

RESEARCH ARTICLE

Neuroblastoma in Iran: An Experience of 32 Years at a Referral Childrens Hospital

Gholamreza Bahoush Mehdiabadi^{1,2,3*}, Elaheh Arab², Khadijeh Arjmandi Rafsanjani^{2,3}, Shahla Ansari², Amir Majid Moinzadeh⁴

Abstract

Background: This survey aim was to evaluate the epidemiology and outcomes of neuroblastoma patients in one the most important children referral hospitals in Iran as a model from developing countries. **Materials and Methods:** This retrospective, non-randomized analytic study was conducted on 219 newly diagnosed neuroblastoma cases. **Results:** The age of patients ranged from 1-156 months with the average of 40.5 ± 2.44 , with a male/female ratio of 1.9/1. Of the total, 172 (78.5%) were children and 47 (21.5%) were infants The adrenals were the most common primary site (60%). Stage 4 at diagnosis accounted for about 54% of all enrolled patients. Infants had significantly better cumulative survival ($85 \pm 8\%$) than children ($33 \pm 7\%$) during the follow up period and the survival rate improved from $33 \pm 7\%$ in 1974-1994 to $58 \pm 9\%$ in 1995-2005. **Conclusions:** This study indicates that our patient population with neuroblastomas tends to have more advanced disease, perhaps with poor biologic markers, but our analysis shows that the outcomes have improved over 32 years although the overall survival of Iranian neuroblastoma patients is still lower than developed countries. Late diagnosis, inability to determine risk group during the years of study and using single protocol for all enrolled patients can be the reasons of lower survival rate.

Keywords: Neuroblastoma - epidemiology - outcome

Asian Pacific J Cancer Prev, 14 (5), 2739-2742

Introduction

Neuroblastoma (NB) is the most common solid tumor occurring in childhood that arises from the sympathetic nervous system. In over 60% of cases, the disease has been metastatic at the time of diagnosis, accounted for about 15% of cancer mortality in children. Children below five years are the most affected group. In the USA, NB accounts for 6-10% of all childhood malignancies. 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 (Hiyama, 2008; Lee, 2012; Tan et al., 2012).

Despite all treatments the majority of patients with neuroblastoma have metastatic tumors and poor prognosis. Many genetic mutations such as *MYCN* gene amplification have been found responsible for progression and worsening outcomes of neuroblastoma tumors (Brodeur and Knowing, 2011).

Survival of NB could be improved by identification of high risk patients based on clinical and molecular prognostic factors. According to the Children's Oncology Group (COG) there is a system for classification of high risk neuroblastoma that was based on clinical data (the patient's age at diagnosis and the tumor stage) and

tumor biology (histology classification, *MYCN* oncogene amplification status, and DNA ploidy) (David et al., 2010). Accordingly, patients with high-risk neuroblastoma have a very poor outcome and infants have better outcome than children older than 1 year of age since the children with advanced stage NB die from the disease despite all treatments (Weinstein et al., 2003; Qing-Rong et al., 2008).

Therefore in some countries such as Japan and some European countries screening methods has been considered a promising approach to make diagnosis in early stages and to improve the outcome (Schilling et al., 2002). But the complex biological behavior of NB tumor makes the diagnosis, treatment and the prediction of outcomes difficult (Harder, 2010).

This study aimed to evaluate epidemiologic data and outcomes of neuroblastoma patients diagnosed at one of the main children hospitals in Tehran (Ali-Asghar Children Hospital) and to find out the causes of outcomes for improving the future of this disease in Iran.

Materials and Methods

The study was a retrospective, non-randomized analytic research on 219 newly diagnosed neuroblastoma cases from 1974-2005 at Ali-Asghar Children Hospital.

¹Onco-Pathology Research Center, ³Department of Pediatrics, Pediatric Hemato/Oncologist, Ali-Asghar Children Hospital, ²Iran University of Medical Sciences, ⁴Farzan Clinical Research Institute, Tehran, Iran *For correspondence: swt_f@yahoo.com

This hospital is one of the oldest and most famous pediatric oncology centers in Iran and is also one of the academic pediatric centers of Tehran University of Medical Sciences. The research project submitted to the Ethics Committee of Tehran Medical University and approved by this committee.

