

## Epidemiology, Management and Treatment Outcome of Medulloblastoma in Singapore

Mei-Yoke Chan,<sup>1</sup>MBBS, MMed (Paeds), MRCP (UK), Wan-Yee Teo,<sup>2</sup>MBBS, Wan-Tew Seow,<sup>3</sup>MBBS, FRACS (Neurosurg), FAMS, Ah-Moy Tan,<sup>1</sup>MMed (Paeds), FRCP, FAMS

### Abstract

**Introduction:** Medulloblastoma/primitive neuroectodermal tumour is the most common type of malignant brain tumour in children. Long-term survival rates have improved over the years with a combination of surgical, radiotherapeutic and chemotherapeutic treatment modalities in the developed world. This paper aims to analyse the epidemiology and outcome of medulloblastoma in Singapore and compare our results with those reported in the literature. **Materials and Methods:** A 9-year retrospective study was done using data reported to the Singapore Children's Cancer Registry from June 1997 to June 2005. Only 39 children up to the age of 15 years diagnosed histologically with medulloblastoma or primitive neuroectodermal tumour arising from the cerebellum were included in the study. Follow-up data were collected up to June 2006 and analysed using SPSS v 13.0 software. **Results:** Medulloblastoma/primitive neuroectodermal tumour was the most common type of brain tumour, accounting for 40.7% of all brain tumours diagnosed in children in Singapore. The 5-year event-free survival rate was 44.5%, while the 5-year overall survival rate was 51.5%. Nearly half (41%) of our patients had spinal metastasis at presentation and this was associated with a worse event-free survival (6.3% vs 71.9%,  $P = 0$ ). Children under 36 months of age had a significantly poorer overall survival (28.8% vs 52.2%,  $P = 0.041$ ). **Conclusions:** The outcome of medulloblastoma in Singapore was inferior to reported figures in the literature. We need to close identified gaps in care, like standardising assessment and treatment protocols, in order to improve our results. Research into molecular and genetic characteristics may also throw light on whether the disease is inherently more aggressive in our population.

Ann Acad Med Singapore 2007;36:314-8

**Key words:** Medulloblastoma, Outcome, Singapore

### Introduction

Medulloblastoma (MBL) is the most common type of malignant brain tumour in childhood. It belongs to the group of tumours known as primitive neuroectodermal tumour (PNET), which is a highly malignant, small round blue cell tumour of the central nervous system. The term "medulloblastoma" is classically reserved for PNETs arising in the cerebellum. It was historically named after the supposed progenitor cell for glia and neurons, called the "medulloblast".<sup>1</sup> Although MBL belongs to the same histopathologic group as PNET arising in the supratentorial region, some investigators believe they arise from different

cells of origin,<sup>2</sup> which may account for their differences in clinical behaviour and prognosis.<sup>3</sup>

The current treatment of MBL combines surgery, radiotherapy and chemotherapy. With better surgical techniques and technology, improved delivery of radiotherapy leading to better therapeutic ratio and better support of more intensive chemotherapeutic regimens, the survival rates of MBL in children have improved from 20% in the 70s to 70% currently.<sup>4,5</sup> However, there is increasing concern over the long-term sequelae of treatment of MBL in children.<sup>6</sup> Risk-stratification systems are being studied in an attempt to reduce sequelae of treatment without

<sup>1</sup> Department of Paediatric Subspecialties

<sup>2</sup> Department of Paediatrics

<sup>3</sup> Department of Paediatric Neurosurgery

KK Women's and Children's Hospital, Singapore

Address for Correspondence: Dr Chan Mei Yoke, Senior Consultant, Department of Paediatric Subspecialties, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.

Email: Chan.Mei.Yoke@kkh.com.sg

compromising survival.<sup>7</sup>

In Singapore, since 1997, MBL in children is mainly treated at the paediatric cancer centre of one of 2 hospitals, KK Women's and Children's Hospital (KKH) and National University Hospital (NUH). This paper aims to review the epidemiology and treatment outcome of MBL in Singapore and to compare our results with those of established centres in the world.

