

# Neuroblastoma: experience from National University Health System, Singapore (1987–2008)

Tan C<sup>1</sup>, BA, Sabai SM<sup>2</sup>, MBBS, Tin AS<sup>3</sup>, MBBS, MMed, Quah TC<sup>4</sup>, MBBS, MMed, Aung L<sup>5</sup>, MD, MPH

**INTRODUCTION** Neuroblastoma is the most common extracranial solid tumour in childhood. We report our experience at National University Health System (NUHS), Singapore.

**METHODS** We performed a retrospective chart review of 43 patients diagnosed with neuroblastoma, who were seen and treated at the Department of Paediatrics, NUHS from November 1987 to November 2008.

**RESULTS** The median age of the patients at diagnosis was 1.9 (range 0.1–20.2) years. The majority (70.1%) of primary tumours were of abdominal and/or adrenal origin. According to the International Neuroblastoma Staging System, six (14.0%) patients were in stages 1 and 2, 11 (25.6%) in stage 3, 19 (44.2%) in stage 4, and seven (16.2%) in stage 4s. Therapy for all patients included surgery and/or chemotherapy and/or radiation therapy. Patients with stage 4 disease also underwent autologous stem cell transplant. The median follow-up for the cohort was 2.5 (range 0.4–21.0) years. At the time of analysis, 29 (67.4%) patients were alive. The two- and five-year overall survival for the cohort was 65.0% (95% confidence interval [CI] 51.0%–80.0%) and 62.0% (95% CI 45.0%–79.0%), respectively. The five-year overall survival rates according to risk status were 100.0% for low-risk, 75.0% for intermediate risk and 28.2% for high-risk neuroblastoma.

**CONCLUSION** The prognosis for those with advanced stage neuroblastoma remains poor. A collaborative effort, with an emphasis on research in detecting biologic characteristics of aggressive disease and tailoring therapy, needs to be strengthened in order to further our understanding of this disease.

Keywords: neuroblastoma, Singapore, survival, treatment  
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## INTRODUCTION

Neuroblastoma is the most common extracranial solid tumour in childhood. It is an embryonal malignancy of the sympathetic nervous system arising from neuroblasts. Children aged five years or below are the most affected group.<sup>(1,2)</sup> The differences in outcome for patients with neuroblastoma are striking. In the USA, neuroblastoma accounts for 6%–10% of all childhood malignancies.<sup>(3)</sup> In Singapore, with a population of 4.5 million people, it is the fifth most common childhood cancer and accounts for 5.3% of all childhood cancers diagnosed each year under the age of 15 years.<sup>(4)</sup>

While the treatment of neuroblastoma has evolved, it continues to pose a therapeutic challenge, since most patients present with stage 4 advanced disease with metastasis frequently to the lymph nodes, bone, bone marrow or liver.<sup>(5)</sup> The Division of Paediatric Haematology/Oncology in National University Health System (NUHS) is a referral centre for new and relapsed Paediatric Oncology cases from Singapore and the Southeast Asia region. According to the first monograph of the Singapore Childhood Cancer Registry, some 100 new cases of childhood cancer are seen annually in Singapore, with up to half of them being referred to and treated in NUHS.<sup>(4)</sup> Our aim was to study the various treatment modalities used and the survival outcomes of children with neuroblastoma treated at our centre. We report here our single-centre experience.

## METHODS

A retrospective chart review of 62 patients diagnosed with neuroblastoma, who were seen and treated in the Department of Paediatrics, NUHS from November 1987 to November 2008, was carried out. A total of 43 patients from the study cohort were included in the analysis. A diagnosis of neuroblastoma was made based on the histopathology obtained from the primary tumour or metastatic sites, such as bone marrow specimen. Disease staging, in accordance with the International Neuroblastoma Staging System (INSS), was based on the clinicopathologic features. The size and location of the primary tumour were defined by imaging studies using computed tomography (CT) or magnetic resonance (MR) imaging. Metastatic disease was further investigated by bone marrow aspiration and biopsies of at least two sites in the iliac crests, as well as additional imaging with <sup>131</sup>I-metaiodobenzylguanidine (MIBG) and <sup>99m</sup>Tc-tin bone imaging. Positive disease findings were monitored serially by further imaging studies for treatment responses. Complete remission was defined as the absence of any evidence of disease on any imaging modality (CT, MR imaging, MIBG or bone scintiscan) and bone marrow studies. Cytogenetic studies of *MYCN* gene, 1p deletion, 17q gain and DNA ploidy, which became available in Singapore in 2003, were performed in 21 of the 43 patients. The presence of *MYCN* amplification, 1p deletion, 17q gain, DNA ploidy status and Shimada histopathology at