Diagnosis was based on bone marrow aspiration (BMA) plus vanillylmandelic acid and homovanillic acid (VMA/HVA) measurement and if these tests were not diagnostic, excisional/incisional biopsy was done.

Staging underwent according to the findings of diagnostic tests including: age at diagnosis, BMA (without biopsy), abnormal sonography, chest-X ray posteroanterior and posterolateral views (CXR, PA and LAT views) and surgery results if it was doable.

Because of lacking enough experience in definition of Shimada histology and DNA ploidy and lacking any center for MYCN gene amplification throughout the period of study, defining risk groups was not feasible during the years of study therefore risk-group stratification was not used for the management of patients.

There are three principal methods for treating of NB including surgery, chemotherapy and radiotherapy (Bhatnagar and Sarin, 2012).

Within two decades of struggling to improve NB outcomes, scientists have tried to introduced new treatments including high-dose chemotherapy with autologous stem cell rescue, retinoids, immunotherapy using anti-GD2 antibodies and anaplastic lymphoma kinase (ALK) inhibitors and aurora kinase A inhibitors (Sung et al., 2010; Hara, 2012).

Almost all of enrolled patients were treated at diagnosis by conventional OPEC regimen (Day 1: Vincristin 1.5 mg/m² and Cycphosphamide 600 mg/m², day2: Cisplatin 60 mg/m², d :Etoposide 100 mg/m² repeated every four weeks for 8 therapy cycles).

In this project we reviewed the records of patients to evaluate epidemiologic data and outcomes of neuroblastoma, as compared with standard rate and other literature.

We entered all neuroblastoma new patients whose documents were kept in the archive of Ali-Asghar Children Hospital in our study but we excluded those patients who did not complete our follow-up or their documents were incomplete.

We analyzed the patient`s data to find out distribution of neuroblastoma according to their age, gender, hometown and the year of diagnosis. We also evaluate the extent of neuroblastoma stages at diagnosis according to the patients age and gender and primary site of tumor frequency at diagnosis were assessed.

Furthermore we found the overall survival of all enrolled patient during the years of study and assessed survival rate according to patients age, gender and primary site of tumor at diagnosis and stage of their disease.

We compared the overall survival of infants and children with neuroblastoma from 1974-2005 in Ali-Asghar Children Hospital. Because of incomplete medical records of some patients, the data of 177 patients were used for staging and survival analysis.

All data were collected from medical archive database of this hospital and entered electronically in statistical analyzing software of SPSS version 16.0 and Log Rank for survival analysis according to Kaplan-Myer method.

Results

Among registered patients in Ali-Asghar Children Hospital, NB tumor was the sixth tumor type of all children and the second more prevalent tumor of infants. According to patients province of residence, most of NB patients lived in Tehran (most populated city of the country), Hamedan, Lorestan and Mazandaran provinces whereas provinces of Khorasan, Kordestan, Sistan and Semnan had the least new cases of neuroblastoma.

Distribution of diagnosis of new patients shows that there was an increasing trend in the diagnosis of NB from 1974-2005 with exception of two periods of decline in diagnosis of NB from 1993-1996 and from 2001-2002. The rate of admission of NB patients was 2.66 per year in 1973 while this rate increased to 12 patients per year in 2005 (Figure 1).

The age of patients ranged from 1 to 156 months with the average of 40.5±2.44. Our evaluation for estimating frequency of NB among all 219 cases showed that 172 patients (78.5%) were children and 47 patients (21.5%) were in infancy age (Table1).

We found that the stage 4 was the most prevalent extend of NB at diagnosis in both age groups of children (59.5%) and infants (35.3%) (Table 2).

Analyzing the distribution of NB according to gender illustrated that the boys tended to have NB about twice more than girls. Male/female ratio of neuroblastoma was 1.9/1. The majority of patients from both genders had NB in stage of 4 at diagnosis although stages 1 and 2 were more frequent among females and stages 3, 4 and 4s were more frequent between male patients.