## Materials and Methods

A retrospective study of all childhood MBL reported to the Singapore Children's Cancer Registry (SCCR) from June 1997 to June 2005 was done. The SCCR, which was started in 1997, collects its data from reporting physicians in KKH and NUH as well as by crosschecking data with the National Singapore Cancer Registry and the National Death Registry in the event that a child was treated in an adult cancer centre or a private hospital. Childhood cancer was defined as cancer occurring up to the age of 15 years.

Data, including patient bio-information, treatment modality and disease outcome, were collected up to June 2006.

The criteria for inclusion in this retrospective review were:

1. Diagnosed with MBL histologically and treated in Singapore
2. Complete epidemiological, treatment and outcome data from SCCR or case notes review

We did not include supratentorial PNETs in this analysis. If the site of tumour was not known or could not be verified, the case was excluded even if it had been reported to SCCR as MBL.

Data analyses were done using standard statistical method in SPSS v13.0 software. The 5-year overall survival (OS) and event-free survival (EFS) rates were estimated by the Kaplan-Meier method.

## Results

There were 51 cases of MBL/PNET reported to SCCR during the recruitment period. Eleven were excluded because the site of tumour was either unknown or reported as supratentorial, and 1 MBL was not analysed because of incomplete data. Therefore, the total number of cases analysed in this retrospective study was 39.

All cases were diagnosed and treated at either KKH (66%) or NUH (33%). The follow-up period ranged from 2 to 104 months, with a median of 32 months and a mean of 42 months.

### *Epidemiology of MBL in Singapore*

According to data from SCCR, brain tumours make up

about 17% of all childhood cancers in Singapore. MBL/PNET is the most common type of brain tumour, comprising 40.7% of all brain tumours diagnosed in children. The incidence of MBL is 0.73 cases per 100,000 per year in Singapore.

Our patients ranged in age from 3 to 162 months, with a median age of 62 months. A third of the patients (13 cases) were less than 36 months of age at diagnosis. Females made up 46% of cases and males made up 54% of cases. Ethnicity of the cases reflected the racial composition in Singapore (70.4% Chinese, 24.1% Malays, 3.7% Indians and 1.9% others). Therefore, there was no sex preponderance or racial bias in our series.

Unfortunately, we do not have complete data on the number of cases with cerebrospinal fluid sent for malignant cells. Neuraxis spread at diagnosis was only made with imaging studies, which may not be very accurate. Nonetheless, based only on imaging studies, the number of children who had MBL with neuraxis spread at diagnosis was 16 (41%). Seven (43%) of these children were <36 months of age.

There was no case of MBL with extraneural spread at diagnosis, although there was 1 case that relapsed both in the neuraxis and the liver.

### *Management of MBL in Singapore*

All cases were histologically diagnosed. Half the cases (19) had partial resection, while the other half (19) had gross total resection as reported by the operating neurosurgeon. We do not have data on postoperative scans done to estimate remnant tumour volume. One case had a biopsy only.

Children <36 months of age at diagnosis had chemotherapy only, while those who were older had radiotherapy followed by chemotherapy. Protocols vary depending on the treating institution and primary physician. In general, "baby brain" protocols were used for those <36 months of age (e.g., Duffner baby brain protocol or the ANZCCSG baby brain 91 protocol). Standard European (PNET 3) or American (CCG 9892) study group chemotherapy protocols were used for those treated with combined radiotherapy and chemotherapy. Details of these protocols had been published previously.<sup>8-11</sup>

Radiotherapy was mainly craniospinal with standard doses of 5000 to 5400 cGy to the posterior fossa and 3500 cGy to the craniospinal axis, regardless of the chemotherapy protocols used. One child had stereotactic radiotherapy to the tumour bed only.

### *Outcome of MBL in Singapore*

An event is defined as disease progression, relapse or death. The 5-year EFS of MBL in Singapore based on our

data was 44.5% (Fig. 1). The time from diagnosis to relapse or progression ranged from 1 to 104 months, with a median of 24 months.