<sup>1</sup>Royal College of Surgeons in Ireland, Dublin, Ireland, <sup>2</sup>Division of Paediatric Haematology-Oncology, National University Health System, Singapore, <sup>3</sup>SingHealth Centre for Health Services Research, Singapore, <sup>4</sup>Viva-University Children's Cancer Centre, National University Hospital, Singapore, <sup>5</sup>Division of Paediatric Haematology-Oncology, Department of Paediatric Subspecialties, KK Women's and Children's Hospital, Singapore

**Correspondence:** Dr LeLe Aung, Consultant, Division of Paediatric Haematology-Oncology, Department of Paediatric Subspecialties, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899. Aung.Lele@khh.com.sg

presentation implies a poorer prognosis.<sup>(6-9)</sup> An attempt was made to perform the investigations stated above in all newly diagnosed patients. For descriptive and prognostic purposes, the patients were then classified into low-risk (stages 1, 2 and 4s), intermediate-risk (stage 3) and high-risk (stage 4) groups.<sup>(10)</sup>

Treatment at our centre for patients with stage 1 neuroblastoma involved complete resection with clear margins. Patients with stages 2 and 3 neuroblastoma underwent gross total or partial resection followed by low-dose chemotherapy. Chemotherapy consisted of the United Kingdom Children's Cancer Study Group's (UKCCSG) OPEC/OJEC regimen for a total of 3–6 cycles depending on the disease status and the decision of the treating physician. The OPEC regimen consisted of intravenous vincristine (1.5 mg/m<sup>2</sup>), cyclophosphamide (600 mg/m<sup>2</sup>), cisplatin (80 mg/m<sup>2</sup>) and etoposide (180 mg/m<sup>2</sup>) given in courses 1, 3 and 5. The OJEC regimen comprised intravenous vincristine (1.5 mg/m<sup>2</sup>), cyclophosphamide (600 mg/m<sup>2</sup>), etoposide (180 mg/m<sup>2</sup>) and carboplatin (480 mg/m<sup>2</sup>) given in courses 2, 4 and 6.<sup>(11)</sup> Patients with stage 4 neuroblastoma underwent surgery, chemotherapy and radiation therapy. Surgery was carried out to remove the primary tumour in stages 3 and 4 neuroblastoma patients after an initial 3–4 cycles of chemotherapy. Prior to 2004, all patients in stages 2, 3, 4 and 4s received chemotherapy as per the OPEC/OJEC regimen. After 2004, all stage 4 neuroblastoma patients received chemotherapy as per the Memorial Sloan Kettering Cancer Centre's (MSKCC) chemotherapy regimen. The MSKCC regimen consisted of intravenous cyclophosphamide (140 mg/kg), doxorubicin (75 mg/m<sup>2</sup>) and vincristine (0.067 mg/kg) for courses 1, 2 and 4, and cisplatin (200 mg/m<sup>2</sup>) and etoposide (600 mg/m<sup>2</sup>) for courses 3 and 5 given every three weeks.<sup>(12)</sup>

The principles of surgery to remove the primary tumour and radiotherapy for the primary tumour and metastatic sites did not change between the time periods. In addition, patients with stage 4 disease underwent autologous peripheral blood stem cell rescue (PBSCR) followed by radiation therapy to the primary tumour and metastatic sites. This was later followed by maintenance chemotherapy with a vitamin A derivative, 13-cis-retinoic acid, to decrease the risk of relapse.<sup>(13)</sup> The conditioning regimen used for the PBSCR consisted of busulfan (4.4 mg/kg/day for four days) and melphalan (140 mg/m<sup>2</sup>). Patients with stage 4s disease were either observed without any therapy or treated with low doses of chemotherapy and surgery, if clinically indicated.

The overall and event-free survival rates were estimated for two and five years using the Kaplan-Meier method.<sup>(14)</sup> Event was defined as a relapse of the disease, as indicated by imaging studies, bone marrow aspirate and trephine studies or death from the disease. A comparison of survival rate difference was made using log-rank test in stage 4 neuroblastoma patients between the various chemotherapy regimens used. All statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (SPSS Inc, Chicago, IL, USA). A *p*-value < 0.05 was considered statistically significant.

