Neuroblastoma Among Omani Children

Clinical characteristics and survival outcome from a dedicated centre

*Abeer Al-Battashi,1 Ameera Al-Rahbi,2 Abdulhakeem Al-Rawahi,3 Mohammed Mamdouh,4 Ibrahim Al-Ghaithi,4 Fatma Ali Ramadhan5

1National Oncology Centre and Departments of 4Pediatric Hematology & Oncology and 5Histopathology, The Royal Hospital, Muscat, Oman; Departments of 2Pediatrics and 3Epidemiology, Oman Medical Speciality Board, Muscat, Oman

*Corresponding Author’s e-mail: abeer_albattashi@hotmail.com

Abstract

Objectives: Neuroblastoma is a common childhood malignancy with limited number of publications from the middle east. This study describes the clinical characteristics and the survival outcome of Omani children with neuroblastoma who are treated at the National Oncology Center from 2010 to 2017. Methods: Data was retrospectively collected for Omani Children aged less than thirteen-years with neuroblastoma from January 2010 to December 2017. The survival data were statistically correlated with known prognostic factors including age, stage of disease, MYCN profile and presence of metastasis. Results: Fifty-six Omani children were included. The male to female ratio was 1:1. The mean age at presentation was one year and ten months. The two most common presenting complaints were body masses (48.2%) and constitutional symptoms (33.9%). About 54.5% were high-risk, 35.7% were intermediate risk and 9.8% were low-risk. High-risk neuroblastoma was mainly in children older than one year (76.6%), with low-risk being mainly observed in less than one year of age (80%). The overall survival of all groups combined was 74% (p value < 0.05); and the event free survival was 67% (p value < 0.05). The five years overall survival for the high-risk, intermediate-risk and low-risk
was 60%, 88% and 100% respectively. Moreover, the event free survival was 51%, 79% and 100% respectively. **Conclusion:** Omani children with neuroblastoma mainly presented with masses or constitutional symptoms. The majority of Omani children with neuroblastoma had an advanced disease at presentation which was associated with inferior survival. The survival outcomes were reasonably similar to published international data.

**Keywords:** Neuroblastoma, Oman, Survival

** Advances in Knowledge**

- Survival of Omani patients with neuroblastoma is similar to other patients in developed countries in spite of the considerable challenges.
- This study highlights the characteristics and management of childhood neuroblastoma in Oman and this information can help to consolidate evidence-based interventions and formulate individualized guidelines for developing countries.
- There is a higher percentage of opsoclonus myoclonus ataxia syndrome as a presentation of neuroblastoma in comparison to other publications.
- Omani patients with neuroblastoma are mainly from Muscat and Al-Batina regions which corresponds with the population distribution.

**Application to Patient Care**

- Understanding the clinical presentation of Omani children with neuroblastoma can help in early detection and improved outcome.
- Elaborating the treatment journey that Omani children with neuroblastoma undertake using the current standard international management guidelines.
- Predicting the outcome based on the stage of the disease upon presentation.

**Introduction**

Neuroblastoma is an extracranial embryonal tumor that mainly affects children, especially those less than five years of age. It has a challenging treatment protocol and diverse clinical presentations. Neuroblastoma can originate from primitive cells of the sympathetic nervous system in any location in the body. Typically, it occurs in the adrenal medulla or the paraspinal
Neuroblastoma occur rarely in adult patients, and there is an increasingly scarce incidence in the elderly population.

When neuroblastoma is suspected, an instant biopsy for histopathological and molecular genetic assessment needs to be performed. Other supportive diagnostic tests include urine catecholamines, serum ferritin, lactate dehydrogenase (LDH) and neuron specific enolase (NSE).

Once the tissue diagnosis is established, patients go through staging with bone marrow assessment and nuclear and cross-sectional imaging to identify distant metastases. Neuroblastoma tends to metastasize to different sites, commonly the bone and bone marrow. Rarely, it can spread to other sites, including the brain.

The treatment of neuroblastoma relies on a constellation of specific factors: age, stage, pathology, and molecular biology. In accordance with the International Neuroblastoma Staging System (INSS), cases are classified into one of six stages: 1, 2A, 2B, 3, 4, or 4s. In 2009, a newer classification system, the International Neuroblastoma Risk Group (INRG), was established to risk stratify patients into different subgroups based on clinical and prognostic implications. It grouped patients into very low risk (benign histology), low risk, intermediate, and high risk categories based on combinations of certain prognostic markers, including the age of the patient (more or less than 18 months), histopathological differentiation, and certain biological markers, including MYCN amplification, 11q deletion, and the presence of ploidy.

