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

Anselm Chi-Wai Lee¹, MBBS, FAMS, Chan Hon Chui², MBBS, FRCS, Robert Kwok³, MBBS, DMRD, Kim Shang Lee⁴, MBBS, FAMS, Chee Meng Fong⁵, MBBS, FRCPath, Wilfred HS Wong⁶, PhD

¹Children’s Haematology and Cancer Centre, Mount Elizabeth Hospital, ²Surgery Centre for Children, Mount Elizabeth Medical Centre, ³Radiology Clinic, ⁴Radiation Oncology Centre, ⁵Parkway Laboratory Services, Mount Elizabeth Hospital, Singapore, ⁶Department of Paediatrics and Adolescent Medicine, the University of Hong Kong, Hong Kong

Correspondence: Dr Anselm Lee Chi-Wai, Children’s Haematology and Cancer Centre, Mount Elizabeth Hospital, Level 4, 3 Mount Elizabeth, Singapore 228510. anselm.cw.lee@gmail.com

Singapore Med J 2021, 1–19
https://doi.org/10.11622/smedj.2021164
Published ahead of print: 24 October 2021

More information, including how to cite online first accepted articles, can be found at: http://www.smj.org.sg/accepted-articles
ABSTRACT

Introduction: In Europe and Northern America, the majority of children with high-risk neuroblastoma survive the disease. Elsewhere, 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 for gross total resection of residual disease after chemotherapy, consolidation with high-dose therapy followed by autologous stem cell rescue, radiotherapy to the primary and metastatic sites, followed by maintenance treatment with either cis-retinoic acid or anti-disialoganglioside (anti-GD2) monoclonal antibody therapy. Survival data were examined on certain clinical and laboratory factors.

Results: There were 57 children with 32 males treated for high-risk neuroblastoma. Their mean age was 3.9 (0.7–14.9) years. The median follow-up time was 5.5 (1.8–13.0) years for the surviving patients. There were 31 survivors with 27 surviving in first remission, and 5-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 5-year overall survival rate, compared with others 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 found from four countries in Southeast Asia with 5-year overall survival rates from 13.5%–28.2%.

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

Keywords: chemotherapy, child, haematopoietic stem cell transplantation, neuroblastoma; Southeast Asia
INTRODUCTION

Neuroblastoma is a malignant embryonal tumour and is the most common extracranial solid tumour in childhood, affecting about 10 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 para-vertebral 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 tumour 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 of 18 months, or disease with MYCN oncogene amplification in patients of any age.\(^{(1-4)}\)

Combination chemotherapy, surgery, and radiotherapy were the mainstay treatment 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 Center (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,\(^{(9)}\) that 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 the outcome improvement were also reported by the various European study groups.\(^{(11)}\)
Outside Europe and North America, the outlook 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 5-year overall survival of 46%,\(^{(12)}\) while in South Africa, the 2-year overall survival rates varies 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. Survivals were measured from the time of diagnosis to the end of July 2020, or censored at the time of death for overall survival (OS) and censored 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 others who had been treated partially elsewhere before coming to our hospital for further treatment (Group 2). Several disease-related and treatment-related factors were selected for statistical analysis with respective to their effect on survivals. These included patient group, tumour-associated MYCN-amplification (amplified vs. non-amplified tumours), disease remission status at the end of induction chemotherapy (complete remission vs. partial remission), conditioning regimen during high-dose therapy (busulfan-melphalan vs. other regimens), and use of immunotherapy after completion of primary treatment. Survivals were 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 non-parametric variables were compared by Fisher’s exact test.
The diagnosis of neuroblastoma was made on histopathology from the primary tumour or from a metastatic tissue with conventional hematoxylin and eosin staining and immunohistochemistry incorporating synaptophysin, chromogranin A. Tumour MYCN-amplification, deletion of chromosome 11q and deletion of chromosome 1p were evaluated by fluorescence in situ hybridization. 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 by no measurable and detectable disease on imaging and bone marrow examination. Partial remission referred to the absence of detectable disease in the primary site, 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 tumoural MYCN-oncogene amplification, or (3) children younger than 18 months with stage 3 and 4 disease and tumoural MYCN amplification.