**Table 1. Patient and tumour characteristics of the study cohort (n = 43).**

Characteristic	No. (%)
Median age at diagnosis; range (yrs)	1.9; 0.1–20.2
Median follow-up period; range (yrs)	3.1; 0.4–21.0
<b>Gender</b>	
Male	21 (48.8)
Female	22 (51.2)
<b>Singaporeans</b>	27 (62.8)
Chinese	21 (77.8)
Malay	3 (11.1)
Indian	3 (11.1)
Foreigners	16 (37.2)
<b>Site of primary tumour</b>	
Abdomen/adrenal	31 (72.1)
Head and neck	5 (11.6)
Spinal cord	3 (7.0)
Mediastinal	4 (9.3)
<b>INSS staging</b>	
Stage 1	2 (4.7)
Stage 2	4 (9.3)
Stage 3	11 (25.6)
Stage 4	19 (44.2)
Stage 4s	7 (16.2)
<b>Chemotherapy</b>	
OPEC/OJEC	26 (60.5)
MSKCC	5 (11.6)
Others	12 (27.9)
<b>Patient status</b>	
Alive with no evidence of disease	28 (65.1)
Died of disease	14 (32.6)
Alive with disease	1 (2.3)

INSS: International Neuroblastoma Staging System; MSKCC: Memorial Sloan Kettering Cancer Centre

## RESULTS

Of the 62 patients seen during the study period, 19 patients were excluded due to the following reasons: lost to follow-up (n = 6); without staging or adequate information (n = 5); only sought second opinion without continuing therapy (n = 2); defaulted treatment in favour of Traditional Chinese Medicine (n = 2); diagnosis of ganglioma, a mature tumour (n = 2); unconfirmed pathology (n = 1); and received only the first dose of chemotherapy at our centre and returned home elsewhere (n = 1). Five of these 19 patients were diagnosed with stage 4 disease. The two patients who sought Traditional Chinese Medicine were both diagnosed with stage 4 disease. Information on the disease and staging status of the remaining patients who were excluded was not available.

The patients' median age at diagnosis of neuroblastoma was 1.9 (range 0.1–20.2) years. There were 21 (49.0%) male and 22 (51.0%) female patients. 27 (62.8%) patients were from Singapore, of which 21 (77.8%) were Chinese and three each were Indian and Malay. These numbers reflect the ethnic diversity of Singapore, which has a predominantly Chinese population. Of these 27 local patients, ten (37.0%) were diagnosed with stage 4 disease and eight with stage 3 disease. There were 16 (37.2%) patients from the surrounding Southeast Asian region, namely

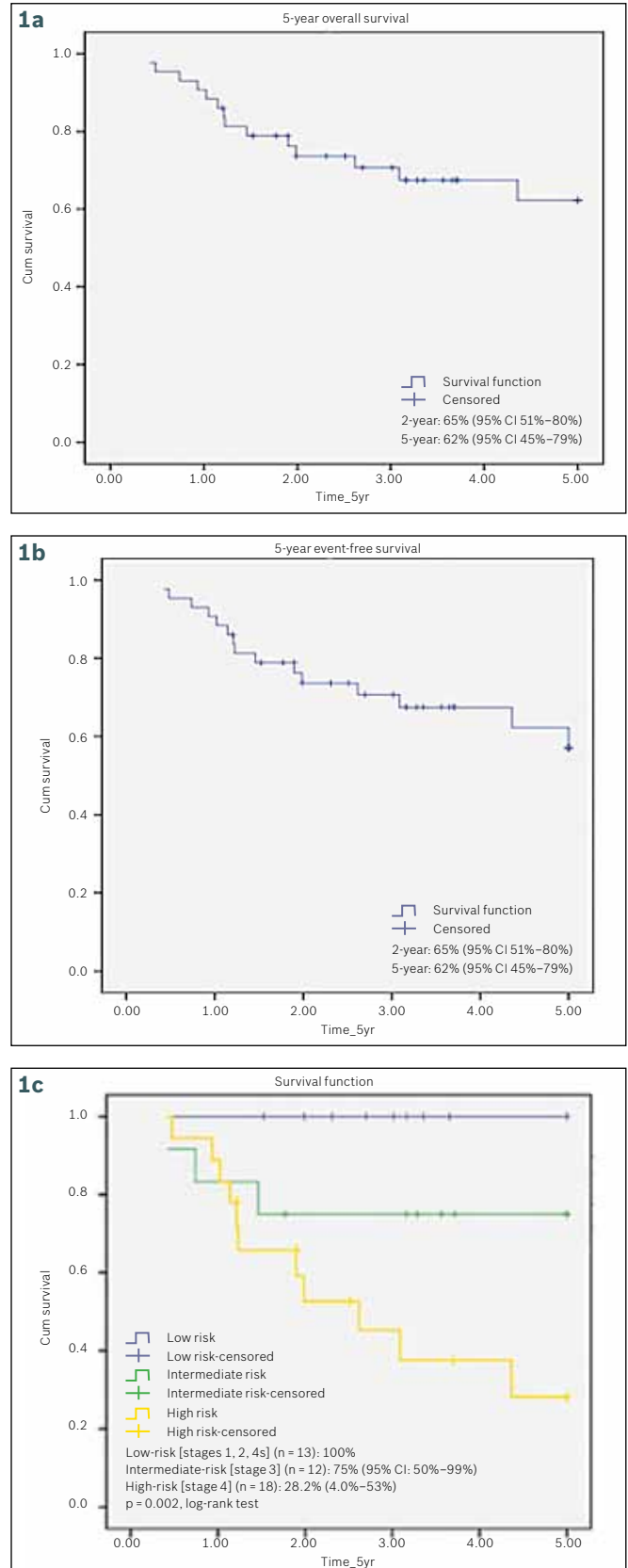
Indonesia, Malaysia, Myanmar and Vietnam. Half of the foreign patients ( $n = 8$ , 50%) were diagnosed with stage 4 disease and four had stage 3 disease (Table I).