The 17 (43.5%) patients who relapsed or progressed were <36 months old (6/17), had incomplete surgery (8/17) or had spinal metastasis at diagnosis (12/17). Of the 13 cases who were <36 months old at diagnosis, 9 (69%) relapsed or progressed. Treatment after relapse varied from debulking surgery to oral chemotherapy to radiotherapy for those children who did not have radiotherapy in the initial treatment. The median time from relapse or progression to death was 2.6 months.

The 5-year EFS was worse for those who were under 36

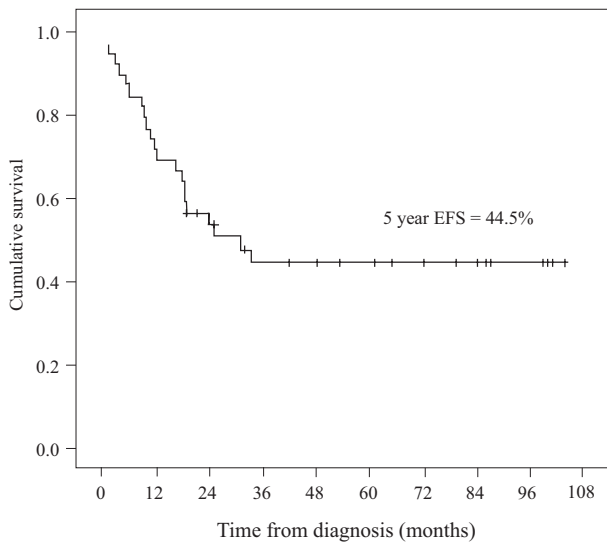


Fig. 1. Event-free survival (EFS) for medulloblastoma.

months old compared to those over 36 months old at diagnosis (Fig. 2). Metastases at diagnosis also carried a significantly poorer prognosis (Fig. 3).

The 5-year OS of MBL in Singapore was 51.5% (Fig. 4). Children under 36 months old or who had metastases at diagnosis had a significantly worse OS (Figs. 5 and 6). Of the 16 patients who died, 12 died of the disease and 4 died of complications from treatment while in disease remission. Two children died of progressive disease 2 and 3 months after diagnosis.

**Discussion**

The reported 5-year EFS of MBL ranged from 55% to

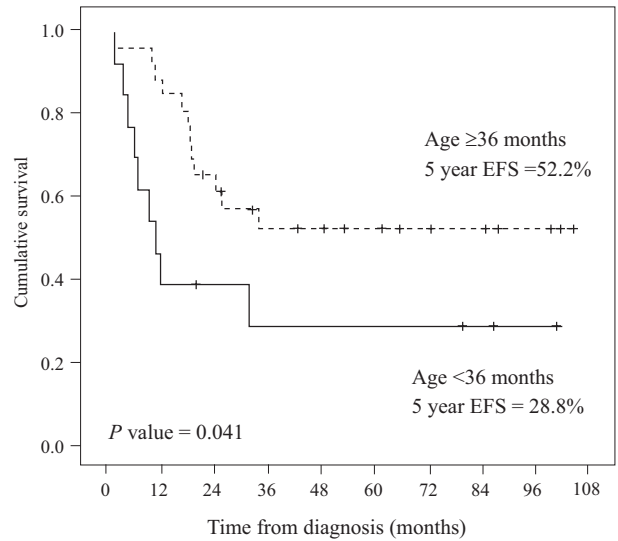


Fig. 2. Event-free survival (EFS) based on age at diagnosis.

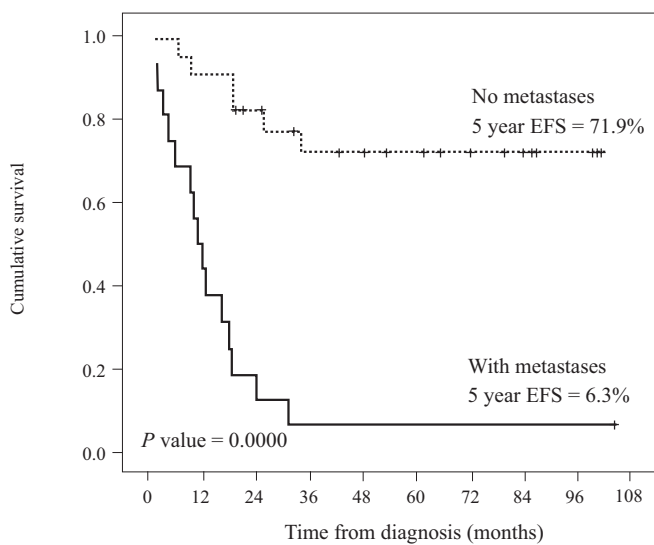


Fig. 3. Event-free survival (EFS) based on the presence of metastases at diagnosis.

