

SURVIVAL OF CHILDREN WITH NEUROBLASTOMA BETWEEN 1975 AND 2010: SINGLE CENTER EXPERIENCE

Thesis

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List of Contents

<i>Title</i>	<i>Page No.</i>
<i>List of Figures</i>	<i>i</i>
<i>List of Tables</i>	<i>iv</i>
<i>List of Abbreviations</i>	<i>vii</i>
<i>Introduction</i>	<i>Error! Bookmark not defined.</i>
<i>Aim of the Work</i>	<i>Error! Bookmark not defined.</i>
<i>Review of Literature</i>	
▪ <i>Introduction of Neuroblastoma</i>	<i>Error! Bookmark not defined.</i>
▪ <i>Risk Stratification of Neuroblastoma</i>	<i>Error! Bookmark not defined.</i>
▪ <i>Treatment of Neuroblastoma</i>	<i>Error! Bookmark not defined.</i>
<i>Patients and Methods</i>	<i>Error! Bookmark not defined.</i>
<i>Results</i>	<i>Error! Bookmark not defined.</i>
<i>Discussion</i>	<i>Error! Bookmark not defined.</i>
<i>Summary</i>	<i>Error! Bookmark not defined.</i>
<i>Conclusion</i>	<i>Error! Bookmark not defined.</i>
<i>Recommendations</i>	<i>Error! Bookmark not defined.</i>
<i>References</i>	<i>Error! Bookmark not defined.</i>
<i>Appendix</i>	<i>Error! Bookmark not defined.</i>
<i>Arabic Summary</i>	

List of Figures

<i>Fig. No.</i>	<i>Title</i>	<i>Page No.</i>
Fig. (1):	Homer Wright rosettes in NB.	Error! Bookmark not defined.
Fig. (2):	Mature ganglion tissue and Schwannian stroma.	Error! Bookmark not defined.
Fig. (3):	Primary distribution of neuroblastomas in children.	Error! Bookmark not defined.
Fig. (4):	Sagittal T1-weighted MR image of the abdomen shows a low-signal-intensity mass arising anterior to the lower lumbar spine.....	Error! Bookmark not defined.
Fig. (5):	MYCN amplification demonstrated by fluorescence in situ hybridisation	Error! Bookmark not defined.
Fig. (6):	Frequency distribution of patients with neuroblastoma in group 1	Error! Bookmark not defined.
Fig. (7):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients in group 1.....	Error! Bookmark not defined.
Fig. (8):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by age group in group 1	Error! Bookmark not defined.
Fig. (9):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by gender in group 1..	Error! Bookmark not defined.
Fig. (10):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Stage in group 1....	Error! Bookmark not defined.
Fig. (11):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by metastasis at presentation in group 1	Error! Bookmark not defined.

List of Figures (Cont...)

<i>Fig. No.</i>	<i>Title</i>	<i>Page No.</i>
Fig. (12):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Hemoglobin level in group 1	Error! Bookmark not defined.
Fig. (13):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Total Leucocytic count (TLC) in group 1	Error! Bookmark not defined.
Fig. (14):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Surgical Interference in group 1	Error! Bookmark not defined.
Fig. (15):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Radiotherapy in group 1	Error! Bookmark not defined.
Fig. (16):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Bone Marrow aspirate in group 1	Error! Bookmark not defined.
Fig. (17):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Bone Marrow biopsy in group 1	Error! Bookmark not defined.
Fig. (18):	Disease free Survival Function from Diagnosis (till Relapse or Death) among Neuroblastoma patients in group 1	Error! Bookmark not defined.
Fig. (19):	Disease free Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by age group in group 1	Error! Bookmark not defined.
Fig. (20):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by gender in group 1.	Error! Bookmark not defined.
Fig. (21):	Event-free Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Stage in group 1	Error! Bookmark not defined.

List of Figures (Cont...)

