MANAGEMENT OF PAEDIATRIC NEUROBLASTOMA

Thesis

Submitted for Partial Fulfillment of **PhD.**

In Surgical Oncology

By

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REVIEW OF LITERATURE

Review of Literature

Historical Review and Background:

Virchow first described neuroblastoma in 1864, and, at that time, it was referred to as a glioma. In 1891, **Marchand** histologically linked neuroblastoma to sympathetic ganglia. More substantial evidence of the neural origins of neuroblastoma became apparent in 1914 when **Herxheimer** showed that fibrils of the tumor stained positively with special neural silver stains.

Further characterization of neuroblastoma was reported in 1927, when **Cushing and Wolbach** first described the transformation of malignant neuroblastoma into its benign counterpart, ganglioneuroma. **Everson and Cole** reported that this type of transformation rarely is observed in children older than 6 months. In 1957, **Mason** published a report of a child with neuroblastoma whose urine contained pressor amines. This discovery further contributed to the understanding of neuroblastoma and its possible sympathetic neural origin.

Spontaneous regression of microscopic clusters of neuroblastoma cells, called neuroblastoma in situ, was noted to occur quite commonly.

According to **Beckwith and Perrin in 1963**, regression occurs nearly 40 times more often than the actual number of clinically apparent neuroblastoma cases. **[Homsy YL et al; 1998].**

The term neuroblastoma is commonly used to refer to a spectrum of neuroblastic tumors (including neuroblastomas, ganglioneuroblastomas, and ganglioneuromas) that arise from primitive sympathetic ganglion cells. The neuroectodermal cells that comprise neuroblastic tumors originate from the neural crest during fetal development, and are destined for the adrenal medulla and sympathetic nervous system. Neuroblastoma originates in the adrenal medulla or the para-spinal sites where sympathetic nervous system tissue is present. **[Schwab M et al, 2000]**

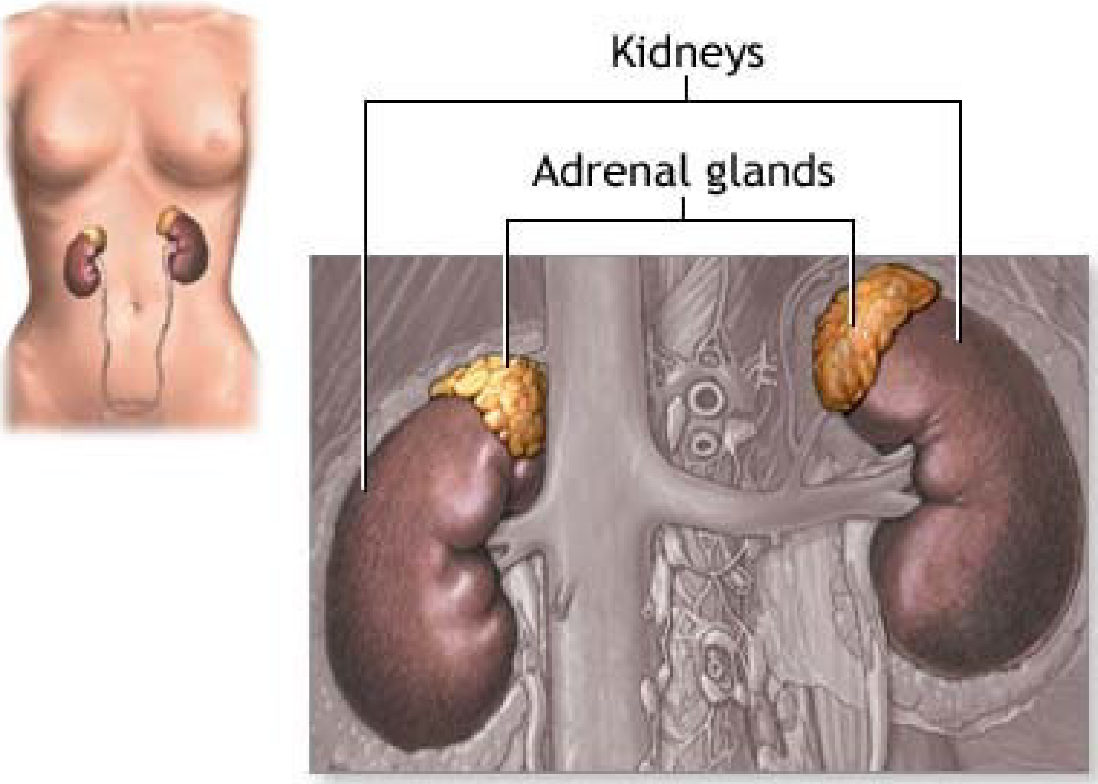


Figure 1: Supra-Renal Glands Anatomy

EPIDEMIOLOGY AND RISK FACTORS:

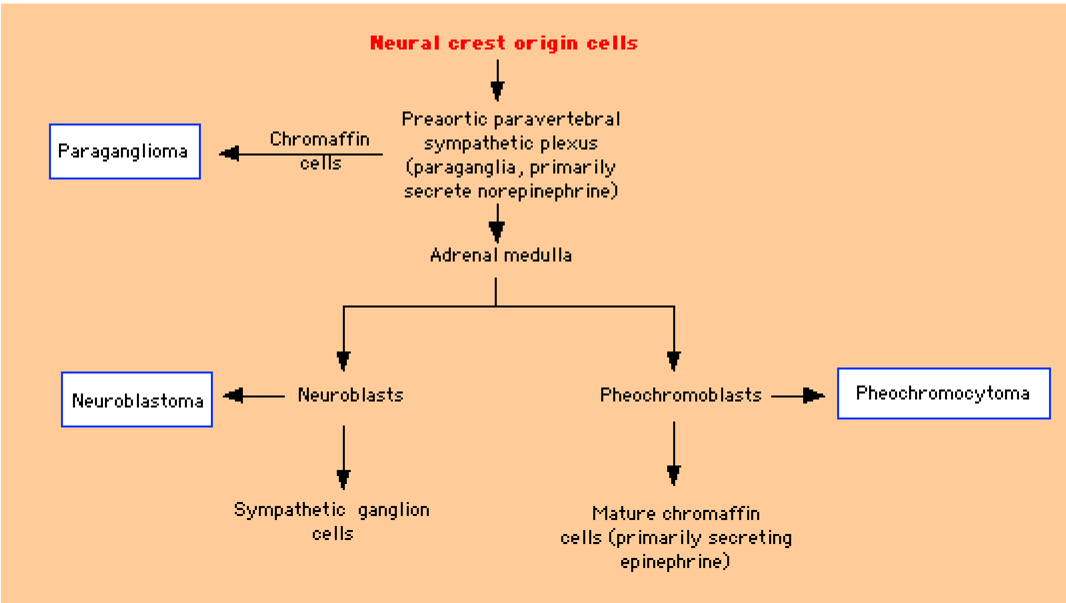
Neuroblastoma is almost exclusively a disease of children. It is the third most common childhood cancer, after leukemia and brain tumors, and is the most common solid extra-cranial tumor in children. More than 600 cases are diagnosed in the United States each year and accounts for approximately 15 percent of all pediatric cancer fatalities; The incidence of neuroblastoma is greater among white than black infants (ratio of 1.7 and 1.9 to 1 for males and females, respectively), but little if any racial difference is apparent among older children [**Goodman MT et al, 1999]**