The sites of the primary tumour were as follows: 31 (72.1%) abdomen/adrenal; 5 (11.6%) head and neck; 3 (7.0%) paravertebral; and 4 (9.3%) mediastinal. According to the INSS, there were two (4.7%) stage 1 patients, four (9.3%) stage 2, 11 (25.6%) stage 3, 19 (44.2%) stage 4 and seven (16.2%) stage 4s patients. The median follow-up for the cohort was 2.5 (range 0.4–21.0) years. The median follow-up periods for stages 1, 2, 3 and 4 disease were 10.0, 2.6, 3.4 and 1.9 years, respectively. At the time of analysis, 29 (67.4%) patients were alive and 14 (32.6%) had died from their disease. The two- and five-year overall survival (OS) for the cohort was 65.0% (95% confidence interval [CI] 51.0%–80.0%) and 62.0% (95% CI 45.0%–79.0%), respectively (Fig. 1a). The two- and five-year event free survival (EFS) for the cohort was 63.0% (95% CI 48.0%–78.0%) and 57.0% (95% CI 39.0%–75.0%), respectively (Fig. 1b). The five-year OS rates according to risk status of neuroblastoma were as follows: 100% for low-risk (stages 1, 2, 4s) ( $n = 13$ ); 75.0% (95% CI 50.0%–99.0%) for intermediate-risk (stage 3) ( $n = 12$ ); and 28.2% (95% CI 4.0%–53.0%) for high-risk (stage 4) ( $n = 18$ ). The survival rates among the three risk groups were statistically significant ( $p = 0.002$ , log-rank test) (Fig. 1c).

All stage 1, 2 and 4s patients were alive at the time of analysis. Three (27.2%) patients with stage 3 disease died from their disease at 5.0, 8.9 and 17.5 months from diagnosis, respectively. Eight (72.7%) patients were alive with no evidence of disease. The MYCN statuses of the three patients who died were no amplification ( $n = 2$ ) and unknown ( $n = 1$ ). Of the eight who were alive with no evidence of disease, the MYCN statuses were no amplification ( $n = 4$ ) and unknown ( $n = 4$ ). Deletion of 1p was found in one of the patients who died.