Studying the primary site of tumor at diagnosis showed that in 72% of patients, abdomen was the main location

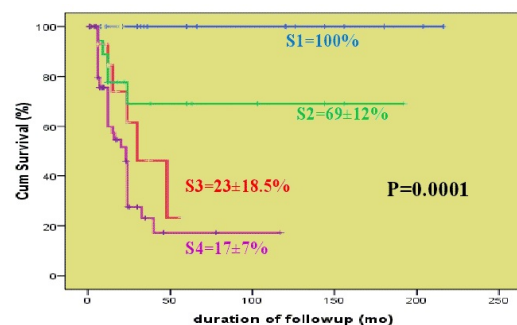


Figure 1. Distribution of New Patients Admission during the Years of Study 1974-2005

Table 1. Frequency of Infants vs. Children with NB in the Years of Study

Age Group	Neuroblastoma	
	Count	% of Total
Infant	47	21.50
Children	172	78.50
Total	219	100

Table 2. Extend of Disease at Diagnosis According to Age, Ali-Asghar Children Hospital vs. COG Report

Stage at diagnosis	COG			Iran		
	<1 yr, N (%)	>1 yr, N (%)	Overall N (%)	>1 yr, N (%)	<1 yr, N (%)	Overall N (%)
1	333 (26)	255 (12)	588 (17)	15 (10.8)	11 (26.5)	26 (14.5)
2	276 (22)	264 (12)	540 (16)	20 (14.4)	8 (20.6)	28 (15.9)
3	184 (14)	354 (16)	538 (16)	21 (15.3)	4 (8.8)	24 (13.8)
4	258 (20)	1264 (59)	1522 (44)	81 (59.5)	14 (35.3)	95 (53.8)
4S	233 (18)	11 (1)	244 (7)	0	4 (8.8)	4 (2.1)
Overall	1284	2148	3432	136	41	177

of NB and Adrenal gland was the most common primary site (60%) of all anatomical regions and mediastinum, head/neck and pelvis were the other frequent sites of NB tumors.

We analyzed the outcome of neuroblastoma and found that the cumulative survival of all enrolled patients during the years of study was $46.7 \pm 6\%$ but female patients had better cumulative survival ($56 \pm 8\%$) than males ($36 \pm 8\%$). Survival of NB patients also depends on the primary site of tumor so we found that patients with primary NB tumor in head or neck region had the best survival of 100%, while the primary site of NB in abdomen resulted in survival of $49 \pm 7\%$ and this outcome was the least, $35 \pm 16\%$, if the primary site of NB was in mediastinum. In comparison of overall survival of children and infants with NB, infants had better cumulative survival ($85 \pm 8\%$) than children ($33 \pm 7\%$) during the follow up period.

Metastasis occurrence of NB was analyzed according to the age (younger than 18 months or older than 18 months) of patients so it was shown that the stage 4 of NB was the most frequent metastasis in both studied groups this means that about 60% of metastatic NB in patients aged more than 18 months was in stage 4 and this data was about 40% for patients aged less than 18 months. In both stages of 1 and 2 patients with less than 18 months of age had more frequency of metastatic NB than children aged more than 18 months. Finally, stage 4s of metastatic NB was seen only in patients younger than 18 months of age.

The overall 3-year survival rate was analyzed in two distinctive periods of time. We found that the survival rate of NB in our study has improved from $33 \pm 7\%$ in 1974-1994 to $58 \pm 9\%$ in 1995-2005 ($p=0.003$) (Figure 2).

Distribution statistics of infants with NB according to the year of study show that 11.1% of all infant patients were diagnosed in the period of 1974-1984 but this data was increased to 30.6% from 1985-1994 and 58.3% from 1995-2005.

By studying the extend of disease at diagnosis among infant patients we found that between 1995 and 2005 there were the most diagnosed patients when most of them had stage 4, 1 and 2 of neuroblastoma but the extend of NB had the least proportion in the period of 1974-1984 with most frequent stages of 1 and 3.

We also analyzed the survival rate of patients according to the stage of NB therefore the best survival of 100% belonged to the patients with stage 1 of neuroblastoma but as it could be predicted there was an inverse relationship between the stage of NB and the survival rate of patients, accordingly the survival rates of patients who diagnosed

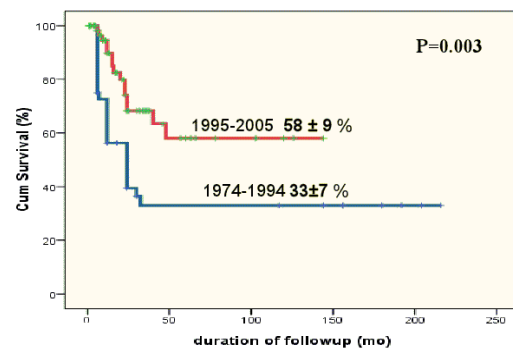


Figure 2. Survival Analysis of Admitted Patients between Years 1974-1994 Versus 1995-2005