This predominantly early childhood tumor has two thirds of the cases presenting in children younger than 5 years of age. In rare cases, neuroblastoma can be discovered prenatally by fetal ultrasonography. **[Jennings RW et al, 1993]**

Incidence rates are age-dependent. The median age at diagnosis is 17.3 months, and 40 percent of patients are diagnosed before one year of age **[Brodeur GM et al; 2002]**

They are the most common extra-cranial solid malignant tumor diagnosed during the first two years of life, and the most common cancer among infants younger than 12 months, in whom the incidence rate is almost twice that of leukemia (58 versus 37 per one million infants) **[Gurney J et al,1997]**

By contrast, pheochromocytomas and paragangliomas arise from a different type of cell, the chromaffin cell, that also migrates from the neural crest to the adrenal gland



The common embryogenesis of chromaffin cells and sympathetic ganglion cells from primitive cells of the neural crest Although the adrenal medulla is well developed by 12 weeks of gestation, most of the chromaffin tissue in the fetus is present in scattered extramedullary paraaortic paraganglia, the largest of which are termed the organs of Zuckerkandl. After birth, these paraganglia gradually atrophy, disappearing by 2-3 years of age. The various tumors that can arise from any site along the migratory path of the cells of the autonomic nervous system are in boxes. The chromaffin cells located in the paraganglia predominantly produce norepinephrine while those in the adrenal medulla typically secrete a greater quantity of epinephrine than norepinephrine.

Figure 2: Neuroblastoma Cell Origin

Together, both types of cells make up the adrenal medulla, a component of the sympathetic nervous system. Neuroblastomas, which account for 97 percent of all neuroblastic tumors, are heterogeneous, varying in terms of location, histopathologic appearance, and biologic characteristics **[Goodman MT et al, 1999]**

MOLECULAR BIOLOGY :

In some instances, neuroblastoma may have a genetic basis, but this is unusual **[Maris JM et al; 1997].** Chromosomal abnormalities, principally affecting chromosomes 1 and 17, are often found in tumor cells **[Ninane J et al; 1991]** , but identifiable constitutional aberrations are unusual **[Michalski AJ, 1994].** The most common abnormality on chromosome 1 is a deletion of the distal region of the short arm. This 1p deletion suggests that loss of a tumor suppressor gene (or genes) may be responsible. The location of the deletion breakpoint varies between 1p31 and 1p36 **[White PS et al; 1994].** Loss of heterozygosis in this region is often associated with poor prognostic factors such as advanced stage and N-*myc* amplification [Michon Jet al; 1994]. Recently, chromosome 17 gain has been shown to have adverse prognostic significance [Lastowska M et al; 1997].

Amplification of the N-*myc* oncogene located on chromosome 2 at 2p23-24, is one of the more powerful prognostic indicators in neuroblastoma **[Seeger RC et al; 1985].** It is found in between one-quarter and one-third of patients, more commonly in association with advanced disease. A relationship has been found in cell lines between N-*myc* amplification and sensitivity to treatment **[Livingstone A et al; 1994].**

It is possible that N-*myc* may exert its effect through the regulation of expression of the multidrug resistance-associated protein gene (MRP) **[Norris MD et al; 1998].**

Assessment of DNA ploidy by flow cytometry can also be of significance. Patients under two years of age whose tumors are hyper-diploid or aneuploid appear to have a better outcome than those with diploid characteristics **[Look AT et al; 1991].**

Lack of expression of the cell surface glycoprotein CD44 is also associated with a poor prognosis. CD44 expression seems to correlate with trk-A expression in patients with a favourable outcome **[Kramer K et al; 1997],** but appears to be independent of N-*myc* amplification **[Combaret V et al; 1997].**

CLINICAL PICTURE AND PRESENTATION:

Neuroblastomas are most remarkable for their remarkable broad spectrum of clinical behavior, **[Miller et al; 1954]** which can range from spontaneous regression, to maturation to a benign ganglioneuroma, or aggressive disease with metastatic dissemination leading to death ; Clinical diversity correlates closely with numerous clinical and biological factors (including patient age, tumor stage and histology, and genetic and chromosomal abnormalities), although its molecular basis remains largely unknown. For example, most infants with disseminated disease have a favorable outcome following treatment with chemotherapy and surgery, while the majority of children over the age of one with advanced-stage disease die from progressive disease despite intensive multimodality therapy. **[Brodeur GM et al, 2002]**

Neuroblastoma originates in the adrenal medulla or the paraspinal sites where sympathetic nervous system tissue is present. The most common symptoms are due to a tumor mass or to bone pain from metastases. Proptosis and periorbital ecchymosis are common and arise from retrobulbar metastasis. Extensive bone marrow metastasis may result in pancytopenia. Abdominal distention with respiratory compromise due to massive liver metastases occurs in infants. Because they originate in paraspinal ganglia, neuroblastomas may invade through neural foramina and compress the spinal cord, causing paralysis. Fever, anemia, and hypertension are found occasionally. Multifocal neuroblastoma occurs rarely, usually in infants, and generally has a good prognosis. **[Hiyama E, et al , 2000]**

Figure 3: Neuroblastoma in Coronal Section

Rarely, children may have severe watery diarrhea due to the secretion of vasoactive intestinal peptide by the tumor and rarely present with paraneoplastic neurologic findings including cerebellar ataxia or opsoclonus/myoclonus**. [Azizkhan RG et al, 1993]**

The opsoclonus / myoclonus syndrome appears to be caused by an immunologic mechanism that is not yet fully defined. **[Connolly AM et al; 1997]** Patients who present with this syndrome often have low-grade disease with good survival, but tumor-related deaths have been reported. Opsoclonus/myoclonus has also been associated with pervasive and permanent neurologic disorders, including psychomotor retardation. Neurologic dysfunction may be the presenting symptom or may first occur after removal of the tumor. Some patients may clinically respond to removal of the neuroblastoma, but improvement may be slow and partial; **[Rudnick E et al; 2001]**

Unlike other neuroblastomas, the primary tumor usually is diffusely infiltrated with lymphocytes. **[Cooper R et al; 2001]**

Patients who present with this syndrome often have neuroblastomas with favorable biologic features and are likely to survive, though tumor-related deaths have been reported. Neurologic dysfunction is most often a presenting symptom but may arise after removal of the tumor. Opsoclonus/myoclonus is frequently associated with pervasive and permanent neurologic and cognitive deficits, including psychomotor retardation. **[Rudnick E et al; 2001 & Pranzatelli MR 1992 & Mitchell WG;2002]**

Approximately 70% of patients with neuroblastoma have metastatic disease at diagnosis. The prognosis for patients with neuroblastoma is related to their age at diagnosis, clinical stage of disease, and, in patients older than 1 year, regional lymph node involvement. Other conventional prognostic variables include the site of the primary tumor and tumor histology **[Adams GA al;1993 & Evans AE et al1976. & Hayes FA et al 1983 & Cotterill SJ et al; 2000]**

Some NB tumors undergo spontaneous regression or differentiate into benign ganglioneuromas **[Haas D et al; 1988].** Most children with stages 1 and 2 disease **[Brodeur GM et al; 1988]** can be cured with surgery alone **[Alvarado CS et al; 2000 and Perez CA et al; 2000]**.