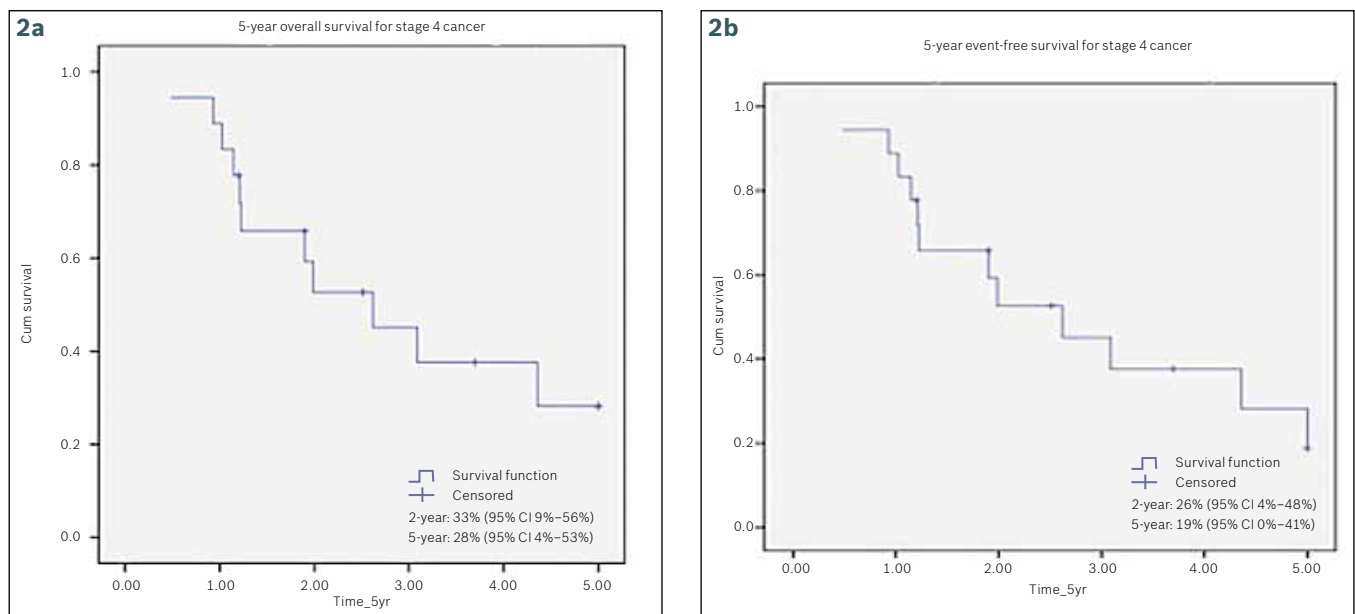
Of the 19 patients with stage 4 disease, 11 (61.1%) died from their disease at an average of 21.6 months from diagnosis; seven (36.8%) were alive with no evidence of disease; and one (5.3%) was alive with disease. MYCN status was available in ten of the 19 patients with stage 4 disease. The remaining nine (47.4%) patients' MYCN status tests were either not done or unknown. Out of these nine, only three (33.3%) were alive with no evidence of disease and six (66.7%) had died from the disease. Of the ten patients tested for MYCN, the tumours of four patients were MYCN amplified and three of these patients were alive at the last follow-up (range 1.2–3.7 years). The MYCN status was not amplified in six patients with stage 4 disease (Table II). The two- and five-year OS rates for stage 4 disease were 33.0% (95% CI 9.0%–56.0%) and 28.2% (95% CI 4.0%–53.0%), respectively (Fig. 2a). The two- and five-year EFS rates for stage 4 disease were 26.0% (95% CI 4.0%–48.0%) and 19.0% (95% CI 0%–41.0%), respectively (Fig. 2b).

A comparison of survival in stage 4 patients between chemotherapy received as per MSKCC vs. OPEC/OJEC regimens revealed that the two-year OS rate for MSKCC regimen was higher than that for the OPEC/OJEC regimen (53.0%, 95% CI