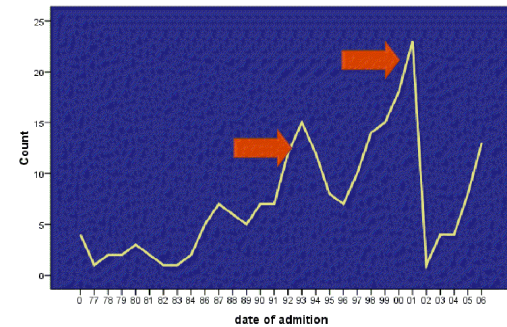


Figure 3. Survival Analysis According to the Stage

in stage 2 was $69 \pm 12\%$, for patients with stage 3 was $23 \pm 18.5\%$ and the patients with stage 4 of NB had the worst survival of $17 \pm 7\%$ ($p=0.0001$) (Figure 3).

Discussion

According to our study the majority of NB patients were from province of Tehran where our hospital is located but it could not prove any difference in the prevalence or outcomes of neuroblastoma between different ethnicities or races due to lack of data about the patients ethnicity/race while in a recent survey high-risk NB and worse outcomes are more prevalent among Black and Native American patients compared with Whites (Tara, 2011).

As with most malignancies, stage of disease is the most important prognostic factor in NB, and several retrospective analyses have confirmed the clinical relevance of the INSS staging system. Age at diagnosis remains the only other independent clinical prognostic factor, as infants less than 1 year of age have significantly better survival rates than older children with the same stages of disease (Weinstein et al., 2003). Some researchers designed a prognostic model using a neuroblastoma classifier, Multi-Signature Ensemble-classifier of neuroblastoma (NB-MuSE). They used the combination of NB-MuSE-classifier with INSS to obtain a single outcome prediction of NB (Cornero et al., 2012).

According to Vermeulen's survey a new and successful system for outcome prediction of NB in children was developed, in which a set of 59 genes is evaluated by PCR technique (Vermeulen et al., 2009).

In Bernstein's study of Canadian patients the overall 10-year survival rate for the 295 cases of neuroblastoma was 55% which is comparable with our finding illustrates

the overall survival of 46.7±6%. The 10-year survival rates for patients with Evans stage I-IV and IVS disease in Bernstein's study were 88%, 90%, 63%, 21%, and 81% that differs with our result specially in stage 3 (Bernstein et al., 1992).

According to the SEER data, the overall survival rate of neuroblastoma patients has improved from 24% in 1960-1963 to 55% in 1985-1994.

Overall survival for neuroblastoma reported in developed countries is comparable.

Another study on evaluation the survival of cancers like neuroblastoma revealed that the overall survival of NB in Thailand is 33.6% which is almost lower than our outcomes (Wiangnon et al., 2011).

According to SEER data (New malignancies among cancer survivors: SEER Cancer Registries, 1973-2000) from 1973-2000 the mean age at initial diagnosis for NB was 6.2 years while in our study the mean age of patients was 3.3 years (40.5±2.44).

SEER Data also shows that the 5-years survival rate from diagnosis is approximately 83% for infants, 55% for children aged 1-5 years, and 40% for children older than 5 years. The survival rate has increased from 54% for patients diagnosed in 1975-1984 to 68.5% for those diagnosed in 1996-2003 (Ries, 2007; StatBite, 2011).

Overall, our study confirms an increase in diagnosing neuroblastoma in Iran and improved outcomes and survival of NB patients in 32 years of study in this regard the patients' age and their tumor stage were two major prognostic factors for neuroblastoma outcomes.

Improvements in diagnostic imaging modalities, medical and surgical management, and supportive care have contributed to the improved survival rates.

Despite of all improvements in outcomes of NB in Iran, still we have a little lower survival rate than developed countries.

Regarding lower survival rate, making use of better treatment modalities according to risk group must be considered. Developing of the advanced registration system of cancer patients could lead to decreased loss of data, being capable of doing multicenter study, decreased different kinds of bias in the results and better judgment in comparison with the results of developed countries.