The treatment consisted of five to seven cycles of induction chemotherapy, surgery aiming at gross total resection, high-dose chemotherapy with autologous haematopoietic stem cell transplantation. After high-dose therapy, all patients received local radiotherapy followed by maintenance therapy. For chemotherapy-naïve patients and patients who had received no more than 3 cycles of chemotherapy elsewhere, they were given upfront chemotherapy as
outlined in Box 1. For patients who had received more than 3 cycles of chemotherapy elsewhere, they 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, thoraco-abdominal, and bilateral adrenal neuroblastoma has been reported before. After completion of induction 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 prior to June 2011 and in selected patients under 18 months of age. Total body irradiation 10 Gy divided into 3 daily fractions or therapeutic MIBG at 12–18 mCi/kg were 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 prior to high-dose therapy.

Prior to 2014, all patients received isotretinoin 160mg/m²/day orally for 26 weeks as maintenance treatment. From 2014, selected patients who could afford continued treatment with anti-GD2 immunotherapy either locally or at overseas institution. At our institution, patients were treated with GM-CSF 250μg/m² SC Days 1 to 14, dinutuximab-beta 25mg/m² IV Days 5 to 8, and isotretinoin 160mg/m² orally Days 12 to 25. Treatment was repeated at 28-day cycles for 5 cycles followed by another 14 days of isotretinoin therapy. Those who went overseas were treated according to the Memorial Sloan Kettering Cancer Center regimens
based on 3F8 immunotherapy. The patients returned to our institution for follow-up after 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 tumours arose from the adrenal/retroperitoneum in 51, thoracic cavity in 3, and were thoraco-abdominal in 3 cases. Seven children had high-risk stage 3 disease with MYCN amplification, four children under 18 months old had metastatic disease associated with MYCN amplification, 46 children over 18 months old had metastatic disease with or without MYCN amplification. 27 were surviving in first complete remission, two were surviving in second complete remission, and two were still receiving treatment after relapse. 21 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 overall survival and event-free survival were 52.5% (95% confidence interval, 39.3-65.9%) and 47.4% (95% confidence interval, 33.0-59.2%), respectively (Fig. 1).

In univariate analysis for risk factors associated with inferior overall survival and event-free survival, only patients who had been treated elsewhere before coming to our centre (group 2) for further treatment was a risk factor for inferior survivals (Table I). 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, the number of patients in this study was small and most probably of not enough power to detect the differences.

Among the 57 patients, 17 received complete treatment according to in-house regimens. Forty had been treated elsewhere before they came to our centre for further management with
stable disease or early signs of progression. The overall survival rates for the two groups of patients were 81.6% (95% confidence interval, 63.2-100%) and 41.1% (95% confidence interval, 25.4-56.8%), respectively (p=0.011) (Fig. 2). In comparison, their event-free survivals were 69.7% (95% confidence interval, 47.4-92.0%) and 36.1% (95% confidence interval, 20.9-51.3%), respectively (p=0.032) (Fig. 3). The two groups of patients were not different by follow-up time, MYCN amplification status, remission status at the end of chemotherapy, conditioning regimens for high-dose therapy, and the use of immunotherapy (Table II). However, patient who received exclusively in-house chemotherapy were significantly older, and they were likely local or residing in the neighbouring countries of Malaysia and Indonesia.

DISCUSSION
The North American and European countries have been leading in the 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 5-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 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 nations (Table III) – Malaysia, Singapore, Thailand and Vietnam. Four of these studies examined stage 4 disease or high-risk neuroblastoma in detail with 5-year overall survival rates from 0 to 28.2%. The two studies from Thailand were registry-based retrospective analysis and reported on patients with all stages with 5-year overall survival rates from 21.0 to 33.6%. With parallel observations from the other four studies, the overall survival rates in both Thai studies were likely below 20% for the high-risk neuroblastoma patients. Thus, treatment outcomes of high-risk neuroblastoma in the 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. Of 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 have 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 that in some cases from their treatment records, the chemotherapeutic dosages were reduced at the first 2 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 when compared with the 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 over-cautious approach in following
intensive chemotherapeutic regimens probably because of inadequacy in supportive care could have undermined the survival of high-risk neuroblastoma patients in the Southeast Asia.