<i>Fig. No.</i>	<i>Title</i>	<i>Page No.</i>
Fig. (22):	Disease free Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by metastasis at presentation in group 1.....	Error! Bookmark not defined.
Fig. (23):	Disease free Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Hemoglobin level in group 1.....	Error! Bookmark not defined.
Fig. (24):	Disease free Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Total Leucocytic count (TLC) in group 1.....	Error! Bookmark not defined.
Fig. (25):	Disease free Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Surgical Interference in group 1.....	Error! Bookmark not defined.
Fig. (26):	Disease free Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Radiotherapy in group 1.....	Error! Bookmark not defined.
Fig. (27):	Overall Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Bone Marrow aspirate in group 1.....	Error! Bookmark not defined.
Fig. (28):	Disease free Survival Function from Diagnosis (till Death) among Neuroblastoma Patients by Bone Marrow biopsy in group 1.....	Error! Bookmark not defined.

List of Tables

<i>Table No.</i>	<i>Title</i>	<i>Page No.</i>
Table (1):	International Neuroblastoma Pathology Classification.....	Error! Bookmark not defined.
Table (2):	Children's Oncology Group (COG) Neuroblastoma Risk Stratification	Error! Bookmark not defined.
Table (3):	International Neuroblastoma Risk Group (INRG) Consensus Pretreatment Classification schema.	Error! Bookmark not defined.
Table (4):	International Neuroblastoma Risk Group Staging System	Error! Bookmark not defined.
Table (5):	Simplified INRGSS and INSS Staging System.....	Error! Bookmark not defined.
Table (6):	Histopathologic Age-linked Grading System of Shimada ..	Error! Bookmark not defined.
Table (7):	Risk Stratification....	Error! Bookmark not defined.
Table (8):	Low Risk Protocol used in group 1 of neuroblastoma patients	Error! Bookmark not defined.
Table (9):	Intermediate Risk Protocol used in group 1 of neuroblastoma patients	Error! Bookmark not defined.
Table (10):	High Risk Protocol used in group 1 of neuroblastoma patients	Error! Bookmark not defined.
Table (11):	Case distribution by treatment modalities.....	Error! Bookmark not defined.
Table (12):	Frequency of neuroblastoma diagnosis among other cancer patients in group 1.	Error! Bookmark not defined.
Table (13):	Demographic data of the studied patients:.....	Error! Bookmark not defined.

List of Tables (Cont...)

<i>Table No.</i>	<i>Title</i>	<i>Page No.</i>
Table (14):	Distribution of primary site of studied neuroblastoma patients at initial diagnosis.....	Error! Bookmark not defined.
Table (15):	Presenting Symptoms at initial diagnosis of studied neuroblastoma patients.....	Error! Bookmark not defined.
Table (16):	Frequency of metastasis among studied neuroblastoma patients at initial diagnosis.....	Error! Bookmark not defined.
Table (17):	Distribution of local and distant metastasis among studied neuroblastoma patients at diagnosis	Error! Bookmark not defined.
Table (18):	Distribution of staging among studied neuroblastoma patients at diagnosis:	Error! Bookmark not defined.
Table (19):	Risk Stratification of the studied patients in group 1...	Error! Bookmark not defined.
Table (20):	N-MYC status of the studied patients in group 1.	Error! Bookmark not defined.
Table (21):	Initial Hematological Laboratory findings in patients with neuroblastoma.....	Error! Bookmark not defined.
Table (22):	Tumor markers for studied neuroblastoma patients.	Error! Bookmark not defined.
Table (23):	Different lines of treatment received as upfront therapy.....	Error! Bookmark not defined.
Table (24):	Relation between chemotherapy and surgery	Error! Bookmark not defined.
Table (25):	Comparison of cumulative doses of different protocols used.	Error! Bookmark not defined.

List of Tables (Cont...)