In addition, most infants with disseminated disease have favorable outcomes following treatment with chemotherapy and surgery **[Schmidt**

ML et al; 2000] . In contrast, the majority of children older than 1 year of age with advanced-stage NB die from progressive disease despite intensive multimodality therapy **[Matthay KK et al; 1999].** This clinical diversity correlates closely with numerous clinical and biological factors, including tumor stage, patient age, tumor histology, and genetic abnormalities **[Shimada H et al; 1999].** However, the molecular basis underlying the variability in tumor growth, clinical behavior, and responsiveness to therapy remains largely unknown.

Because outcome is significantly better for patients with localized disease and younger age, many investigators speculated that screening infants for NB would lead to reduced mortality. Pioneering studies performed in Japan in the 1980s demonstrated that NB could be detected by screening for urinary catecholamines at 6 months of age and suggested that preclinical detection led to improved survival **[Nishi M et al; 1992].**

However, population-based approaches for screening were not used in these studies and no concurrent control groups were evaluated. Subsequent trials demonstrated that the incidence of diagnosis of NB was increased in Japan and that virtually all tumors detected by screening had favorable biologic features **[Yamamoto K et al; 1995 & Kaneko Y et al; 1990].**

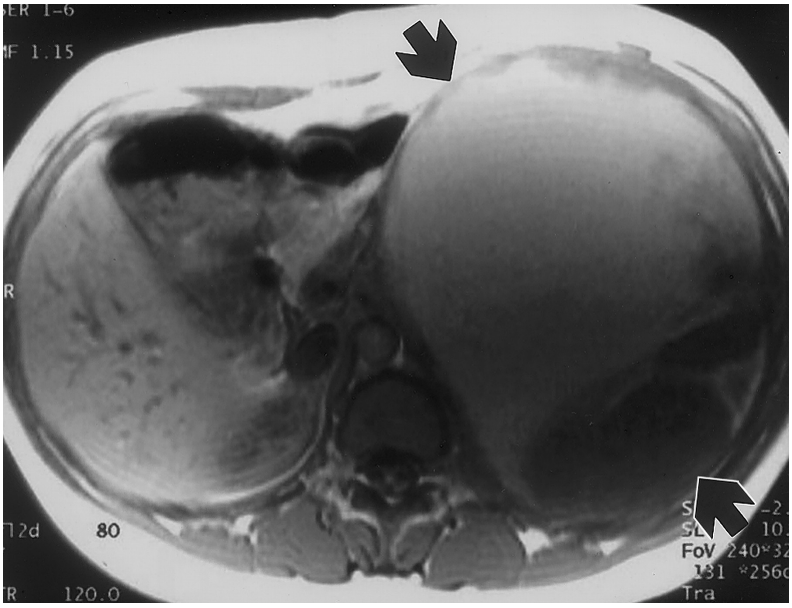


Figure 4: Neuroblastoma appearance / CT View

These observations suggest that many of the tumors detected by screening were likely to undergo spontaneous regression and would never have been diagnosed clinically. To directly answer the question of whether routine screening for NB would result in lower mortality, two prospective population-based, controlled trials were recently conducted in Germany and North America **[Woods WG et al, 2002 & Schilling FH et al; 2002]**.

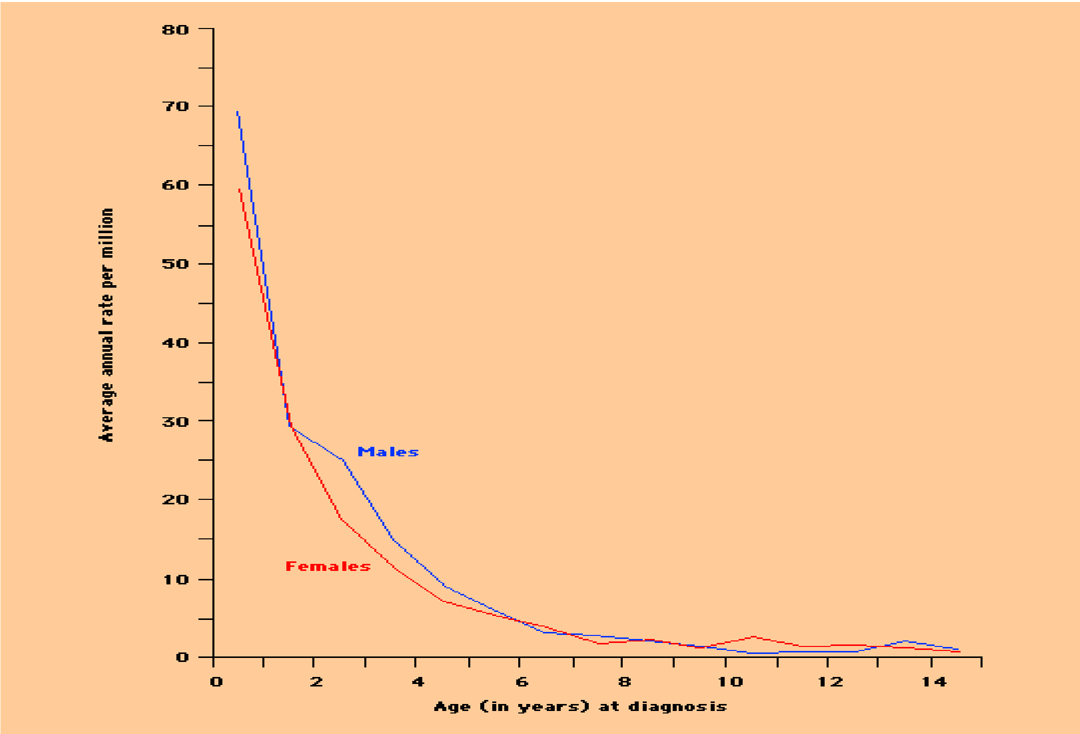
The studies demonstrated that screening infants for NB at 3 weeks, 6 months, or 1 year did not reduce mortality due to this disease. Furthermore, similar to the previous reports from Japan, almost all tumors detected by screening had favorable biologic features. Thus, there appears to be no role for screening infants for NB.