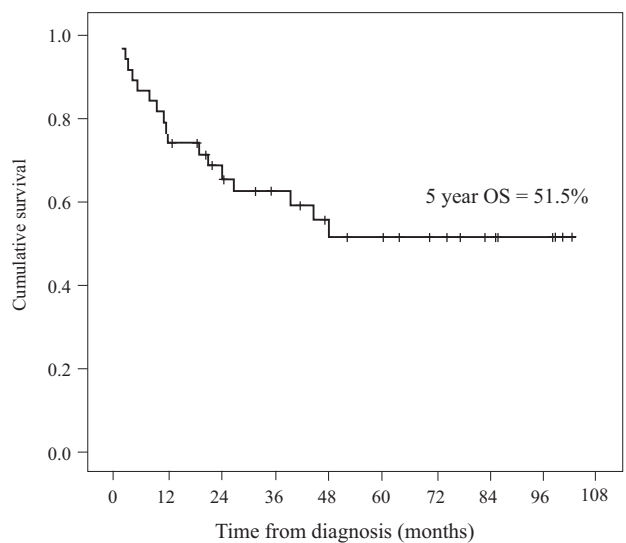


Fig. 4. Overall survival (OS) of medulloblastoma.

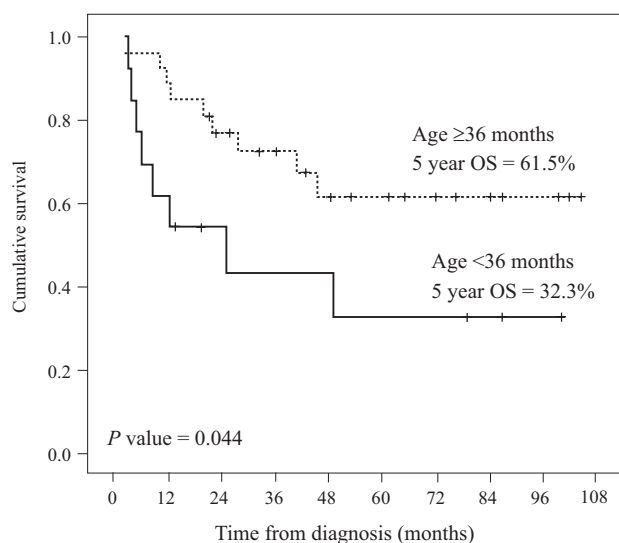


Fig. 5. Overall survival (OS) based on age at diagnosis.

85%.<sup>12,13</sup> Compared to these results, our 5-year EFS of 44.5% is inferior. Our 5-year OS of 51.5% is also below par compared to reported figures.<sup>14</sup> Some of the postulated reasons that could explain this inferior result include:

#### *Inconsistent Assessment and Risk Stratification*

There were no consistent assessment and risk stratification protocols between the 2 centres and indeed sometimes within the centre itself. Risk stratification was most likely inaccurate as well because there was no central pathological review, no CSF examination in some cases, and no molecular studies done. Remnant tumour size estimation was also not consistently done. However, this may not be important in the outcome.<sup>14</sup> Anaplasia had been identified as a poor prognostic factor<sup>15</sup> and metastatic leptomeningeal disease had been reported to be underestimated if only imaging studies were done.<sup>16</sup> Recently, molecular and genomic-based studies, especially alterations in chromosome 17,<sup>7</sup> myc gene amplification,<sup>17</sup> expression of *ErbB2*<sup>18</sup> and *TrkC*,<sup>19</sup> have found that histologically similar tumours have vastly different responses to treatment, and more accurate prognostication could be had by including these predictors in risk and treatment stratification.

