# Treatment and outcomes of high-risk neuroblastoma in Southeast Asia: a single-institution experience and review of the literature

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## Abstract

**Introduction:** In Europe and North America, the majority of children with high-risk neuroblastoma survive the disease. Elsewhere, the treatment outcomes are poor.

**Methods:** A retrospective review of children treated for high-risk neuroblastoma in a single institution in Singapore from 2007 to 2019 was carried out. Treatment consisted of intensive chemotherapy, surgery aimed at gross total resection of residual disease after chemotherapy, consolidation with high-dose therapy followed by autologous stem cell rescue, and radiotherapy to the primary and metastatic sites followed by maintenance treatment with either cis-retinoic acid or anti-disialoganglioside monoclonal antibody therapy. Survival data were examined on certain clinical and laboratory factors.

**Results:** There were 57 children (32 male) treated for high-risk neuroblastoma. Their mean age was 3.9 (range 0.7–14.9) years. The median follow-up time was 5.5 (range 1.8–13.0) years for the surviving patients. There were 31 survivors, with 27 patients surviving in first remission, and the five-year overall survival and event-free survival rates were 52.5% and 47.4%, respectively. On log-rank testing, only the group of 17 patients who were exclusively treated at our centre had a survival advantage. Their five-year overall survival rate compared to patients whose initial chemotherapy was done elsewhere was 81.6% versus 41.1% ($P = 0.011$), and that of event-free survival was 69.7% versus 36.1% ($P = 0.032$). Published treatment results were obtained from four countries in Southeast Asia with five-year overall survival rates from 13.5% to 28.2%.

**Conclusion:** Intensified medical and surgical treatment for high-risk neuroblastoma proved to be effective, with superior survival rates compared to previous data from Southeast Asia.

**Keywords:** Chemotherapy, child, haematopoietic stem cell transplantation, neuroblastoma, Southeast Asia

## INTRODUCTION

Neuroblastoma is a malignant embryonal tumour and the most common extracranial solid tumour in childhood, affecting about ten children per million population per annum.[1,2] It arises from the peripheral sympathetic nervous system and can be found mostly in the midline or paravertebral regions from the neck to the pelvis. The adrenal and the retroperitoneum, however, remain the most common primary sites. Neuroblastoma is a group of heterogeneous neoplastic diseases. Low- to intermediate-risk neuroblastoma has excellent prognosis after treatment, and some tumours may even regress spontaneously. High-risk neuroblastoma, on the contrary, has guarded prognosis even with aggressive chemotherapy and surgery. The latter is defined by metastatic tumour in children over the age

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of 18 months, or a disease with *MYCN* oncogene amplification in patients of any age.[1-4]

Combination chemotherapy, surgery and radiotherapy were the mainstay treatments for high-risk neuroblastoma in the last century, when long-term survival rates of 10% or less were reported.[5] The use of high-dose chemotherapy with autologous bone marrow or peripheral blood stem cell rescue further improved prognosis, with survival rates around 50% at the turn of the millennium.[6,7] Researchers at the Memorial Sloan Kettering Cancer Centre (MSKCC) had come up with dose-intense chemotherapy regimens that resulted in consistently better outcomes.[8] Their regimens are now widely adopted in North America. At the same time, the MSKCC has also been leading in the use of anti-disialoganglioside (anti-$G_{D2}$) immunotherapy,[9] which later led to the development of a Children's Oncology Group trial with dinutuximab. In that multicentre trial, the addition of anti-$G_{D2}$ therapy after standard chemotherapy, surgery, local radiotherapy and high-dose therapy with autologous stem cell transplantation resulted in survival rates of over 60%.[10] Similar trends in outcome improvement were also reported by various European study groups.[11]

Outside Europe and North America, the outcome of children with high-risk neuroblastoma is largely unknown. Limited published information from the literature suggests the outlook is not as optimistic. A recent population-based study from Australia reported a five-year overall survival (OS) of 46%,[12] while in South Africa, the two-year OS rates vary from 21.4% to 41.0% under different chemotherapy regimens.[13] In Mexico and India, metastatic neuroblastoma is reportedly an incurable disease.[14,15] This prompted us to report our experience and review others in Southeast Asia.