There are approximately 600 new cases of NB in the U.S. each year, with a prevalence of approximately one case per 7,000 births **[Gurney JG et al; 1997]**.

This tumor is derived from neural crest cells, and it most commonly arises in the adrenal medulla or Para-spinal sympathetic ganglia. The etiology of NB remains obscure. To date, no environmental influences or parental exposures that significantly impact on disease occurrences have been identified **[Ries LAG et al; 1999]**.

Neuroblastoma usually occurs sporadically; however, in 1%–2% of cases there is a family history **[Maris JM et al; 1996]**.

Interestingly, considerable biological and clinical heterogeneity is also observed in the familial cases **[Maris JM et al; 2000]**. While the occurrence of familial NB suggests the presence of a unifying underlying genetic abnormality, studies to date have failed to identify a specific tumor suppressor gene responsible for NB tumorigenesis **[Maris JM, et al; 1997 & 2000]**



Age-specific neuroblastoma incidence rates by sex, all races, SEER 1976-84 and 1986-94 From Goodman, MT, Gurney, JG, Smith, MA, Olshan, AF. Sympathetic nervous system tumors. In: Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995, Ries, LA, Smith, MA, Gurney, JG, et al, National Cancer Institute, SEER Program. NIH Pub No. 99-4649; Bethesda, MD 1999. p. 66-67.

Figure 5: Age-Specific Neuroblastoma rates

DIAGNOSIS:

Cancer in children is rare. A team approach that incorporates the skills of the local physician, pediatric surgeon, radiation oncologists, pediatric medical oncologists/hematologists, rehabilitation specialists, and social workers is imperative to ensure that patients receive treatment, supportive care, and rehabilitation that will achieve optimal survival and quality of life. For advances to be made in treating these patients, therapy should be delivered in the context of a clinical trial at a major medical center that has expertise in treating children. Only through entry of all eligible children into appropriate, well-designed clinical trials will progress be made against these diseases. Guidelines for pediatric cancer centers and their role in the treatment of pediatric patients with cancer have been outlined by the American Academy of Pediatrics. **[Sanders J et al; 1997]**

The gold standard for the diagnosis of neuroblastoma is examination of tumor tissue by histopathology and immunohistochemistry. However, as initial surgery is not indicated in patients with advanced disease who require systemic therapy, International Neuroblastoma Diagnostic Criteria (INDC) have been established which permit a reliable diagnosis to be made without a biopsy **[Brodeur GM et al; 1988]**.

A diagnosis of neuroblastoma is established if bone marrow contains unequivocal tumor cells (e.g., syncytia or clusters of cells positive on immunocytology) and urine contains increased urinary catecholamine metabolites. This may be defined by urinary VMA and/or HVA levels greater than three standard deviations above the mean per milligram creatinine for the age of the patient. The age is important here, as normal levels are highest in neonates and gradually diminish over the first two years of life. Both the VMA and HVA levels should be measured. Normalization per milligram of creatinine makes a timed collection unnecessary and avoids potential false negatives due to dilute urine. Although histopathological confirmation may not be essential in these circumstances, it is still desirable to obtain tissue for biological studies. This is because biological information is not merely of prognostic relevance **[Castleberry RP et al; 1997]**, but may, more importantly, be used to guide treatment. In those patients for whom the diagnosis of metastatic neuroblastoma is certain before biopsy on the basis of bone marrow examination and urinary catecholamine metabolite studies, tumor tissue can be obtained for biological studies, including histopathological assessment, at the time of insertion of an indwelling venous access catheter. This is a reasonable way of maximizing valuable prognostic information while keeping the number of anesthetic sessions to a minimum. **[Matthay KK et al; 1998]**

The diagnosis of neuroblastoma requires the involvement of pathologists who are familiar with childhood tumors. Some neuroblastomas cannot be differentiated from other small round-blue cell tumors of childhood, such as lymphomas, primitive neuroectodermal tumor, and rhabdomyosarcoma, by conventional light microscopy. Evidence for sympathetic neuronal differentiation may be demonstrated by immunohistochemistry, electron microscopy, or by finding elevated levels of serum catecholamines (e.g., dopamine and nor-epinephrine) or urine catecholamine metabolites such as Vanillyl-Mandelic acid (VMA) or Homovanillic acid (HVA).

The minimum criterion for a diagnosis of neuroblastoma that has been established by international agreement is based on one of the following:

(1) An unequivocal pathologic diagnosis made from tumor tissue by light microscopy (with or without immunohistology, electron microscopy, or increased levels of serum catecholamines or urinary catecholamine metabolites); or

(2) The combination of bone marrow aspirate or trephine biopsy containing unequivocal tumor cells (e.g., syncytia or immunocytologically-positive clumps of cells) and increased levels of serum catecholamines or urinary catecholamine metabolites as described above**. [Brodeur GM et al; 1993]**

CLASSIFICATION AND CELLULAR INFORMATION:

CELLULAR CLASSIFICATION:

One clinicopathologic staging system involves evaluation of tumor specimens for the amount of stromal development, the degree of neuroblastic maturation, and the mitosis-karyorrhexis index of the neuroblastic cells. **[Chatten J et al; 1988]** Favorable and unfavorable prognoses are defined on the bases of these histological parameters and on patient age. The prognostic significance of this classification system, and of related systems using similar criteria, has been confirmed in several studies. **[Joshi VV et al; 1991 & Joshi VV et al; 1992]**