Depending on the risk stratification of the disease, patients undergo either surgery and observation if low-risk, or a lengthy and intense journey of therapy for the high-risk counterparts. The treatment of high-risk patients includes almost all of the modalities used to date in the treatment of cancer, including conventional chemotherapy, surgery, radiotherapy, autologous bone marrow transplant, immunotherapy, and maturation therapy (13-cis retinoic acid).

In the United Kingdom, neuroblastoma accounted for 6% of the total new cancer cases in children between 2001 and 2015 with a five-year overall survival rate of 71% from 2011 to 2015. In the United States, the five-year overall survival of the high-risk group was 40% to 50% compared to 95% for the low and the intermediate-risk groups. Epidemiological records
regarding neuroblastoma in the developing world, specifically in the Middle East, are scarce. In 2015, a study from Egypt showed that 76.7% of patients had stage 4 disease, and the majority were older than one year of age (75.8%). In 2015, a Saudi study of 32 years’ worth of data revealed that high-risk children were also the majority (47.6%) and had the worst survival rates. Meanwhile, in a 32-year retrospective study from Iran, most of the children (54%) were in the advanced stage with a 10-year overall survival rate of 58%. Overall, these findings highlight that the main challenge in neuroblastoma cases in the developing world is the failure of early detection.

Oman is a country in the southeastern coast of the Arabian Peninsula with a population of five million. In Oman, children aged less than 13 years with solid tumors receive treatment in the National Oncology Centre that is the only oncology center in the capital of Muscat for the treatment of pediatric solid tumors. Children with different malignancies share the diagnostic and treatment resources with their adult counterparts. This study retrospectively analyses the initial clinical presentation of Omani children with neuroblastoma and the survival outcomes in relation to other prognostic factors, which were previously established through recognized international studies. We will also discuss the main challenges faced in the management of neuroblastoma in Oman and provide some recommendations to improve the outcomes of patients with an aggressive form of the disease.

**Methods**

Data was collected from the Royal Hospital Al-Shifa Patient Electronic Record System and inputted into a Microsoft Excel data collection sheet. Records of all pediatric patients who were diagnosed with neuroblastoma from 2010 to 2017 were obtained through the medical records department. The data was collected exclusively by the study investigators. The diagnosis of neuroblastoma was established with a histological confirmation of the diagnosis based on the World Health Organization (WHO) classification and staging based on the Union for International Cancer Control (UICC). The MYCN amplification was considered positive if neoplastic cells exhibited more than 10 copies using fluorescent in situ hybridization (FISH). Staging and risk stratification was done based on the INSS and INRG. In the absence of the MYCN testing the risk stratification followed the rest of the other parameters in the previously
mentioned classifications system. All MYCN profiling and autologous bone marrow transplants were done in centers outside the country due to its local unavailability. Patients older than 13 years of age on diagnosis, patients who abandoned treatment, benign histology cases (very low risk), and patients of non-Omani nationalities were excluded from the study cohort.

For statistical analysis, SPSS Statistics software version 22 was used. Categorized variables are described as percentages, and continuous variables are presented as a mean with a standard deviation or a median. Proportions are presented as percentages with a 95% confidence interval. The survival rate is illustrated by Kaplan Mayer (KM) survival curves. Events for the EFS were relapses and for OS were deaths. This research has been granted an ethical approval by the Research and Ethical Review and Approve Committee of the Ministry of Health, Oman.

**Results**

**Demographics**

A total of 56 patients were included in this retrospective analysis. The male to female ratio was 1:1. The regional distribution of the patients within the Sultanate of Oman showed that most patients (35.7%) were from Al-Batinah, followed by Muscat (23.2%), while only 1.8% were from Al-Wusta (Fig. 1). This corresponds to the fact that 50% of the population of Oman lives in Muscat and the Al-Batinah coastal plain northwest of the capital. The mean age at presentation was 1 year and 10 months, with ages ranging from straight after birth to a maximum of 11 years. Children were categorized into three age groups: less than one year of age, as they showed a better outcome in previous studies compared to older children; one to three years of age; and more than three years old. Patients were also distributed homogenously for significant statistical comparisons. Children were almost equally distributed among the different age groups; 33.9% were less than one year of age, 33.9% were between one and three years of age, and the remaining 32.1% were more than three years of age.