<i>Table No.</i>	<i>Title</i>	<i>Page No.</i>
Table (26):	Response to first line of therapy in neuroblastoma patients at end of protocol Error! Bookmark not defined.	
Table (27):	Etiology of death among studied neuroblastoma patients in group 1 Error! Bookmark not defined.	
Table (28):	Overall survival among neuroblastoma patients..... Error! Bookmark not defined.	
Table (29):	Overall survival among neuroblastoma patients according to prognostic factors in group 1 Error! Bookmark not defined.	
Table (30):	Overall survival among neuroblastoma patients according to prognostic factors in group 2 Error! Bookmark not defined.	
Table (31):	Disease free Survival Function among neuroblastoma patients Error! Bookmark not defined.	
Table (32):	Disease free survival rate among neuroblastoma patients according to prognostic factors in group 1 Error! Bookmark not defined.	

List of Abbreviations

Abb.	Full term
ALK	<i>Anaplastic lymphoma kinase</i>
Amp	<i>Amplified</i>
BM	<i>Bone marrow</i>
BMT	<i>Bone marrow transplantation</i>
CA/PE	<i>Cyclophosphamide, adriamycin/Cisplatinum, etoposide</i>
CARBO	<i>Carboplatinum</i>
CAV	<i>Cyclophosphamide, adriamycin, Vincristine</i>
CBC	<i>Complete blood picture</i>
CCSG	<i>Children's Cancer Study Group</i>
CDDP	<i>Cisplatinum</i>
cmm	<i>Cubic millimeter</i>
COG	<i>Children Oncology Group</i>
CPM	<i>Cyclophosphamide</i>
CR	<i>Complete response</i>
CT	<i>Computerized tomography</i>
DOXO	<i>Doxorubicin</i>
EFS	<i>Event-free survival</i>
FDG	<i>Fluro-2-deoxy-D-glucose</i>
FH	<i>Favorable histology</i>
GD₂	<i>Disialoganglioside</i>
gm	<i>Gram</i>
GM-CSF	<i>granulocyte–macrophage colony-stimulating factor</i>
GNB	<i>Ganglioneuroblastoma</i>
Hb	<i>Hemoglobin</i>
HDCBDCA/VP16	<i>High-dose Carboplatinum/ VP16</i>
HDP/VP	<i>High- dose cisplatinum/VP16</i>
HSCT	<i>Hematopoietic stem cell transplantation</i>

HVA	<i>Homovanillic acid</i>
I-131or I-123	<i>radioactive iodine isotopes</i>
IF/VP	<i>Ifosfamide/VP16</i>
INPC	<i>International Neuroblastoma Pathology Classification</i>
INRGSS	<i>International Neuroblastoma Risk Group Staging System</i>
INSS	<i>International Neuroblastoma Staging System</i>
KFT	<i>Kidney function test</i>
LDH	<i>Lactate dehydrogenase</i>
LFT	<i>Liver function test</i>
m²	<i>Meter square</i>
mg	<i>Milligram</i>
MIBG	<i>Metaiodobenzylguanidine</i>
MKI	<i>Mitosis Karyorrhexis Index</i>
mL	<i>Milliliter</i>
MRI	<i>Magnetic resonance imaging</i>
NA	<i>Non-amplified</i>
NB	<i>Neuroblastoma</i>
ng	<i>nanogram</i>
NR	<i>No response</i>
NSE	<i>Neuron specific enolase</i>
OJEC	<i>Vincristine(Oncovin), carboplatin, etoposide,cyclophosphamide</i>
OPEC	<i>Vincristine(Oncovin), cisplatinum, etoposide,cyclophosphamide</i>
OS	<i>Overall survival</i>
PD	<i>Progressive disease</i>
PET	<i>Positron emission tomography</i>
pNTs	<i>Peripheral Neuroblastic Tumors</i>
POG	<i>Pediatric Oncology Group</i>
PR	<i>Partial response</i>
SIOPEN	<i>International Society of Pediatric Oncology Europe Neuroblastoma Group</i>