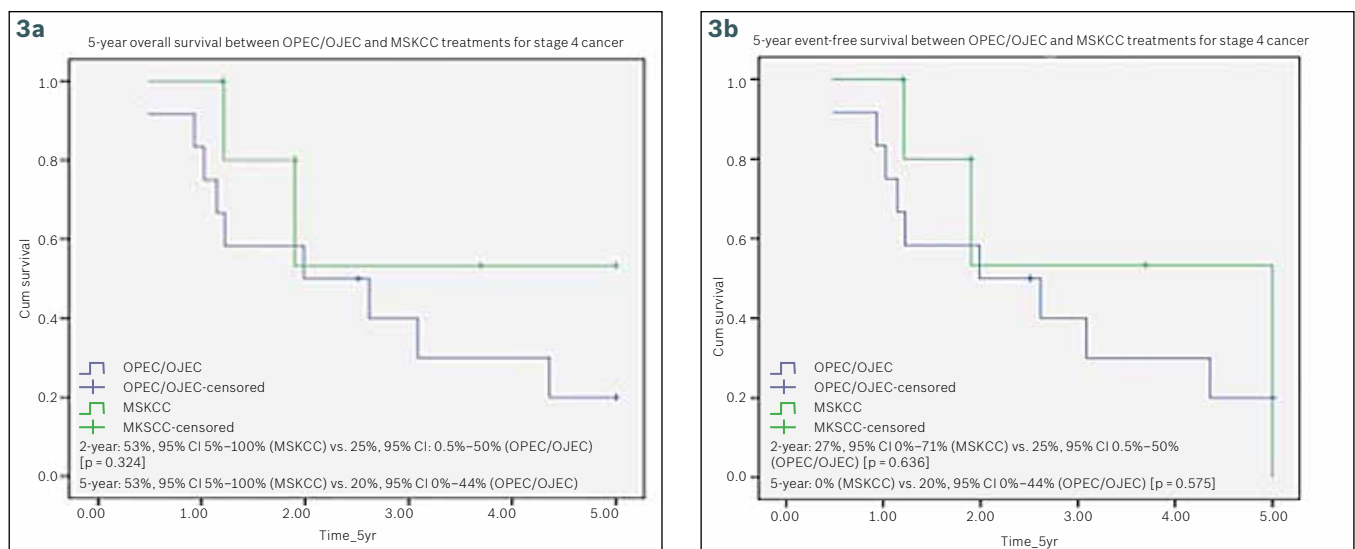


**Fig. 1** Graphs show (a) overall survival; (b) event-free survival and (c) event-free survival by stage in the study cohort ( $n = 43$ ).

5.0%–100.0% vs. 25.0%, 95% CI 0.5%–50.0%, respectively). However, there was no statistically significant difference in the survival rates between the two regimens ( $p = 0.324$ ) by log-rank test (Fig. 3a). Similarly, the two-year EFS rates between the two



**Fig. 2** Graphs show (a) overall survival and (b) event-free survival in stage 4 neuroblastoma patients (n = 19).



**Fig. 3** Graphs show (a) overall survival and (b) event-free survival by chemotherapy in stage 4 neuroblastoma patients.

groups were not statistically significant (27.0%, 95% CI 0.0%–71.0% vs. 25.0%, 95% CI 0.5%–50.0%,  $p = 0.636$ , log-rank test) (Fig. 3b). Additionally, no significant differences were observed in the five-year EFS and OS rates between the MSKCC and OPEC/OJEC chemotherapy regimens. The EFS rate was 0.0% vs. 20.0%, (95% CI 0.0%–44.0%,  $p = 0.575$ , log-rank test), respectively. The OS rate was 53.0% (95% CI 5.0%–100.0%) vs. 20.0% (95% CI 0.0%–44.0%,  $p = 0.309$ , log-rank test), respectively.

## DISCUSSION

We report the first single-centre experience on neuroblastoma in Singapore. The local incidence of neuroblastoma continues to be low, similar to the rest of the world.<sup>(15)</sup> However, the majority of children diagnosed with this cancer present at an advanced stage. Despite aggressive therapies, the survival rates range from 4.0% up to 50.0%. Survival rates for low-risk disease, i.e. stages 1, 2 and 4s, may reach up to 90.0%, while those for intermediate risk,

i.e. stage 3, can reach up to 60.0%–80.0%. For high-risk stage 4 disease, the survival rates can be as low as 4.0%.<sup>(7-9,11-13,16-23)</sup>

The INSS is a staging system for neuroblastoma, which was revised and first implemented in 1993. This staging system is based on age, stage and biological characteristics of the disease.<sup>(10)</sup> Cytogenetic studies, the single most important investigation that significantly correlates with prognosis, were only performed in 21 of the 43 patients in our study. This test was performed in patients diagnosed after 2003, as the technology only became available in Singapore then. To date, the fast and easy urinary screening of homovanillic acid (HVA) and vanillymandelic acid (VMA) ratios, which are usually elevated in neuroblastoma, were also not performed.<sup>(24)</sup> When performed serially during and after completion of therapy, urinary HVA and VMA ratios can provide a safe and non-invasive rapid monitoring of disease remission or early relapse status. At our centre, a random collection of urinary dopamine and creatinine ratios, believed to be the best