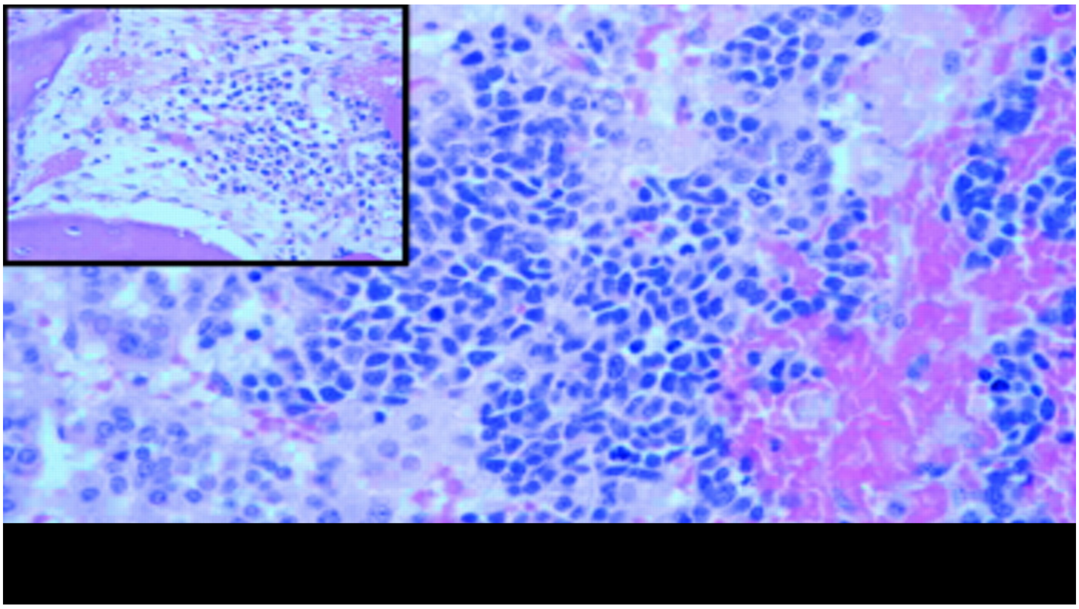


Figure 6: Magnified Neuroblastoma Cells

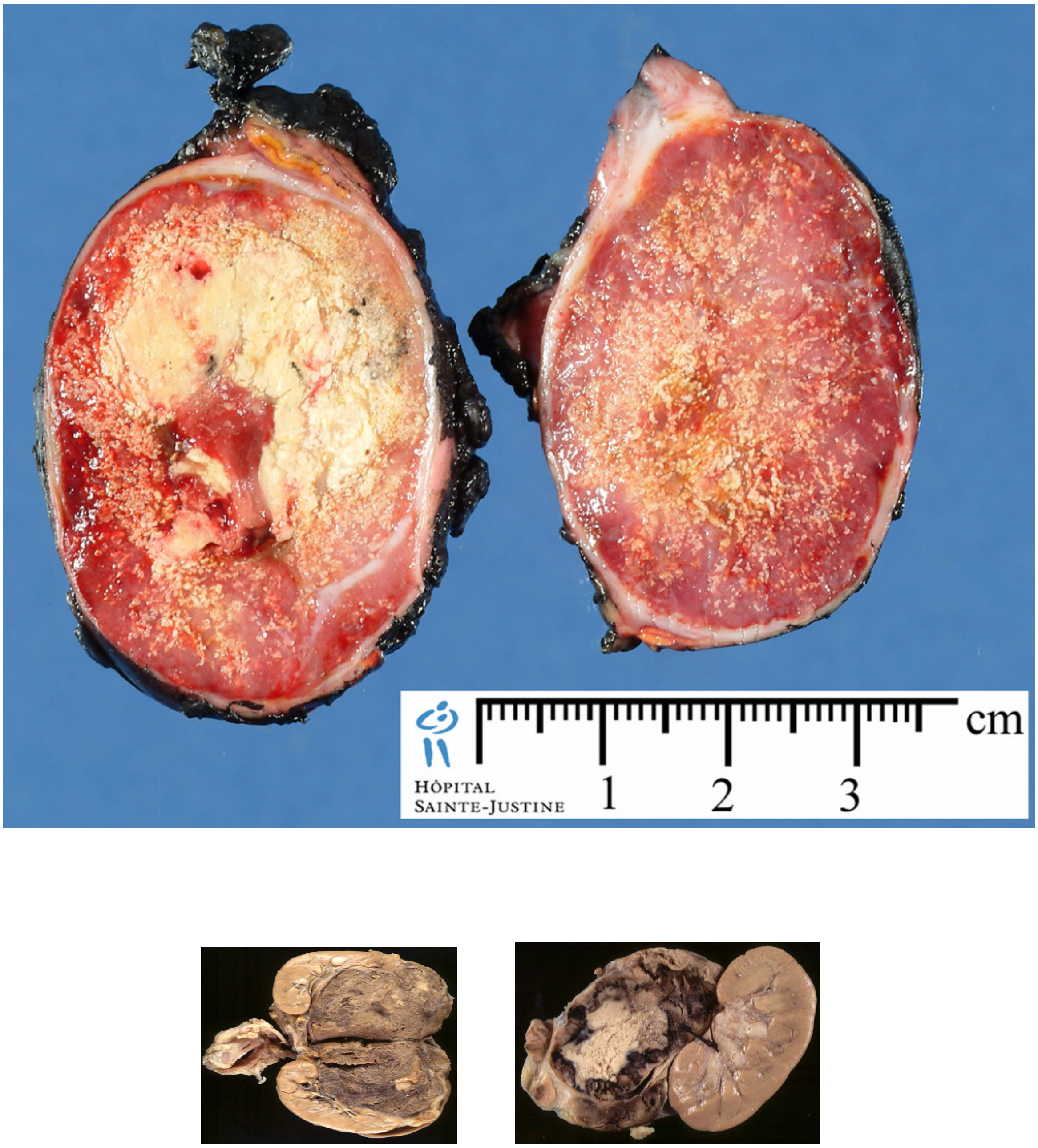


Figure 7: Cut Sections in Neuroblastoma

STAGING SYSTEMS:

There are several staging systems currently used for neuroblastoma. The system used in the treatment section of this document (localized, regional, disseminated, and special) is based on the Children Cancer Group (CCG), St. Jude, and the Pediatric Oncology Group (POG) staging systems. An International Neuroblastoma Staging System (INSS) has been proposed, which combines elements of the POG and CCG staging systems. Current protocols use the POG or CCG staging system to assign treatment, but also specify that the INSS stage be defined for all patients. If the INSS is validated in current studies, it will replace previous systems in future protocols. Each of these staging systems is described below.

Children Cancer Group (CCG) staging system

The CCG uses a clinical staging system based on physical examination, radiographic evaluation, and bone marrow examination. Follow-up of patients staged according to the CCG system has demonstrated the prognostic significance of this staging system. [**Evans AE et al; 1990]**

Stage I: tumor confined to the organ or structure of origin.

Stage II: tumor extending in continuity beyond the organ or structure of origin but not crossing the midline. Regional lymph nodes on the homolateral side may be involved.

Stage III: tumor invasively extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally.

Stage IV: remote disease involving skeleton, parenchymatous organs, soft tissues, distant lymph node groups, etc. (See stage IVS.)

Stage IVS: patients who would otherwise be stage I or II but have remote disease confined to one or more of the following sites only: liver, skin, or bone marrow (without radiographic evidence of bone metastases on complete skeletal survey). **[Hayes FA et al; 1983]**

Pediatric Oncology Group (POG) staging system

Investigators at St. Jude Children's Research Hospital developed a clinical, surgical, and pathologic staging system that places major emphasis on the presence of regional lymph node metastases. **[Hayes FA et al; 1983]** From this system evolved the Pediatric Oncology Group (POG) staging system outlined below. The prognostic significance of the POG staging system has been documented in several studies. **[[Castleberry RP et al; 1991 & Kun LE et al; 1991]**

The major differences between the CCG and POG systems are in the staging of patients with involved ipsilateral lymph nodes (stages I and II in CCG, stage C in POG), and in patients with tumors that cross the midline and who have negative nodes (POG stage A or B, CCG stage III).

Stage A: complete gross resection of the primary tumor, with or without microscopic residual disease. Intra-cavitary lymph nodes, not adherent to but removed with the primary, must be histologically free of tumor. Nodes adherent to the surface of or within the primary tumor may be positive without upstaging the patient to stage C. If the primary is in the abdomen or pelvis, the liver must be histologically free of tumor.