## METHODS

This was a retrospective chart review of all children treated at Mount Elizabeth Hospital, Singapore, with a curative intent for high-risk neuroblastoma. The study period was from March 2007 to June 2019. Survival was measured from the time of diagnosis to the end of July 2020, or censored at the time of death for OS and at the time of death or relapse for event-free survival (EFS). There were two categories of patients according to treatment history — patients who were treated exclusively with our in-house regimens (group 1) and those who had been treated partially elsewhere before presenting to our hospital for further treatment (group 2). Several disease- and treatment-related factors were selected for statistical analysis with respect to their effect on survival. These included patient group, tumour-associated *MYCN* amplification (amplified vs. nonamplified tumours), disease remission status at the end of induction chemotherapy (complete vs. partial remission), conditioning regimen during high-dose therapy (busulfan–melphalan vs. other regimens) and use of immunotherapy after completion of primary treatment. Survival was measured by Kaplan–Meier analysis, and comparisons of survival were done with log-rank tests. Parametric variables were compared by Student's *t*-test, while nonparametric variables were compared by Fisher's exact test.

The diagnosis of neuroblastoma was made based on histopathology of the primary tumour or of a metastatic tissue with conventional haematoxylin and eosin staining and immunohistochemistry incorporating synaptophysin and chromogranin A. Tumour *MYCN* amplification, deletion of chromosome 11q and deletion of chromosome 1p were evaluated by fluorescence *in situ* hybridisation. Imaging of the primary tumour was done with computed tomography and/or magnetic resonance imaging. Staging or evaluation for metastatic disease was carried out with $^{131}$I-metaiodobenzylguanidine (MIBG) scan and/or $^{18}$F-fluorodeoxyglucose positron emission tomography (PET) scan, plus bone marrow aspiration and trephine from both sides of the posterior iliac crests. Staging was according to the International Neuroblastoma Risk Group (INRG) staging system after 2009[3] and the International Neuroblastoma Staging System (INSS) in previous years.[4] Response to treatment was measured by imaging of the primary tumour and all metastatic sites with bone marrow examination. Complete remission was defined as no measurable and detectable disease on imaging and bone marrow examination. Partial remission referred to the absence of detectable disease in the primary site and reduced but residual disease in the bones and/or bone marrow, but without new lesions.

High-risk neuroblastoma was defined by any one of the following: (1) children 18 months or older with stage 4 or stage M (metastatic disease), (2) children 18 months or older with stage 3 disease and tumoral *MYCN* oncogene amplification or (3) children younger than 18 months with stage 3 and 4 disease and tumoral *MYCN* amplification.

The treatment consisted of five to seven cycles of induction chemotherapy, surgery aimed at gross total resection and high-dose chemotherapy with autologous haematopoietic stem cell transplantation. After high-dose therapy, all patients received local radiotherapy followed by maintenance therapy. Chemotherapy-naïve patients and patients who had received no more than three cycles of chemotherapy elsewhere were given upfront chemotherapy as outlined in Box 1. Patients who had received more than three cycles of chemotherapy elsewhere were offered salvage chemotherapy [Box 1]. The first days of consecutive cycles of chemotherapy were set to be no more than 21 days unless treatment break was necessary for surgery. Pegfilgrastim was used as growth factor support after each cycle of chemotherapy. The technical aspects of surgical management to attain gross total resection for abdominal, thoracic, thoracoabdominal and bilateral adrenal neuroblastoma have been reported before.[16-19] After completion of induction

**Box 1. Chemotherapy regimens.**

**Upfront chemotherapy: minimum 5 cycles; maximum 7 cycles**

Cycles 1, 2, 4, 6

- Cyclophosphamide 70 mg/kg IV Days 1 and 2
- Vincristine 0.67 mg/m$^2$ admixed with doxorubicin 25 mg/m$^2$ IV as continuous infusion Days 1–3