**Table II. Patients with stage 4 neuroblastoma treated as per the OPEC/OJEC protocol.**

No.	Age (yrs)/gender	MYCN status	Primary site	Metastatic site	Relapse site	Dx-FU (yrs)	Dx-R1 (yrs)	Status
1	4.6/M	Unknown	Adrenal, R	BM/bone	NA	0.5	NA	DOD
2	4.4/M	No	Abdominal	BM	Duodenum	0.9	0.9	DOD
3	1.3/M	No	Adrenal, R	BM	NA	1.0	NA	DOD
4	2.5/M	Unknown	Retroperitoneum	Bone/BM	NA	1.1	NA	DOD
5	2.6/F	Unknown	Spinal cord	Brain	NA	1.2	NA	DOD
6	4.1/M	Unknown	Kidney, R	Brain/bone/BM	NA	2.0	NA	DOD
7	2.9/F	Unknown	Mediastinum	BM	Unknown	2.5	NA	ANED
8	2.4/M	Unknown	Adrenal, R	BM	Liver/BM	2.6	1.1	DOD
9	7.1/F	Unknown	LN of neck, L	Bone	NA	3.1	NA	DOD
10	1.9/F	Unknown	Retroperitoneum	Bone	Absent	7.4	NA	ANED
11	1.9/M	Unknown	Maxillary sinus, R	Bone	Unknown	9.4	NA	ANED
12	1.0/M	No	LN of neck	Bone	Absent	10.4	NA	ANED

Dx-FU: diagnosis to follow-up; Dx-R1: diagnosis to 1st relapse; M: male; F: female; R: right; L: left; BM: bone marrow; LN: lymph node; NA: not applicable; DOD: died of disease; ANED: alive with no evidence of disease; No: not amplified

**Table III. Patients with stage 4 neuroblastoma treated as per the MSKCC protocol and others.**

No.	Age (yrs)/gender	MYCN status	Primary site	Metastatic site	Relapse site	Dx-FU (yrs)	Dx-R1 (yrs)	Status
13	4.1/F	Yes	Adrenal, L	Brain/bone/BM	NA	1.2	NA	DOD
14	4.1/M	Yes	Mediastinum	BM	Absent	1.2	NA	ANED
15	1.9/F	No	Adrenal, R	Brain/bone/BM	NA	1.9	NA	DOD
16	2.4/F	Yes	Adrenal, R	Liver/bone/BM	Absent	1.9	NA	ANED
17	5.1/F	Yes	Kidney, L	Bone	Absent	3.7	NA	ANED
18*	2.6/M	No	Adrenal, L	Bone/BM	Bone	4.4	2.1	DOD
19*	1.9/M	No	Retroperitoneum	Bone/BM	Bone	7.7	5.8	AWD

\*Patient was initially treated with OPEC/OJEC before the MSKCC protocol.

Dx-FU: diagnosis to follow-up; Dx-R1: diagnosis to 1st relapse; M: male; F: female; R: right; L: left; BM: bone marrow; NA: not applicable; DOD: died of disease; ANED: alive with no evidence of disease; AWD: alive with disease; No: not amplified; Yes: amplified; MSKCC: Memorial Sloan Kettering Cancer Centre

non-invasive screening test, continues to be the standard urinary investigation for neuroblastoma patients. In a separate, not-yet-published preliminary analysis, there appears to be no clinical correlation between urinary dopamine and creatinine ratios and disease status in our cohort.

The standard treatment protocol adopted by our centre in 1987–2003 for both neuroblastoma stage 3 (with high-risk features such as MYCN amplification and 1p deletion) and stage 4 was that proposed by the UKCCSG group, which consists of the OPEC/OJEC regimen, as described elsewhere.<sup>(11)</sup> Subsequently, based on published reports that revealed an improved survival with intensive, high-dose chemotherapy followed by autologous stem cell rescue, we modified our treatment protocol for high-risk disease patients.<sup>(12,18,25)</sup> Hence, after 2003, the MSKCC dose-intensive induction chemotherapy regimen was adopted for patients with high-risk disease in NUHS.<sup>(12)</sup> Although the drugs used are the same, the actual dose intensity in mg/m<sup>2</sup> per dose is different between the two regimens. 3F8, a murine IgG<sub>3</sub> monoclonal antibody that binds to protein G<sub>D2</sub>, has been associated with high long-term survival in children with high-risk neuroblastoma.<sup>(18–20)</sup> However, as the monoclonal antibody therapy is not yet widely

available at this time, it is not a part of our treatment protocol for children with high-risk disease.