**Risk stratification**

Patients were distributed into different INSS groups (Table 1) to determine the appropriate treatment. Overall, 55.4% were stage 4, 25% were stage 3, 3.5% were stage 2, and 7.1% were stage 1, while the 4s group accounted for 9% of the total number of patients.
Regarding risk, 54.5% were categorized into the high-risk group, 35.7% in the intermediate-risk group, and 9.8% in the low-risk group. Among the high-risk group, 23.4% were less than one year of age, 43.3% were between one and three years of age, and the remaining 33.3% were more than three years of age at diagnosis. For the intermediate-risk group, 55% were less than one year of age, 40% were between one and three years of age, and the remaining 5% were more than three years of age. Eighty percent of the low-risk group were less than one year of age. Most of the patients in the high-risk category were males (63.3%), while most of the patients in the intermediate- and low-risk groups were females (60% and 80%, respectively).

**Clinicopathological features**
The mean duration of symptoms from the first symptom to the first health care visit was around 5.25 weeks. Although patients had one major presenting complaint upon their initial clinical encounter, they also had other associated symptoms. The two most common presenting complaints were identification of body masses (48.2%) and constitutional symptoms (33.9%). Masses were specifically described as lumps that were commonly felt in the abdomen or neck swelling. Constitutional symptoms included fever, lethargy, excessive crying, and poor oral intake, which was associated with weight loss. Almost one third of patients had racoon eye on presentation (28.6%). Additionally, 26.8% had gastrointestinal complaints (e.g., diarrhea, vomiting, constipation) with an equal percentage presenting with central nervous system complaints (e.g., opsoclonus myoclonus, seizures, lower limb weakness). The least common symptomatology was respiratory (e.g., shortness of breath), constituting 8.9% all presenting complaints.

Subtypes of neuroblastoma included neuroblastoma with opsoclonus myoclonus ataxia syndrome (OMAS) (14.3%) and 4s neuroblastoma (10.7%). Patients with OMAS were predominantly females with a male to female ratio of 1:4. The most common locations were adrenal (55%), followed by paraspinal primaries (22%). Stage 3 constituted 44.4%, and equally stage 2 (44.4%). Around 11.2% had stage 1, and none had stage 4 disease. They are all currently in remission and free of neurological symptoms.
Favorable histology in the form of poorly differentiating or differentiating histological features was seen in 19.6% out of the total number of patients (Fig. 2A and 2B). Unfavorable histology included undifferentiated neuroblastoma (Fig. 2C) and compromised 46.4% of the total. Around 34% of the neuroblastoma samples had inconclusive histological characterization which was mainly due to small or inadequate tissue sample size which was insufficient for proper assessment. Residual tumor pathology can reveal a combination of different histological features (Fig 2D) which is mainly due to exposure to neoadjuvant therapy.

The most common neuroblastoma site was the suprarenal glands (49%), followed by the paraspinal region (21.4%). Meanwhile, 13.5% of patients had a tumor in the suprarenal gland with paraspinal extension. Other sites included the mediastinum (7.1%), the pelvis and retroperitoneum (3.6%), and the head and neck (5.4%).

In terms of metastasis, bone was the most common site of involvement, which was detected in 41% of patients using either a meta-iodobenzylguanidine (MIBG) scan, a bone scan, or both. The second most common site was bone marrow (35.7%), followed by the liver (14.3%), the lungs (10.7%), and the brain (5.4%).

**Treatment**

Treatment decisions were based on the constellation of factors making up the risk group of each patient. Patients in the low-risk group were treated with observation after surgical resection. The intermediate-risk group was treated with surgical resection and four to eight cycles of chemotherapy for local control and to prevent spread. The main chemotherapy agents used included carboplatin, etoposide, vincristine, cyclophosphamide, and doxorubicin.

The children in the high-risk group underwent an extensive treatment regimen involving six cycles of induction chemotherapy in accordance with the high-risk international treatment recommendations. Once remission status was established by imaging and marrow assessments, they proceeded to local control in the form of surgery. Only two patients in the high-risk group did not undergo surgical excision because of the tumor location (one was para-spinal, and the other was maxillary). Since 2012, all patients who are eligible for autologous bone marrow transplantation (ABMT), using a busulfan and melphalan conditioning regimen, have undergone
the procedure. After ABMT, patients got assessed for residual disease after which they receive 13-cis retinoic acid (maturation therapy) with the incorporation of radiation therapy for local control with a dose of 21 Gy. Specifically, 63.3% of high-risk patients (a total of 20 patients) underwent transplant. All patients who managed went through the transplant received radiotherapy. None of the patients received immunotherapy as it was not available.