Cycles 3, 5, 7

- Cisplatin 50 mg/m$^2$ IV Days 1–4
- Etoposide 200 mg/m$^2$ IV Days 1–3

**Salvage chemotherapy: alternating cycles**

Vincristine-topotecan-cyclophosphamide

- Cyclophosphamide 70 mg/kg IV days 1 and 2
- Vincristine 0.67 mg/m$^2$ admixed with topotecan 2 mg/m$^2$ IV as continuous infusion days 1–3

Vincristine-irinotecan-temozolomide

- Vincristine 1.5 mg/m$^2$ IV day 1
- Irinotecan 62.5 mg/m$^2$ IV days 1–4
- Temozolomide 150 mg/m$^2$ PO days 1–5

Ifosfamide-carboplatin-etoposide

- Ifosfamide 2.4 g/m$^2$ IV days 1–3
- Carboplatin 560 mg/m$^2$ IV day 1
- Etoposide 100 mg/m$^2$ IV days 1–3

**High-dose chemotherapy: with haematopoietic stem cell rescue**

Carboplatin-etoposide-melphalan (prior to June 2011)

- Carboplatin 270 mg/m$^2$ IV as continuous infusion days 1–4
- Etoposide 300 mg/m$^2$ IV as continuous infusion days 1–4
- Melphalan 70 mg/m$^2$ IV days 1–3

Busulfan-melphalan (June 2011 and after)

- Busulfan 30 mg/m$^2$/dose 6-hourly IV days 1–4
- Melphalan 140 mg/m$^2$ IV day 5

High-dose ifosfamide-carboplatin-etoposide (for graft with low CD34$^+$ content)

- Ifosfamide 3 g/m$^2$ IV days 1–3
- Carboplatin 500 mg/m$^2$ IV days 1 and 2
- Etoposide 150 mg/m$^2$ IV days 1–3

IV: intravenous, PO: per os

chemotherapy and surgery, and when complete remission or good partial remission had been achieved, patients received consolidation with high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation. Busulfan and melphalan were used as conditioning treatment in and after June 2011. Pharmacokinetic monitoring for busulfan was not done, as the test was not available in Singapore. Carboplatin, etoposide and melphalan were used before June 2011 and in selected patients under 18 months of age. Total body irradiation with a dose of 10 Gy divided into three daily fractions or therapeutic MIBG at 12–18 mCi/kg was added in eight cases each before 2015 when immunotherapy was not available. After discharge from the transplantation, patients continued local radiotherapy at a dose of 21.0–30.6 Gy to the primary site, residual bone disease or heavily involved metastatic sites before high-dose therapy.

Before 2014, all patients received isotretinoin 160 mg/m$^2$/day orally for 26 weeks as maintenance treatment. From 2014, selected patients who could afford the treatment continued with anti-$G_{D2}$ immunotherapy, either locally or at an overseas institution. At our institution, patients were treated with granulocyte-macrophage colony-stimulating factor at 250 mcg/m$^2$ subcutaneously (SC) from days 1 to 14, dinutuximab-beta at 25 mg/m$^2$ intravenously (IV) from days 5 to 8 and isotretinoin at 160 mg/m$^2$ orally from days 12 to 25. Treatment was repeated at 28-day cycles for five cycles, followed by another 14 days of isotretinoin therapy. Those who went overseas were treated according to the MSKCC regimens based on 3F8 immunotherapy. The patients returned to our institution for follow-up after the completion of their treatment abroad.

## RESULTS

During the study period, 57 children with high-risk neuroblastoma received treatment in our hospital. They included 32 males with a mean age of 3.9 (range 0.7–14.9) years. The primary tumour arose from the adrenal/retroperitoneum in 51 cases and from the thoracic cavity in three cases, and it was thoracoabdominal in three cases. Seven children had high-risk stage 3 disease with *MYCN* amplification, four children under 18 months of age had metastatic disease associated with *MYCN* amplification, and 46 children over 18 months of age had metastatic disease with or without *MYCN* amplification. Twenty-seven children were surviving in first complete remission, two were surviving in second complete remission and two were still receiving treatment after relapse. Twenty-one children died from the disease after relapse. Four died in first remission from treatment-related complications. One child died from an accident. At a median follow-up of 5 years among survivors, the OS and EFS were 52.5% (95% confidence interval [CI], 39.3%–65.9%) and 47.4% (95% CI, 33.0%–59.2%), respectively [Figure 1].