With 90 operations recorded over a 9-year period, 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 how aggressive surgical management was necessary for optimal overall treatment outcome. With a tumour that frequently infiltrates and intertwines with the major abdominal vasculature, the disease is often considered inoperable or only partial resection (25-75% tumour resection) is possible in less experienced centres. Recent studies and meta-analysis have concluded that near-complete resection (more than 90%) or more is associated with superior survival rates. 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, 5 (19.2%) are due to non-relapse-related causes. Four of them were treatment-related mortalities. Two deaths occurred during early post-transplantation period from transplant-associated vasculopathies and multi-organ failure, an emerging fatality in recipients of high-dose chemotherapy. Another patient died three months after transplantation with idiopathic pneumonia syndrome. The fourth patient died 20 months post-transplant with 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 suggests 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\textsubscript{D2} monoclonal antibody is the latest additional to the armamentarium against high-risk neuroblastoma\textsuperscript{(39)}. As G\textsubscript{D2} is expressed by all neuroblastoma cells, anti-G\textsubscript{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\textsubscript{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 and it doubles the overall expenditure for neuroblastoma treatment. Of the 24 patients who were treated with immunotherapy, only eight of them received the treatment in Singapore. Nine patients went elsewhere to enrol in experimental studies because of cost concerns. Seven went for treatment in MSKCC with their in-house anti-G\textsubscript{D2} monoclonal antibody treatment. This heterogeneity of immunotherapy in this study may also explain why a 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 regimen combined with total or near-complete surgical excision will help to catch up the survival rates in Europe and Northern America.

**REFERENCES**


Fig. 1 Overall survival (52.5%) and event-free survival (47.4%) rates for the whole group of 57 patients.
**Fig. 2** Comparison of overall survival rates between Group 1 and Group 2 patients.

**Fig. 3** Comparison of event-free survival rates between Group 1 and Group 2 patients.
## Box 1. Chemotherapy regimens:

**Upfront chemotherapy** – minimum 5 cycles; maximum 7 cycles  
Cycles 1, 2, 4, 6  
Cyclophosphamide 70mg/kg IV Days 1 and 2  
Vincristine 0.67mg/m² admixed with  
Doxorubicin 25mg/m² IV as continuous infusion Days 1 to 3  

Cycles 3, 5, 7  
Cisplatin 50mg/m² IV Days 1 to 4  
Etoposide 200mg/m² IV Days 1 to 3  

**Salvage chemotherapy** – alternating cycles with  
*Vincristine-Topotecan-Cyclophosphamide*  
Cyclophosphamide 70mg/kg IV Days 1 and 2  
Vincristine 0.67mg/m² admixed with  
Topotecan 2mg/m² IV as continuous infusion Days 1 to 3  

*Vincristine-Irinotecan-Temozolomide*  
Vincristine 1.5mg/m² IV Day 1  
Irinotecan 62.5mg/m² IV Days 1 to 4  
Temozolomide 150mg/m² PO Days 1 to 5  

*Ifosfamide-Carboplatin-Etoposide*  
Ifosfamide 2.4g/m² IV Days 1 to 3  
Carboplatin 560mg/m² IV Day 1  
Etoposide 100mg/m² IV Days 1 to 3  

**High-dose chemotherapy** (with haematopoietic stem cell rescue)  
*Carboplatin-Etoposide-Melphalan* (prior to June 2011)  
Carboplatin 270mg/m² IV as continuous infusion Days 1 to 4  
Etoposide 300mg/m² IV as continuous infusion Days 1 to 4  
Melphalan 70mg/m² IV Days 1 to 3  

*Busulfan-Melphalan* (June 2011 and after)  
Busulfan 30mg/m²/dose 6-hourly IV Days 1 to 4  
Melphalan 140mg/m² IV Day 5  