While our five-year survival results for stage 4 disease look promising, a closer examination of the seven children enrolled into our new treatment protocol (the MSKCC regimen) continues to paint a dismal picture. Of the 13 patients treated with the OPEC/OJEC regimen, only four were alive at the time of analysis (range 2.5–10.4 years). Three of the seven children undergoing the MSKCC regimen died from their disease at 1.2, 1.9 and 4.4 years from the time of initial diagnosis despite undergoing intensive treatment, while three are alive with no evidence of disease and one is alive with disease. Five of the seven children underwent peripheral blood stem cell transplantation and two died within their first year of transplantation at seven and nine months, respectively, with a third child, later at 27 months. At the time of analysis, one child relapsed in the vertebral bone five years post completion of the initial therapy (Table III). The longest surviving patient (patient 12), who had stage 4 disease with metastasis to the bone, had no MYCN gene amplification. However, this patient was first diagnosed with neuroblastoma at one year of age, which correlated with the excellent prognosis. In our cohort of patients, the MYCN status was only available in ten of the 19 patients with

stage 4 disease. The test was not performed in the remaining nine; this was almost half of our study cohort. Hence, we were unable to conclude in accordance with the published data that MYCN status confers a poor prognosis, as a large number of our patients did not have the study performed. It is of importance to note that of the nine whose tumours were not tested, six had died from the disease (Table III).

Varying survival rates have been reported from Singapore's neighbouring countries. When comparing the survival rates for a cohort of children diagnosed with stage 4 neuroblastoma with neighbouring countries, Hong Kong's five-year OS stands out at an impressive 50.0% (Chan CF, personal communication, April 5, 2010). The first Japanese study group protocol reported a five-year OS of 34.4% for patients with stage 4 disease.<sup>(21)</sup> Malaysia reported their experience in 78 patients with neuroblastoma, with an overall two-year disease-free survival rate of 39.0%. However, not all the patients had stage 4 disease in the study.<sup>(22)</sup> In a cohort of 103 children with neuroblastoma in Chandigarh, India, 74 of whom had stage 4 disease, the authors reported a dismal outcome of only four (8.7%) children who were disease-free for a period of  $16.5 \pm 6.7$  months.<sup>(23)</sup> The variations in survival are likely related to many factors, namely disease factors such as the extent of metastatic disease, the cytogenetic status of the tumour, the chemotherapy regimens used and resectability of the tumour. In addition, various socioeconomic factors (e.g. accessibility and availability of care) as well as the number of children who defaulted in the study also contribute to a lower survival rate. It is possible that Hong Kong has managed to achieve such a high five-year survival rate (median follow-up about five years) due to the availability of the anti-G<sub>D2</sub>, 3F8 monoclonal antibody. Immunotherapy holds the key to better long-term survival in children with advanced stage neuroblastoma. Therefore, there is an urgent need at our centre to improve the long-term survival of children with high-risk neuroblastoma through novel treatments. This would, in turn, help our centre to achieve the excellent results described by institutions in neighbouring countries and other developed nations.

Our findings are limited by a high percentage (30.6%) of patients being excluded from analysis due to a lack of adequate medical records, especially for patients from the earlier time period of the study. Additionally, as most of our patients lived outside of Singapore, regular follow-up and accurate documentation of disease status are also lacking, as the patients returned to their home country following the completion of therapy and did not return for regular follow-up. Other limitations of our study were the short follow-up period (median of 2.5 years) and the small number of patients. Furthermore, although the staging criteria of disease was reviewed and reclassified using all the investigations performed and information available in the medical records, there was no uniformity in the clinical, surgical and histopathological investigations performed for the patients in the study cohort. Although minimally necessary investigations such as biopsy of the tumour and imaging (e.g. CT) of the primary tumour were

performed in some patients, no further consistent staging evaluations were done using bone or MIBG imaging for all patients; hence, a retrospective confirmation of diagnosis and staging could not be carried out thoroughly and accurately. This may in turn have contributed to either understaging or overstaging of some patients in our study cohort.

This first study of the disease characteristics and treatment outcomes of neuroblastoma at NUHS has identified many important findings and implications for Singapore. First, the majority of children diagnosed with neuroblastoma had high-risk disease at the time of presentation. Second, although survival for low- and intermediate-risk neuroblastoma was excellent, survival for those with high-risk disease remained dismal in our cohort of patients despite aggressive therapies. Finally, our study identified some gaps in collaboration between clinicians and scientists within the country and region. An emphasis on research into neuroblastoma should be mooted to further our understanding in order to maximise the cure rates for affected children in the region and beyond. It is imperative that education, training and continuous communication and collaboration between various healthcare institutions locally and within Southeast Asia are instituted to facilitate and strengthen our efforts in the treatment of children with neuroblastoma.

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