In univariate analysis for risk factors associated with inferior OS and EFS, only getting treated elsewhere before coming to our centre (group 2) for further treatment was a risk factor for inferior survival [Table 1]. *MYCN* amplification status, complete remission at the end of induction chemotherapy, conditioning regimens other than busulfan–melphalan for high-dose therapy and absence of immunotherapy were not predictive of survival disadvantage. However, owing to the small number of patients in this study, there is likely insufficient power to detect the differences.

Among the 57 patients, 17 received complete treatment according to in-house regimens. Forty patients with stable disease or early signs of progression had been treated elsewhere before they came to our centre for further management. The OS rates for the two groups of patients were 81.6% (95% CI, 63.2%–100%) and 41.1% (95% CI, 25.4%–56.8%), respectively ($P$ = 0.011) [Figure 2]. In comparison, their EFS rates were 69.7% (95% CI, 47.4%–92.0%) and 36.1% (95% CI, 20.9%–51.3%), respectively ($P$ = 0.032) [Figure 3]. The two groups of patients were not different by follow-up time,

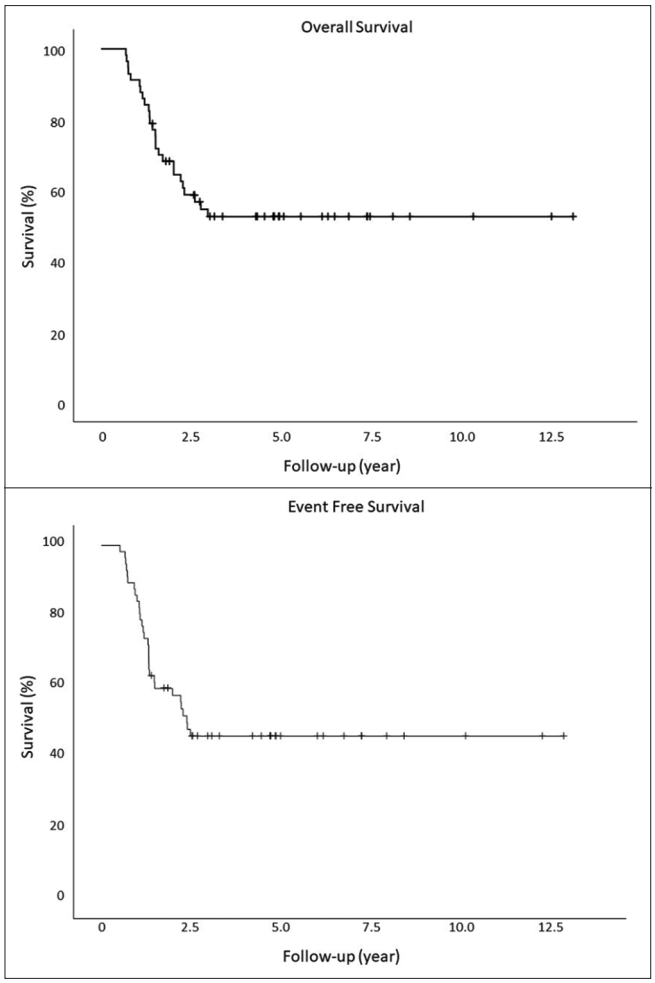


**Figure 1:** Overall survival (52.5%) and event-free survival (47.4%) rates of the entire study cohort ($n$=57).

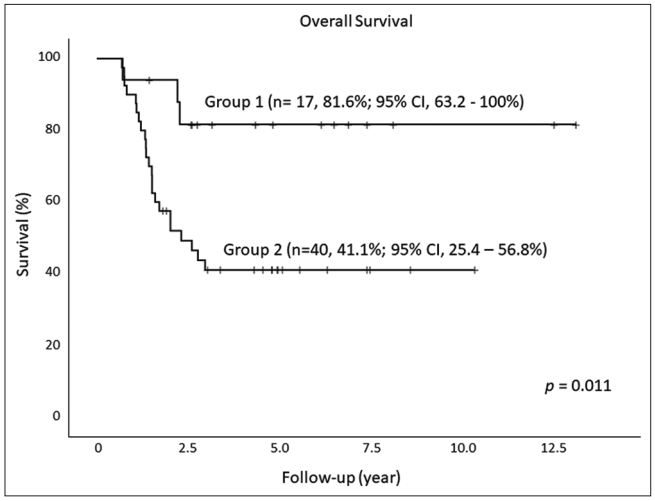


**Figure 2:** Comparison of overall survival rates between group 1 and group 2 patients.

*MYCN* amplification status, remission status at the end of chemotherapy, conditioning regimens for high-dose therapy and the use of immunotherapy [Table 2]. However, patients who received exclusively in-house chemotherapy were significantly older, and they were likely local or residing in the neighbouring countries of Malaysia and Indonesia.