SRD	<i>shortest region of deletion</i>
99^m TC MDP	<i>99m Technetium methylene-diphosphinate</i>
TLC	<i>Total leucocytic count</i>
TRK-A	<i>Nerve growth factor receptor</i>
U	<i>Unit</i>
UH	<i>Unfavorable histology</i>
US	<i>Ultrasound</i>
VAC	<i>Vincristine, adriamycin, cyclophosphamide</i>
VCR	<i>Vincristine</i>
VGPR	<i>Very good partial response</i>
VMA	<i>Vanillylmandelic acid</i>
VP-16	<i>Etoposide</i>
WBCS	<i>White blood cells</i>

Abstract

Purpose To study outcome of NB patients and compare different protocols used for treatment at Ain Shams University-Children's Hospital Hematology- Oncology unit since 1975 to 2010.

Patients and Methods The study includes data from 221 children diagnosed between 1975 and 2010. Overall survival (OS) was analyzed by clinical and investigational features at presentation and patients are categorized into two groups: group 2 includes patients in the period from 1975 to 2003 and group 1 includes patients in the period from 2004 to 2010.

Results Increased incidence of NB was found from 7.7% to 9.9% of total pediatric malignancies. Significant older mean age at diagnosis (4 ± 2.6 years) in group 2 compared to group 1 (3 ± 3.2 years). Suprarenal gland was the most frequent primary site in both groups (51.2% and 68.4%). Abdominal mass was the most common presenting symptoms among patients and the paraaortic lymph nodes were the most frequent local metastatic site in both groups. Stage 4 represented 69.7% and 61.8% of patients in both groups respectively. five-year OS increased over time from 27.7% to 33.9% ($P=0.002$); it was significantly better for patients age 0 to 12 months at diagnosis, stage 2, patients underwent surgical resection, patients with no BM involvement and for patients receive OPEC/OJEC regimen in group 2 and for patients who had hemoglobin level above 8 gm/dl and TLC above 9000 in group 1. Five-year EFS also increased over time from 23.6% to 35.9% ($P=0.004$).

Conclusion The outcome of children with neuroblastoma remained poor with worst outcome among the high risk group, and although it has progressively improved; yet new strategies are needed to improve survival

INTRODUCTION

Neuroblastoma, a neoplasm of peripheral neural crest origin, is the most common malignant extracranial solid tumor of childhood and accounts for 15% of cancer deaths in children (**Park et al., 2008**). Approximately 650 new cases are diagnosed in the United States annually with peak incidence in early childhood (ages 0–4 years) (**Gustafson and Weiss, 2010**).

The Children Oncology Group (COG) investigated a risk-based neuroblastoma treatment plan that assigned all patients to a low-, intermediate-, or high-risk group based on age, INSS stage, and tumor biology. The relevant biological attributes of the tumor included MYCN status, International Neuroblastoma Pathologic Classification (INPC) histopathology classification, and tumor DNA index (**National Cancer Institute, 2011**).

Low risk patients can frequently be observed without any treatment at all or cured with surgery alone (**National Cancer Institute, 2008**).

The intermediate-risk group received limited chemotherapy, additional surgery in some instances, and avoided radiation therapy (**Baker et al., 2010**).

Patients classified as high risk receive treatment with an aggressive regimen of combination chemotherapy consisting of

very high drug doses, generally termed induction (**Park et al., 2006**). After a response to chemotherapy, resection of the primary tumor should be attempted, followed by myeloablative chemotherapy and stem cell rescue (i.e., bone marrow and/or peripheral blood stem cell transplantation). Radiation to the primary tumor site should be undertaken whether or not a complete excision was obtained. The optimal dose of radiation therapy has not been determined. Radiation of sites of metastatic disease is determined on an individual case basis. After recovery, patients are treated with oral 13-*cis*-retinoic acid for 6 months. Both myeloablative therapy and postchemotherapy retinoic acid improve outcome in patients categorized as high risk (**Matthay et al., 1999; Berthold et al., 2005; Matthay et al., 2009**).