*High-dose Ifosfamide-Carboplatin-Etoposide* (for graft with low CD34⁺ content)  
Ifosfamide 3g/m² IV Days 1 to 3  
Carboplatin 500mg/m² IV Days 1 and 2  
Etoposide 150mg/m² IV Days 1 to 3
Table I. Comparison of risk factors for overall survival and event-free survival.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>OS</th>
<th>p value</th>
<th>EFS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient grouping</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=17)</td>
<td>14</td>
<td>0.011</td>
<td>12</td>
<td>0.015</td>
</tr>
<tr>
<td>Group 2 (n=40)</td>
<td>17</td>
<td></td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Remission status at end of induction chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (n=39)</td>
<td>22</td>
<td>0.836</td>
<td>20</td>
<td>0.580</td>
</tr>
<tr>
<td>PR (n=18)</td>
<td>9</td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>MYCN amplification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=17)</td>
<td>10</td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>No (n=24)</td>
<td>14</td>
<td>0.949</td>
<td>12</td>
<td>0.725</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bu-Mel (n=34)</td>
<td>19</td>
<td></td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Others (n=18)</td>
<td>7</td>
<td>0.318</td>
<td>6</td>
<td>0.388</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=24)</td>
<td>15</td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>No (n=33)</td>
<td>16</td>
<td>0.263</td>
<td>15</td>
<td>0.872</td>
</tr>
</tbody>
</table>

Abbreviations: Bu-Mel, Busulfan + Melphalan; CR, complete remission; EFS, event-free survival; OS, overall survival; PR, partial remission

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

<table>
<thead>
<tr>
<th>Patient grouping</th>
<th>Group 1 [N=17]</th>
<th>Group 2 [N=40]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>5.3 ± 3.9 years</td>
<td>3.3 ± 1.8 years</td>
<td>0.0125</td>
</tr>
<tr>
<td>From Singapore, Malaysia or Indonesia</td>
<td>13</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Complete remission at end of induction chemotherapy</td>
<td>13</td>
<td>26</td>
<td>Not significant</td>
</tr>
<tr>
<td>MYCN amplified tumour</td>
<td>5/12</td>
<td>12/29</td>
<td>Not significant</td>
</tr>
<tr>
<td>Conditioning with busulfan-melphalan</td>
<td>9/12</td>
<td>25/40</td>
<td>Not significant</td>
</tr>
<tr>
<td>Immunotherapy used</td>
<td>10</td>
<td>14</td>
<td>Not significant</td>
</tr>
<tr>
<td>Diagnosis-end of induction chemotherapy interval*</td>
<td>5.1 ± 0.6 months</td>
<td>7.9 ± 2.8 months</td>
<td>0.0002</td>
</tr>
<tr>
<td>Follow-up interval for survivors*</td>
<td>5.8 ± 3.6 years</td>
<td>5.2 ± 2.2 years</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± S.D.
### Table III. Treatment and outcomes of high-risk neuroblastoma from the Southeast Asia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>No. of patients</th>
<th>Survival</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng, 1999 [26]</td>
<td>Malaysia</td>
<td>49</td>
<td>2-yr DFS 27%</td>
<td>Infants included; 5 lost to FU excluded from survival analysis; 2-yr DFS 39% if patients of all stages were included</td>
</tr>
<tr>
<td>Wiangnon, 2011 [27]</td>
<td>Thailand</td>
<td>-</td>
<td>-</td>
<td>163 patients of all stages with 5-yr OS 33.6%</td>
</tr>
<tr>
<td>Tan, 2012 [24]</td>
<td>Singapore</td>
<td>19</td>
<td>5-yr OS 28.2%; EFS 19.0%</td>
<td>5-yr OS 65% if patients of all stages were included</td>
</tr>
<tr>
<td>Wongmeerit, 2016 [28]</td>
<td>Thailand</td>
<td>-</td>
<td>-</td>
<td>124 patients of all stages with 5-yr OS 22.6% in an early cohort and 21.0% in a latter cohort</td>
</tr>
<tr>
<td>Bui, 2019 [29]</td>
<td>Vietnam</td>
<td>96</td>
<td>5-yr OS 13.5%</td>
<td>Including both Stage 3 and 4 cases; 5-yr OS 39.8% if patients of all stages were included</td>
</tr>
<tr>
<td>This report</td>
<td>Singapore</td>
<td>57</td>
<td>5-yr OS 52.5%</td>
<td>5-yr OS 81.6% in a subgroup of 17 patients treated exclusively in the authors’ institution</td>
</tr>
</tbody>
</table>

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