Stage B: incomplete gross resection of the primary tumor. Nodes and liver must be histologically free of tumor.

Stage C: complete or incomplete gross resection of the primary tumor. Intracavitary nodes not adherent to the primary must be histologically positive for tumor. Liver must be histologically free of tumor.

Stage D: any dissemination of disease beyond intracavitary nodes (i.e., Extra-cavitary nodes, liver, skin, bone marrow, bone, etc.).

Stage DS: infants less than 1 year of age with stage IVS disease (see CCG staging system).

International Neuroblastoma Staging System (INSS)

The INSS combines certain features of both the POG and CCG systems and is under evaluation by both groups. **[Brodeur GM et al; 1993 & Brodeur GM et al;1998]** It has been shown to identify distinct prognostic groups. **[Castleberry RP et al; 1997]**

Stage 1: localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).

Stage 2A: localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.

Stage 2B: localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.

Stage 3: unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contra-lateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement. The midline is defined as the vertebral column.

Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.

Stage 4: any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S).

Stage 4S: localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants less than 1 year of age).

Marrow involvement should be minimal (i.e., <10% of total nucleated cells identified as malignant by bone biopsy or by bone marrow aspirate). More extensive bone marrow involvement would be considered to be stage IV disease. The results of the meta- iodobenzylguandine (MIBG) scan (if performed) should be negative for disease in the bone marrow.

Regardless of the staging system used, a thorough evaluation for metastatic disease is important. The following investigations are recommended before therapy is initiated. **[Brodeur GM et al; 1993]**

1) Bone marrow should be assessed by bilateral posterior iliac crest marrow aspirates and trephine (core) bone marrow biopsies to exclude

bone marrow involvement. To be considered adequate, core biopsy specimens must contain at least 1 cm of marrow (excluding cartilage).

2) Bone should be assessed by MIBG scan (applicable to all sites of disease) and by technetium 99 scan if the results of the MIBG scan are negative or unavailable. Plain radiographs of positive lesions are recommended.

3) Palpable lymph nodes should be clinically examined and histologically confirmed. Nonpalpable lymph nodes should be assessed by computerized tomography (CT) scan with three-dimensional (3D) measurements.

4) The abdomen and liver should be assessed by CT scan and/or magnetic resonance imaging (MRI). Ultrasound is considered suboptimal for accurate 3D measurements.

5) The chest should be examined by anteroposterior and lateral chest radiography. CT scans and/or MRI are necessary if the results are positive or if abdominal disease extends into the chest.

TREATMENT:

Some patients may clinically respond to removal of the neuroblastoma, but improvement may be slow and partial; symptomatic treatment is often necessary. Adrenocorticotropic hormone (ACTH) treatment is thought to be effective, but some patients do not respond to ACTH. **[Connolly AM et al; 1997 & Pranzatelli MR;1992]**

Various drugs, plasmapheresis, and intravenous gamma-globulin have been reported to be effective in selected cases. **[Pranzatelli MR;1992& Russo C et al;1997]**

The long-term neurologic outcome may be superior in patients treated with chemotherapy, possibly by means of its immunosuppressive effects. **[Russo C et al;1997]**

A] LOCALIZED RESECTABLE NEUROBLASTOMA :

Localized disease includes those with INSS stage 1 disease, Childrens Cancer Group (CCG) stage I, II, or III tumors that have been resected and have negative nodes, Pediatric Oncology Group (POG) stage A disease, and favorable biologic features.**[Matthay KK et al; 1998]** These children -of any age- have a cure rate of greater than 90%. **[Hayes FA et al, 1983, EvansAR;1984]**

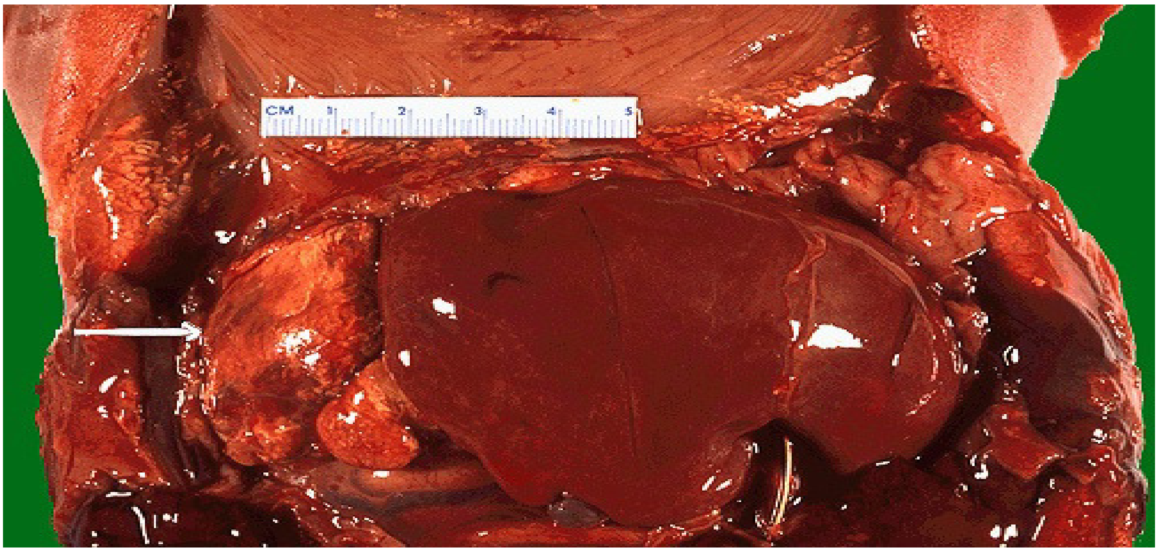


Figure 8: Intraoperative view / Neuroblastoma in 3 Yrs Old Patient

Treatment options:

Patients with stage 1 and stage 2A disease have localized tumors which are usually suitable for curative surgery. Adjuvant treatment with radiotherapy or chemotherapy is not indicated, even if there is microscopic residual disease **[Ninane J et al; 1982 & Hayes F et al; 1983]**. Unfavorable histology and diploidy predict for local recurrence **[Cheung N-KV et al; 1997]** . Careful follow-up is therefore necessary, as local recurrence or distant metastasis may rarely occur and require salvage treatment.

Complete gross resection produces disease-free survivals that are indistinguishable from those obtained with operation plus adjuvant chemotherapy or operation plus radiation therapy. [**Hayes FA et al, 1983 & Evans AR 1984 & Nitschke R].** Microscopic residual disease in the tumor bed does not adversely affect survival and does not indicate the need for therapy beyond operation. However, in light of other information relating to prognosis, including patient age, the Shimada grade, ferritin, NSE, LDH, and N-myc amplification, further therapy may be indicated.