**Table 1. Comparison of risk factors for overall survival and event-free survival.**

| Clinical feature | OS | *P* | EFS | *P* |
|---|---|---|---|---|
| Patient grouping | | | | |
| Group 1 ($n$=17) | 14 | 0.011 | 12 | 0.015 |
| Group 2 ($n$=40) | 17 | | 15 | |
| Remission status at the end of induction chemotherapy | | | | |
| CR ($n$=39) | 22 | 0.836 | 20 | 0.580 |
| PR ($n$=18) | 9 | | 7 | |
| *MYCN* amplification | | | | |
| Yes ($n$=17) | 10 | 0.949 | 9 | 0.725 |
| No ($n$=24) | 14 | | 12 | |
| Conditioning regimen | | | | |
| Bu-Mel ($n$=34) | 19 | 0.318 | 18 | 0.388 |
| Others ($n$=18) | 7 | | 6 | |
| Immunotherapy | | | | |
| Yes ($n$=24) | 15 | 0.263 | 12 | 0.872 |
| No ($n$=33) | 16 | | 15 | |

Bu-Mel: busulfan + melphalan, CR: complete remission, EFS: event-free survival, OS: overall survival, PR: partial remission

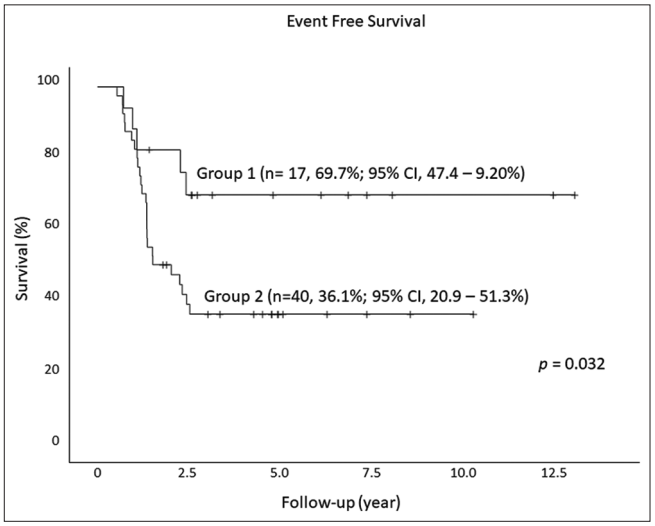


**Figure 3:** Comparison of event-free survival rates between group 1 and group 2 patients.

## DISCUSSION

North American and European countries have been leading research and treatment in paediatric oncology. The 12 most prolific countries account for over 80% of the research articles published in peer-reviewed journals after 1980.[20] To date, over 75% of newly diagnosed cancer children in these countries are expected to be long-term survivors.[21] For acute lymphoblastic leukaemia, the most common childhood malignancy, the five-year survival rates are approaching 90%.[22] Among the more affluent Asian countries or administrative

regions such as Hong Kong, Japan, Singapore and Taiwan, survival rates for childhood leukaemias are comparable to those of the West.[23,24] However, when it comes to high-risk neuroblastoma, their results are either unreported or inferior.[25,26]