**Survival**
The five-year overall survival (OS) and event-free survival (EFS) rates for all children during the eight-year study period were 74% and 67%, respectively (Fig. 3A and 3B). Patients who were 12 months of age and under had excellent OS and EFS rates compared to the rest of the patients (p-value = 0.029) (Fig. 4A and 4B). Children between one and three years of age and children older than three years of age had similar OS rates of 61% and 65%, respectively (Fig. 4B). However, the EFS rate of children older than three years of age was 52%, while children between one and three years of age had an EFS rate of 60% (Fig. 4A). The high-risk group had the worst outcome among all groups with a five-year OS rate of 60% and an EFS rate of 51% (p-value = 0.029) (Fig. 5A and 5B). The low-risk group had an excellent EFS rate and an OS rate of 100% for both, while, for the intermediate-risk group, the OS rate was 88%, and the EFS rate was 79% (Fig. 5A and 5B).

**Discussion**
Neuroblastoma is a massive challenge for pediatric oncologists worldwide and, to a special degree, the pediatric oncologists of the developing world for several reasons. First, the affected children typically present late with progressive symptoms and an advanced stage of the disease. In the present study the average time to presentation was 5.25 weeks which is considered significant for such a rapidly growing malignancy. Second, getting a timely pathological diagnosis and staging (specifically imaging procedures) can be difficult. Third, gathering the proper treatment assets, especially for high-risk patients, can be a huge challenge due to a lack of resources. For example, access to high dose chemotherapy and immunotherapy might not be possible for some children in the developing world. It has been reported that 73% of patients with neuroblastoma in sub-Saharan African countries presented with metastatic disease due to lack of proper medical resources and staging systems. In Oman, access to autologous stem cell
transplant was established through private or government funds in 2012. The delay caused by assigning patients to treatment centers abroad and by travel to those centers can impact the outcomes of this already compromised patient population.

The initial symptoms of neuroblastoma, like many other childhood malignancies, can be nonspecific and difficult to detect, especially in younger children and infants. In the present study, almost half of the children presented with body masses (48.2%), and almost one third also had general constitutional symptoms (33.9%). The combination of these two symptoms is vague and can be missed by the primary health care system, especially in rural areas lacking resources for measures, such as laboratory investigations and imaging. Respiratory compromise due to lung or mediastinal involvement was the least common symptom in the study population (8.9%), which was supported by the fact that the lungs were found to be an uncommon site of metastasis in these patients (10.7%). According to the literature, OMAS is reported in around 2-3% of patients with neuroblastoma and is believed to be driven by a para-neoplastic autoimmune process that affects the central nervous system. In the present study, around 14.3% of the patients presented with OMAS, which is higher than in other reports in the literature. A further study in this subset of patients is recommended to determine why OMAS was more common in the present sample.

In relation to the INRG system, most of the patients in the present study were high-risk (55.4%); this parallels the results of previous studies in which most children presented with high-risk disease. Patients less than one year of age had excellent survival rates, which can be explained by the fact that 80% of them were in the low-risk group. The INRG system in our patients was applied despite the limitations of tumor genetic analysis.

Staging neuroblastoma requires swift access to cross-sectional and nuclear imaging and tissue examination with a proper histopathological and biological interpretation. With a significant proportion of the people of Oman living in rural areas, proper risk stratification can get compromised. In the present study, 34% of the patients’ pathology reports did not classify them into the three known pathological categories: differentiated, poorly differentiated, and undifferentiated. Also, despite the fact that MYCN is an established prognostic factor for
neuroblastoma outcomes, only 26.8% of the patients were tested. Among the tested samples, 9% were found to be MYCN amplified. As of 2018, all Omani patients who are newly diagnosed with neuroblastoma get their tumors molecularly evaluated for MYCN amplification in laboratories abroad. All patients in the present study who had MYCN amplification had a metastatic disease upon presentation. Other important biological markers include deletions of 1p or 11q and unbalanced gain of 17q, which were also not available in our pediatric oncology treatment center. The lack of proper molecular genetic assessment in these patients might have led many patients to be undertreated.

