as cured remains problematic.

Treatment

The treatment of patients with recurrent disease remains a major challenge. For local recurrence, surgery should be considered if the lesion is surgically accessible and the patient's general condition allows. Surgery can provide a

histological diagnosis in case of doubt, and excision of the lesion for better chance of disease control. Same as primary management of the disease, surgery alone is not curative. Although disease regression has been achieved with a variety of conventional chemotherapeutic regimens, both alone and in combination with repeated RT, long-term disease control is uncommon.^{71,72} The role of conventional RT is limited for recurrent patients. For re-irradiation, three-dimensional stereotactically guided radiotherapy (SRT) and radiosurgery are feasible.^{73,74} In a series of 20 recurrent cases with 29 lesions, 21 lesions were treated by SRT and 8 by radiosurgery. Mean total dose for re-irradiation was 24 Gy for SRT and 15 Gy for radiosurgery. The overall control was 89.7%, with 13 partial or complete response and 13 stable disease. Thirteen patients died with disseminated cranio-spinal progression after 72.6 months median. There was no brain radionecrosis.⁷⁴ For spinal recurrence, local irradiation can be applied. In recent years, the use of highly intensive chemotherapy coupled with bone marrow or peripheral blood stem cell reconstitution has shown some promise in the control of progressive disease.^{75,76}

Management of Medulloblastoma in Prince of Wales Hospital

From 1994 to 2000, we followed the Hong Kong Paediatric Haematology Oncology Study Group's Brain Tumour Protocol (HKPHOSG 1994). According to the protocol, standard-dose RT (36 Gy craniospinal with posterior fossa boost up to 50 Gy in hyperfractionation) was used for all children with medulloblastoma except for children <3 years old. For them, chemotherapy was used and radiotherapy would be delay until 3 years old. Since 2000, the HKPHOSG-PNET-CNS-2000 Protocol for Medulloblastoma & Central Nervous System Primitive Neuroectodermal Tumours for Children >36 months has been used. This protocol is modified from the CCG-9892 study.⁵⁷ According to our protocol, after surgery and postoperative staging, RT is to be started within 21 days of surgery. For children with average-risk, the reduced-dose (23.4 Gy craniospinal with posterior fossa boost up to 54 Gy) is the choice while the standard-dose regime is for children with high-risk. The radiation is delivered in daily fraction of 1.8 Gy. Weekly vincristine will be administered during RT. For children <36 months chemotherapy is administered until 3 years of age when RT will be offered. Since 1980, we have managed 35 cases of medulloblastoma,

14 of them since 2000. Preliminary results show encourage in the survival rate. The overall survival rate is more than 70% at 4 years. Since 2000, we have been able to obtain early postoperative MRI for staging and to achieve total resection of local tumour in all cases. No CSF shunting was required in these cases. To achieve performing postoperative MRI within 24 hours and to start radiotherapy within 21 days, a smooth postoperative course is the key factor. The most important experience in our management of children with medulloblastoma is a close collaboration of multi-disciplinary teams involving Paediatric Oncology, Paediatric Intensive Care Unit, Radiation Oncology, Radiology, Neuroanaesthesiology and Paediatric Neurosurgery.

Summary

The modern management of neuroblastoma starts with early diagnosis, preoperative craniospinal MRI followed by aggressive surgery. The aim of the surgery is a total or near-total resection of the tumour while avoiding major neurological deficit such as from impaired brainstem function. Hydrocephalus can be managed at the same operation for most of the cases without CSF shunting. Accurate postoperative staging is essential for further oncological management, which includes MRI brain within 48 hours of the surgery, and lumbar CSF cytology immediately after the surgery or 15-20 days postoperatively. Children with medulloblastoma can be separated into two risk groups: 1) *average-risks patients* who have localised disease at the time of diagnosis and total tumour resection or subtotal with residual tumour <1.5 ml; 2) *high-risk patients* who have disseminated disease and a residual tumour ≥1.5 ml. Age ≤3 years old may be also a factor considered as high-risk. If a residual tumour >1.5 ml is found on early postoperative image study and if it still resectable, early re-operation is undertaken. However, radical surgery is not cure of the disease. All patient needs early postoperative adjuvant therapy. The standard dose of RT is 36 Gy to the neuroaxis with posterior fossa boost to a total dose of 50-55 Gy. Postoperative chemotherapy is useful in three aspects: 1) in conjunction with standard-dose craniospinal RT to increase the survival rate of "high-risk" children; 2) in conjunction with reduced-dose craniospinal RT (less than 30 Gy to the neuroaxis and boost up to 54 Gy to the posterior fossa) for the average-risk children. The result of such approach is comparable with

the standard dose treatment but with less long-term neuropsychological impairment; 3) as the sole adjuvant therapy for children under 3 years of age so that RT can be delayed in order to avoid the toxic effect of radiation on the immature brain. Studies are ongoing towards further improving the survival rate, especially children with high-risk disease and children with recurrent disease, while minimising the treatment-induced morbidity.

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