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

Thesis

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By

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# List of Abbreviations

| *Abb.* | *Full term* |
|---|---|
| **ALK** | *Anaplastic lymphoma kinase* |
| **Amp** | *Amplified* |
| **BM** | *Bone marrow* |
| **BMT** | *Bone marrow transplantation* |
| **CA/PE** | *Cyclophosphamide, adriamycin/Cisplatinum, etoposide* |
| **CARBO** | *Carboplatinum* |
| **CAV** | *Cyclophosphamide, adriamycin, Vincristine* |
| **CBC** | *Complete blood picture* |
| **CCSG** | *Children's Cancer Study Group* |
| **CDDP** | *Cisplatinum* |
| **cmm** | *Cubic millimeter* |
| **COG** | *Children Oncology Group* |
| **CPM** | *Cyclophosphamide* |
| **CR** | *Complete response* |
| **CT** | *Computerized tomography* |
| **DOXO** | *Doxorubicin* |
| **EFS** | *Event-free survival* |
| **FDG** | *Fluro-2-deoxy-D-glucose* |
| **FH** | *Favorable histology* |
| **$GD_2$** | *Disialoganglioside* |
| **gm** | *Gram* |
| **GM-CSF** | *granulocyte–macrophage colony-stimulating factor* |
| **GNB** | *Ganglioneuroblastoma* |
| **Hb** | *Hemoglobin* |
| **HDCBDCA/VP16** | *High-dose Carboplatinum/ VP16* |
| **HDP/VP** | *High- dose cisplatinum/VP16* |
| **HSCT** | *Hematopoietic stem cell transplantation* |

| | |
|---|---|
| **HVA** | *Homovanillic acid* |
| **I-131or I-123** | *radioactive iodine isotopes* |
| **IF/VP** | *Ifosfamide/VP16* |
| **INPC** | *International Neuroblastoma Pathology Classification* |
| **INRGSS** | *International Neuroblastoma Risk Group Staging System* |
| **INSS** | *International Neuroblastoma Staging System* |
| **KFT** | *Kidney function test* |
| **LDH** | *Lactate dehydrogenase* |
| **LFT** | *Liver function test* |
| **$m^2$** | *Meter square* |
| **mg** | *Milligram* |
| **MIBG** | *Metaiodobenzylguanidine* |
| **MKI** | *Mitosis Karyorrhexis Index* |
| **mL** | *Milliliter* |
| **MRI** | *Magnetic resonance imaging* |
| **NA** | *Non-amplified* |
| **NB** | *Neuroblastoma* |
| **ng** | *nanogram* |
| **NR** | *No response* |
| **NSE** | *Neuron specific enolase* |
| **OJEC** | *Vincristine(Oncovin), carboplatin, etoposide,cyclophosphamide* |
| **OPEC** | *Vincristine(Oncovin), cisplatinum, etoposide,cyclophosphamide* |
| **OS** | *Overall survival* |
| **PD** | *Progressive disease* |
| **PET** | *Positron emission tomography* |
| **pNTs** | *Peripheral Neuroblastic Tumors* |
| **POG** | *Pediatric Oncology Group* |
| **PR** | *Partial response* |
| **SIOPEN** | *International Society of Pediatric Oncology Europe Neuroblastoma Group* |

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

# 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).**