B] LOCALIZED UNRESECTABLE NEUROBLASTOMA:

Localized unresectable disease includes those with INSS stage 2 disease, Childrens Cancer Group (CCG) stages I, II, or III tumors that are incompletely resected and have negative nodes, and Pediatric Oncology Group (POG) stage B disease. In these patients, there are no metastases to regional lymph nodes, but the tumor is not completely resected. The probability of long-term survival is 75%-90% depending on age of patient, favorable biologic features, and therapy delivered. **[Hayes FA et al, 1983 & Ninane J et al, 1982& Evans AE; 1976 & Matthay KK 1998]**

Treatment options:

Treatment of patients with lymph node involvement; that is, stage 2B and some stage 3 cases is again principally surgical. The need for adjuvant treatment depends on age. In infants younger than six months, chemotherapy is controversial. In older children, chemotherapy is definitely warranted, using a schedule such as "OPEC," which comprises vincristine, cisplatin, etoposide and cyclophosphamide **[Shafford EA et al; 1984]**. In these patients, it is often preferable to use chemotherapy as the initial treatment with the aim of reducing the tumor bulk, making complete removal more likely and the operation safer. Data from the

Pediatric Oncology Group (POG) in patients with stage 2B and 3 disease have shown that while complete resection is not associated with a significantly better event-free survival than incomplete resection, patients with favorable Shimada histology have a significantly better event-free survival rate at two years—92%—compared with only 58% for unfavorable cases **[Strother D et al; 1997].**

Irradiation of the tumor bed to eradicate residual disease is controversial. In a retrospective review of patients with Children's Cancer Study Group (CCSG) Stage II disease, no significant benefit was seen in irradiated patients **[Matthay KK et al; 1989].** A POG randomized trial was designed to evaluate the place of radiotherapy in addition to chemotherapy in patients over one year of age found to have nodal disease at resection of the primary tumor **[Castleberry RP et al; 1991]**.

In irradiated patients, significantly improved local control and survival rates were seen. The chemotherapy schedule used in this study was less intensive than that now considered standard, and it remains possible that results with more intensive chemotherapy might be as good as those in the combined modality arm of the trial. As patients with biologically favorable tumors generally have a good prognosis **[Strother D et al; 1997]**, even in the presence of residual disease, it is reasonable not to give radiotherapy to patients with biologically favorable stage 2B and 3 tumors, with or without residual disease after chemotherapy and surgery. Despite the adverse effects in young children, radiotherapy should be considered in the management of patients with biologically unfavorable stage 2B and 3 tumors with residual disease **[Matthay KK,et al; 1998].**

The initial management generally consists of subtotal resection or biopsy followed by chemotherapy.[**Evans AE; 1976 Nitschke R et al, 1991 & McGuire WA et al; 1985, Haase GM et al; 1989 & Garaventa A et al; 1993**] Second-look operation is used subsequently to remove residual tumor, and radiation therapy may be given to patients with residual disease following second-look operation. The chemotherapeutic agents most commonly used include cyclophosphamide and doxorubicin, with cisplatin and either teniposide or etoposide reserved for more resistant tumors. Short-term therapy for 4-6 months is usually adequate. However, in light of other information relating to prognosis, including patient age, the Shimada grade, ferritin, NSE, LDH, and N-myc amplification, either more or less therapy may be indicated.

C] REGIONAL NEUROBLASTOMA:

Regional neuroblastoma includes those with INSS stage 3 disease, Childrens Cancer Group (CCG) stage II or stage III tumors that have positive nodes, and Pediatric Oncology Group (POG) stage C disease. Infants younger than 1 year of age have a greater than 80% chance of cure while older children have a cure rate of 50%-70% with current, relatively intensive therapy**. [Castleberry RP et al, 1991 & Bowman LC et al; 1997 & Castleberry RP et al; 1992 & West DC et al, 1993]** In those cases of abdominal neuroblastoma thought to involve the kidney, nephrectomy should not be undertaken before a trial of chemotherapy has been given**. [Shamberger RC et al; 1998]**

Treatment options for patients younger than 1 year of age:

1. Surgical resection of the primary tumor may be possible at diagnosis or as a delayed procedure. Complete resection of the primary tumor, either as a primary or secondary procedure, may improve outcome**. [Haase GM et al; 1989 & DeCou JM et al; 1995]** Select groups of patients whose tumors have favorable biologic features may not require treatment other than surgery. **[Kushner BH et al, 1996]**

2. Chemotherapy with cyclophosphamide and doxorubicin, cisplatin with teniposide or etoposide or vincristine with cisplatin and teniposide or etoposide for more resistant tumors. [**Bowman LC et al; 1997** & **Castleberry RP et al, 199**2]

Treatment options for patients older than 1 year of age:

1. Surgical resection of the primary tumor may be possible at diagnosis or following tumor reduction with chemotherapy +/- radiation therapy. Complete resection of the primary tumor, either prior to chemotherapy or as a secondary procedure, may improve outcome. [**Haase GM et al; 1989**] Select groups of patients whose tumors have favorable biologic features may not require treatment other than surgery **[Kushner BH et al, 1996]**

2. Aggressive chemotherapy using combinations of cyclophosphamide, doxorubicin, cisplatin, and teniposide or etoposide.[**Castleberry RP et al, 1991 & Bowman LC et al; 1997**]

3. Radiation therapy to nodal drainage areas may improve outcome. [**Castleberry RP et al, 1991**]

Under clinical evaluation for patients older than 1 year of age and/or patients who are predicted to have a poor prognosis:

1. High-dose chemotherapy, radiation therapy, and bone marrow reconstitution for patients with poor prognostic characteristics (e.g., N-myc amplification). **[Hartmann O et al; 1998 & Matthay KK et al 1994; Evans AE et al; 1994]**

2. Aggressive chemotherapy and radiation therapy given simultaneously.

D] DISSEMINATED NEUROBLASTOMA:

Disseminated disease includes those with Childrens Cancer Group (CCG) stage IV and Pediatric Oncology Group (POG) stage D disease. Differentiating patients with stage IVS ("special") neuroblastoma from other disseminated disease patients is important; stage IVS patients should be treated as described in the treatment section on stage IVS neuroblastoma. Survival of patients with disseminated disease is strongly dependent on age. Children younger than 1 year of age at diagnosis have a good chance of long-term survival (5-year disease-free survival rate of 50%-80%), **[Paul SR et al; 1991 & Bowman LC et al; 1991]** with outcome particularly dependent on tumor cell ploidy (hyperploidy confers a favorable prognosis while diploidy predicts early treatment failure). **[Look AT et al;1991 & Bowman LC et al; 1991]**