To focus on the treatment of high-risk neuroblastoma in Southeast Asia, a literature search from PubMed, MEDLINE, EMBASE and Google was carried out using the terms {Neuroblastoma AND (Brunei OR Cambodia OR Indonesia OR Laos OR Malaysia OR Myanmar OR Philippines OR Singapore OR Thailand OR Timor OR Vietnam)}, and results were screened for treatment of high-risk or metastatic neuroblastoma. Six studies reporting treatment and outcomes for neuroblastoma were found from four countries: Malaysia,[27,28] Singapore,[26] Thailand[29,30] and Vietnam[31] [Table 3]. Four of these studies examined stage 4 disease or high-risk neuroblastoma in detail, with five-year OS rates from 0 to 28.2%. The two studies from Thailand were registry-based retrospective analyses and reported on patients with all stages, with five-year OS rates from 21.0% to 33.6%. With parallel observations from the other four studies, the OS rates in both Thai studies were likely below 20% for the high-risk neuroblastoma patients. Thus, treatment outcomes of high-risk neuroblastoma in Southeast Asia are far behind those of the leading countries.

The reasons for such a discrepancy in treatment outcomes are not immediately clear. However, our experience in this report may provide some clues. In the subgroup of patients who received exclusive treatment under our care, in which treatment regimen, intensity and supportive care closely followed those from the North American centres, survival rates were excellent. Patients who had received prior treatment elsewhere had inferior survival rates despite having received similar therapy when they continued their treatment in our hospital. We suspected that their prior treatment was suboptimal. It was obvious from some of the treatment records that the chemotherapeutic dosages were reduced at the first two cycles of treatment simply because the children could have been too ill to tolerate the full doses. At other times, despite similar chemotherapeutic drugs and dosages, the patients reported much less toxicities at the outside centre than with treatment of the same prescribed intensity at our centre. In particular, no blood product support was needed when they were receiving treatment in their home countries, while transfusion therapy was almost always required after each cycle of chemotherapy in Singapore. Several patients did not experience hair loss at home, while treatment-related alopecia was a constant feature following our regimens with alkylating agents. However, incomplete medical records do not permit an actual dose intensity analysis for the other centres. But an overcautious approach in following intensive chemotherapeutic regimens, probably because of inadequacy in supportive care, could have undermined the survival of high-risk neuroblastoma patients in Southeast Asia.

**Table 2. Comparison of the clinical characteristics between patient groups according to treatment.**

| Patient grouping | Group 1 ($n=17$) | Group 2 ($n=40$) | *P* |
|---|---|---|---|
| Age[a] (yr) | 5.3±3.9 | 3.3±1.8 | 0.0125 |
| From Singapore, Malaysia or Indonesia | 13 | 0 | <0.0001 |
| Complete remission at the end of induction chemotherapy | 13 | 26 | Not significant |
| *MYCN*-amplified tumour | 5/12 | 12/29 | Not significant |
| Conditioning with busulfan-melphalan | 9/12 | 25/40 | Not significant |
| Immunotherapy used | 10 | 14 | Not significant |
| Diagnosis-end of induction chemotherapy interval[a] (mth) | 5.1±0.6 | 7.9±2.8 | 0.0002 |
| Follow-up interval for survivors[a] (yr) | 5.8±3.6 | 5.2±2.2 | Not significant |

[a]Data presented as mean ± standard deviation.