Our study evaluated a large scale of medical records during a long period of time and our referral center was an asset because of its important role in diagnosing and management of neuroblastoma so we had more accurate epidemiologic data to analyze the outcomes although this study should be interpreted in light of its potential limitations. One limitation is the lack of using *MYCN* oncogene amplification and DNA ploidy for determining prognosis. Another limitation is that this survey did not use integrated systems for diagnosing high risk patients such as merging clinical findings and genetic status data. Furthermore, this study used only limited treatment options for treating neuroblastoma patients.

Future studies could apply several classification and risk-stratification models to evaluate the severity of neuroblastoma for choosing better treatment options so they can use a wide range of new and efficient therapies with careful follow-up studies to make an accurate

estimation of neuroblastoma outcomes.

Acknowledgements

We wish to thank Farzan Institute for Research and Technology for technical assistance.

References

- Bernstein ML, Leclerc JM, Bunin G, et al (1992). A population-based study of neuroblastoma incidence, survival, and mortality in North America. *J Clin Oncol*, **10**, 323-9.
- Bhatnagar SN, Sarin YK (2012). Neuroblastoma: a review of management and outcome. *Indian J Pediatrics*, **79**, 787-92.
- Brodeur GM (2011). Knowing your ABCCs: novel functions of ABCC transporters. *J Natl Cancer Inst*, **103**, 1207-8.
- Chen QR, Song YK, Wei JS, et al (2008). An integrated cross-platform prognosis study on neuroblastoma patients. *Genomics*, **92**, 195-203.
- Cornero A, Acquaviva M, Fardin P, et al (2012). Design of a multi-signature ensemble classifier predicting neuroblastoma patients' outcome. *BMC Bioinformatics*, **13**, 13.
- David L, Baker MLS, Susan L, et al (2010). Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. *N Engl J Med*, **363**, 1313-23.
- Hara J (2012). Development of treatment strategies for advanced neuroblastoma. *Int J Clinical Oncology*, **17**, 196-203.
- Harder T, Plagemann A, Harder A (2010). Birth weight and risk of neuroblastoma: a meta-analysis. *Int J Epidemiol*, **39**, 746-56.
- Henderson TO, Bhatia S, Pinto N, et al (2011). Racial and ethnic disparities in risk and survival in children with neuroblastoma: a children's oncology group study. *J Clin Oncol*, **29**, 76-82.
- Hiyama E (2008). Neuroblastoma screening in Japan: population-based cohort study and future aspects of screening. *Ann Acad Med Singapore*, **37**, 88-91.
- Lee A (2012). Neuroblastoma: the challenge remains. *Singapore Med J*, **53**, 1-2.
- Ries LAG, Krapcho M, Mariotto A, et al (2007). SEER cancer statistics review, 1975-2004. National Cancer Institute, 2007.
- Schilling FH, Spix C, Berthold F, et al (2002). Neuroblastoma screening at one year of age. *N Engl J Med*, **346**, 1047-53.
- Stat B (2011). Neuroblastoma: five-year survival. *J Natl Cancer Inst*, **103**, 1220.
- Sung KW, Ahn HS, Cho B, et al (2010). Efficacy of tandem high-dose chemotherapy and autologous stem cell rescue in patients over 1 year of age with stage 4 neuroblastoma: the Korean Society of Pediatric Hematology-Oncology experience over 6 years (2000-2005). *J Korean Med Sci*, **25**, 691-7.
- Tan C, Sabai SM, Tin AS, Quah TC, Aung L (2012). Neuroblastoma: experience from National University Health System, Singapore (1987-2008). *Singapore Med J*, **53**, 19-25.
- Vermeulen J, De Preter K, Naranjo A, et al (2009). Outcome Prediction of children with neuroblastoma using a multigene expression signature, a retrospective SIOPEX/COG/GPOH study. *Lancet Oncol*, **10**, 663-71.
- Weinstein JL, Katzenstein HM, Cohn SL (2003). Advances in the diagnosis and treatment of neuroblastoma. *Oncologist*, **8**, 278-92.
- Wiangnon S, Veerakul G, Nuchprayoon I, et al (2011). Childhood cancer incidence and survival 2003-2005, Thailand: study from the Thai pediatric oncology group. *Asian Pac J Cancer Prev*, **12**, 2215-20.