This study encountered several limitations. First, its retrospective nature made it prone to missing information and possible inaccuracies. Another drawback was the small sample size. Despite being the only pediatric oncology treatment center in the country for solid tumors, the sample might still not represent the entire Omani pediatric neuroblastoma cases due to the significant number of patients travelling abroad for treatment without seeking any local medical attention.

Considering the significant proportion of children who live in remote areas of Oman, access to oncological services can be a significant challenge. In terms of treatment, the local unavailability of autologous stem cell transplant, immunotherapy, and local tumor molecular profiling can have detrimental effects on the outcomes of Omani children with neuroblastoma, especially among high-risk patients. Furthermore, MYCN was previously not done for most patients unless they were diagnosed outside the country in an institution that runs this test. The main reasons were lack of resources and probably the understanding of the significance of the test. Another major challenge was the lack of adequate diagnostic material for proper pathological classification and the absence of any molecular genetics. This might have subjected a group of high-risk patients to undertreatment and a higher risk for relapse.

Conclusion
The survival outcomes of Omani children with neuroblastoma who were treated at the National Oncology Center from 2010 to 2017 were comparable to those described in the literature in developed and developing countries. Despite the difficulties in diagnosis and management, our
results are very promising and comparable with known published international cohorts and reveal excellent outcomes for intermediate- and high-risk neuroblastoma. However, the prognosis for high-risk disease remains rather poor. Neuroblastoma displayed non-specific clinical manifestations in the studied cohort. A high level of suspicion for neuroblastoma is necessary, especially in children under five years of age with an abdominal mass and/or bone pain, irritability, or fever with an unknown cause. That can be only established by proper education of health care providers about this aggressive childhood malignancy.

Conflict of Interest
The authors declare no conflicts of interest.

Funding
No funding was received for this study.

References


Table 1: Demographic characteristics of Omani children with neuroblastoma diagnosed between 2010 to 2017.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Total patients</td>
<td>56 (100%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>28 (50%)</td>
</tr>
<tr>
<td>Females</td>
<td>28 (50%)</td>
</tr>
<tr>
<td>Age (in weeks)</td>
<td></td>
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<tr>
<td>Mean</td>
<td>174.7</td>
</tr>
<tr>
<td>Median</td>
<td>102.1</td>
</tr>
<tr>
<td>Range</td>
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</tr>
<tr>
<td>Histopathology</td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>11 (19.6%)</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>26 (46.4%)</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>19 (34%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (7.1%)</td>
</tr>
<tr>
<td>II</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>III</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>IV</td>
<td>31 (55.4%)</td>
</tr>
<tr>
<td>4s</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>N-MYC</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
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</tr>
<tr>
<td>Negative</td>
<td>10 (17.8%)</td>
</tr>
<tr>
<td>Not done</td>
<td>41 (73.2%)</td>
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Clinical presentation

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<tbody>
<tr>
<td>Body masses</td>
<td>27 (48.2%)</td>
</tr>
<tr>
<td>Constitutional</td>
<td>19 (33.9%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>15 (26.8%)</td>
</tr>
<tr>
<td>Neurological</td>
<td>15 (26.8%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>5 (8.9%)</td>
</tr>
</tbody>
</table>

Figure 1: Distribution of Omani children less than 13 years of age with neuroblastoma between 2010 – 2017 among the main regions of Oman.

Figure 2: Low power microscopy examination (Hematoxylin & eosin stain) of the different known histopathological entities of Neuroblastoma which were obtained from Omani patients:
(A) undifferentiated neuroblastoma showing densely packed small to medium sized cells, indiscernible to small amount of cytoplasm with vague cytoplasmic borders, (B) Poorly differentiated neuroblastoma with ≤ 5% of tumor cells are differentiating neuroblasts, (C) Ganglioneuroblastoma or differentiating neuroblastoma showing at least 5% of tumor cells being differentiating neuroblasts, and (D) Residual neuroblastoma with mixed histological combinations.

**Figure 3:** The event free survival (A) and the overall survival (B) for Omani children diagnosed with neuroblastoma between 2010 and 2017.
Figure 4: The event free survival (A) and the overall survival (B) for Omani children diagnosed with neuroblastoma between 2010 and 2017 is illustrated according to the age group.
Figure 5: The event free survival (A) and the overall survival (B) for Omani children diagnosed with neuroblastoma between 2010 and 2017 according to the risk group stratification.