We have started tumour tissue banking since 2000 and in the near future, would embark on molecular and genetic studies.

#### *Variable Treatment Protocols*

The chemotherapy protocols used were varied and the numbers were small, therefore meaningful comparisons cannot be made. Although we adopted chemotherapy protocols from published studies, the radiotherapy delivered was not necessarily risk-adapted and was not always consistent with guidelines recommended in those studies.

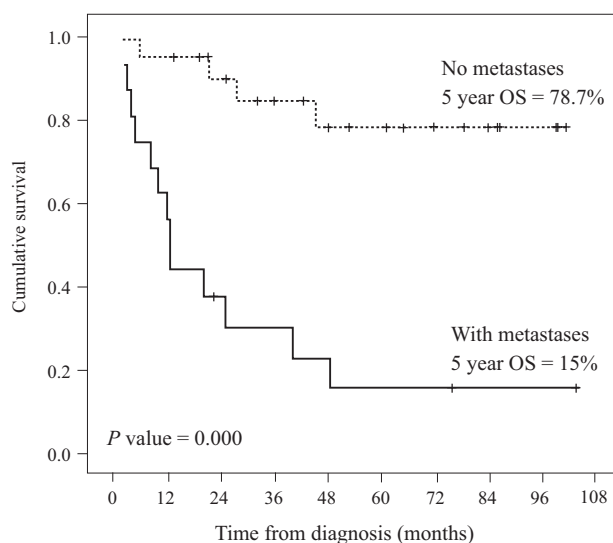


Fig. 6. Overall survival (OS) based on the presence of metastases at diagnosis.

Therefore, it is uncertain if some patients received sub-optimal treatment by current standards.

Perhaps more intensive chemotherapy treatment protocols need to be adopted for our patients. As high-dose chemotherapy with stem cell rescue remains controversial, researchers are looking at other treatment modalities. MBL is one of a few myc-driven embryonal tumours of childhood, so studies of myc blockade may yield promising and more effective therapies.<sup>17</sup>

#### *More Aggressive Disease in our Population*

Nearly half of our patients presented with spinal metastases at diagnosis, compared to reported figures of 20% to 30%,<sup>14,20</sup> and some of these cases were only diagnosed on imaging studies alone. It has been reported that using magnetic resonance imaging (MRI) alone, up to 18% of leptomeningeal disease would be missed,<sup>16</sup> therefore it would not be unreasonable to assume that our number of cases with metastatic disease may have been underestimated. As metastatic disease at diagnosis impacted negatively on survival in our series, our inferior outcome may be due to either more aggressive disease in our population or delayed presentation of disease.

It is also interesting to note that MBL/PNET is the most common type of brain tumour reported in our population as well as in Malaysia,<sup>21</sup> in contrast to low-grade gliomas, which are the most common type of brain tumour reported in Western epidemiological studies.<sup>22</sup> Whether this has any clinical significance is uncertain.

We did not look at the complications and long-term morbidity of treatment in our study population as there was no formal long-term follow-up assessment schedule and no collection of data yet.

## Conclusion

The clinical outcome of MBL in Singapore in our 9-year retrospective study was inferior to reported outcomes in established centres in the world. Before we attempt to improve our results, certain gaps in care would have to be addressed:

1. Better disease staging and risk stratification.
2. Common treatment protocols so that results can be compared and improved upon between our centres.
3. Formal assessment of long-term morbidity of disease and treatment.
4. Research into the molecular and genetic characterisations of MBL in our population to compare with those reported worldwide, to see if there are any inherent differences.

Although we hope to improve our outcome on standard-risk MBL in Singapore, the outcome of high risk MBL (i.e., under 36 months of age or metastatic disease at diagnosis) remains poor universally. For this group of patients, novel treatment ideas like an effective mycn-targeted drug would need to be studied.

## Acknowledgment

*The authors would like to thank Christina Ha, data manager of SCCR, for help rendered with the collection of information and data in this series.*

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