**Table 3. Treatment and outcomes of high-risk neuroblastoma from Southeast Asia.**

| Study | Country | No. of patients | Survival | Remarks |
|---|---|---|---|---|
| Tan *et al*.[26] | Singapore | 19 | 5-year OS 28.2%; EFS 19.0% | 5-year OS 65% if patients of all stages were included |
| Looi *et al*.[27] | Malaysia | 15 | 0 | – |
| Ng *et al*.[28] | Malaysia | 49 | 2-year DFS 27% | Infants included; five lost to FU excluded from survival analysis; 2-year DFS 39% if patients of all stages were included |
| Wiangnon *et al*.[29] | Thailand | – | – | 163 patients of all stages with 5-year OS 33.6% |
| Wongmeerit *et al*.[30] | Thailand | – | – | 124 patients of all stages with 5-year OS 22.6% in an early cohort and 21.0% in a later cohort |
| Bui *et al*.[31] | Vietnam | 96 | 5-year OS 13.5% | Including both stage 3 and 4 cases; 5-year OS 39.8% if patients of all stages were included |
| Current study | Singapore | 57 | 5-year OS 52.5% | 5-year OS 81.6% in a subgroup of 17 patients treated exclusively in the authors' institution |

DFS: disease-free survival, EFS: event-free survival, FU: follow-up, OS: overall survival

With 90 operations recorded over a nine-year period,[16] our hospital is one of the leading surgical centres in Southeast Asia. In all cases, over 90% of tumour resection can be achieved and in the majority of cases, we accomplish gross total resection. In the last two decades, neuroblastomatologists were still arguing about how aggressive surgical management was necessary for optimal overall treatment outcome.[32,33] With a tumour that frequently infiltrates and intertwines with the major abdominal vasculature, the disease is often considered inoperable or only partially resectable (25%–75% tumour resection) in less-experienced centres. Recent studies and a meta-analysis have concluded that near-complete resection (more than 90%) or more is associated with superior survival rates.[34-36] Thus, patients with high-risk neuroblastoma require combined intensive chemotherapy and aggressive surgery for long-term survival.

Treatment-related complications remain a concern. Of the 26 deaths, five (19.2%) were due to non-relapse-related causes. Four of them were treatment-related mortalities. Two deaths occurred during the early posttransplantation period from transplant-associated vasculopathies and multiorgan failure, an emerging fatality in recipients of high-dose chemotherapy.[37] Another patient died of idiopathic pneumonia syndrome 3 months after transplantation. Twenty months posttransplantation, the fourth patient died due to massive upper gastrointestinal haemorrhage from suspected portal hypertension and oesophageal variceal bleeding. A better understanding of these complications may help to prevent and reduce the fatal consequences of the aggressive treatment in high-risk neuroblastoma. The frequent occurrence of hepatic sinusoidal obstruction syndrome or veno-occlusive disease in our patients[38] suggests that busulfan exposure may be a common underlying factor for these adverse events. Viral hepatitis was not involved in any of the cases. Therapeutic drug monitoring or use of alternative conditioning regimens may improve our patients' survival in the future.

Of note, immunotherapy with anti-$G_{D2}$ monoclonal antibody is the latest addition to the armamentarium against high-risk neuroblastoma.[39] As $G_{D2}$ is expressed by all neuroblastoma cells, anti-$G_{D2}$ immunotherapy exerts its clinical effects by antibody-dependent cell-mediated cytotoxicity and complement-mediated cytotoxicity. Dinutuximab is currently the only commercially available anti-$G_{D2}$ preparation. It was first approved by the US Food and Drug Administration in 2015, and hence, it was not available in the early part of our study. The cost of dinutuximab is substantial, doubling the overall expenditure for neuroblastoma treatment. Of the 24 patients who were treated with immunotherapy, only eight received the treatment in Singapore. Nine patients went elsewhere to enrol in experimental studies because of cost concerns. Seven received treatment in MSKCC with their in-house anti-$G_{D2}$ monoclonal antibody treatment. The heterogeneity of immunotherapy in this study may also explain why the treatment advantage of immunotherapy is not seen. However, this reflects a real-life experience, as treatment availability is often determined by cost.

In conclusion, treatment outcomes for high-risk neuroblastoma are generally poor in Southeast Asia. Effective chemotherapeutic regimens combined with total or near-complete surgical excision will help Southeast Asian centres to catch up with the survival rates from Europe and North America.

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## Conflicts of interest

There are no conflicts of interest.

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