For children older than 1 year of age, long-term survival ranges from 10%-40%. A randomized study was performed comparing high-dose therapy with purged autologous bone marrow transplantation versus three cycles of intensive consolidation chemotherapy. The 3 year event-free survival was significantly better in the autologous bone marrow transplantation arm (34%) compared to the consolidation chemotherapy arm (18%). **[Matthay KK et al; 1998]** In addition, patients on this study were subsequently randomized to stop therapy or to receive 6 months of 13 cis- retinoic acid.[**Reynolds CP et al; 1998]** The use of 13 cis-retinoic acid can induce differentiation and growth of neuroblastoma in vitro. Overall, the 3 year event-free survival from the time of the second randomization was 47% for patients receiving 13 cis-retinoic acid and 25% for patients randomized to receive no further therapy. For patients randomized to receive 13 cis-retinoic acid, an apparent advantage in 3 year event-free survival was seen for stage IV patients (40% vs 18%), high-risk stage III patients (77% vs 49%), patients randomized to receive consolidation chemotherapy alone (32% vs 16%), patients randomized to receive autologous bone marrow transplantation (55% vs 39%), and patients with MYCN genomic amplification (39% vs 13%). Based on these results, future clinical trials will build upon autologous stem cell transplantation and cis-retinoic acid for high-riskneuroblastoma**. [Matthay KK et al; 1998 & Reynolds CP et al; 1998]**

The potential benefit of aggressive surgical approaches to achieve complete tumor resection, either at the time of diagnosis or following chemotherapy, has not been unequivocally demonstrated. Two studies reported that complete resection of the primary tumor at diagnosis improved survival; however, the outcome in these patients may be more dependent on the biology of the tumor than on the extent of surgical resection.**[Haase GM et al, 1991 & DeCou JM et al, 1998 & Shorter NA et al; 1998**] Consideration should also be given to enrollment of poor-prognosis patients older than 1 year of age in a clinical trial that incorporates new agent testing prior to initiating standard therapy. These studies appear to have no deleterious effect on outcome and have identified ifosfamide, iproplatin, and carboplatin as effective agents in newly diagnosed neuroblastoma**. [Shorter NA et al; 1995]**

Treatment options:

Patients with advanced disease, that is, those with stage 4 or inoperable stage 3 disease should receive initial chemotherapy with "OPEC" or a similar schedule. If chemotherapy has rendered the stage 3 tumor operable, it should be removed. In stage 4 patients, surgery to remove residual primary tumor should also be considered if there has been a complete remission at metastatic sites.

Dose intensification strategies, designed to achieve a greater degree of cytoreduction and to circumvent the development of resistant clones by using a larger number of non-cross-resistant drugs in higher doses over a shorter period, are feasible but have not yet proved significantly superior to OPEC **[Bernard JL et al; 1987]**. The European Neuroblastoma Study Group (ENSG) trial 5 compares a standard, three-weekly chemotherapy regimen of carboplatin, cisplatin, vincristine, cyclophosphamide, and etoposide with a more dose-intensive regimen combining the same total doses of the same drugs given fortnightly regardless of hematological recovery. So far, this trial, which is due to close later in 1998, has recruited more than 200 randomized patients with stage 4 disease over one year of age. The results of this trial are awaited with interest. **[Pinkerton CR et al; 1990]**

1. Intensive conventional chemotherapy, using combinations of cyclophosphamide, doxorubicin, cisplatin, teniposide or etoposide, and vincristine. **[Bowman LC et al; 1991 & Hartmann O et al; 1988 & Kushner BH et al; 1994 & Pinkerton CR et al; 1999]** Surgery and radiation therapy may be used with chemotherapy, depending on the clinical presentation and course. Post- chemotherapy treatment includes 13 cis-retinoic acid. **[Matthay KK et al; 1998 & Reynolds CP et al; 1998]**

2. Clinical trials evaluating myeloablative chemotherapy and radiation therapy followed by stem cell reconstitution and 13 cis-retinoic acid. **[Reynolds CP et al; 1998, Philip T et al; 1991 & Matthay KK et al; 1994 & Pole JG et al, 1991]**

3. The use of prolonged isotretinoin treatment following intensive chemotherapy. Neuroblastoma cells in vitro often respond to retinoic acid by differentiation and/or growth inhibition, and several patients treated with retinoic acid have shown prolonged decreases in bone marrow tumor involvement. **[Reynolds CP et al; 1998, Baker D et al; 1997]** The potential benefit of maintenance therapy with isotretinoin is being tested at CCG institutions, where patients were randomly allocated following their intensive chemotherapy to receive isotretinoin for 6 months or to receive no further therapy.

STAGE IV-S NEUROBLASTOMA:

Stage IV-S "special" neuroblastoma typically presents in very young infants and has a 2-year survival rate greater than 90%. **[Nickerson HJ et al; 1985]** The International Neuroblastoma Staging System (INSS) has been revised to include, in stage 4S only, infants younger than 1 year of age at diagnosis. Bone marrow disease must also be very limited to qualify for stage 4S (see the Stage Information section above). **[Brodeur GM et al; 1993]** Stage IVS neuroblastoma has a higher rate of spontaneous regression than other neuroblastomas, often making chemotherapy unnecessary. In specific circumstances, mild chemotherapy may be indicated.

Treatment options:

The treatment of children with stage IVS disease is controversial. **[McWilliams et al; 1986 & Guglielmi M et al; 1996]** Children with this special pattern of neuroblastoma may not require therapy, although the development of complications, such as functional compromise from massive hepatomegaly, and is an indication for intervention, especially in infants younger than 2 months of age. **[Guglielmi M et al; 1996 & Hsu LL et al; 1996]**

Because of the unpredictable clinical course of this entity, these children should be entered into cooperative group studies and observed by a multidisciplinary team of physicians who are prepared to individualize therapy according to the requirements of each case.

Infants with stage 4S disease have, in general, a good prognosis, and treatment is not always necessary, as the tumor may regress spontaneously as a result of programmed cell death. If the disease is not causing distressing or life-threatening symptoms, it is possible to follow a policy of observation in the hope of spontaneous regression due to apoptosis. Sometimes limited, nonintensive chemotherapy is called for if there are major symptoms such as massive hepatomegaly causing respiratory distress. Alternatively, low-dose irradiation may precipitate regression. Rarely, tumors in such patients may be found to have adverse biological features such as N-*myc* amplification. In these circumstances, the prognosis is poor, and full, intensive treatment is indicated. [**Joanna K et al; 1998]**

RECURRENT NEUROBLASTOMA:

The prognosis and treatment of recurrent or progressive neuroblastoma depend on the site and extent of the recurrence or progression and on the previous therapy. Recurrence is usually widespread and prognosis poor despite additional intensive therapy. **[Pole JG et al; 1991]**

Unlike at initial presentation, central nervous system involvement is common. Most commonly, there is inward compression of the brain from cranial metastases, but meningeal and isolated intracranial metastasis can occur. Early recognition and treatment of central nervous system involvement may result in reduced neurologic impairment. The selection of further treatment depends on many factors, including the site of recurrence and previous treatment as well as individual patient considerations. Clinical trials are appropriate and should be considered. **[Hayes FA et al; 1985 & Frappaz D et al; 1992]**

Recent Advances and new approach in Neuroblastoma management:

Megatherapy:

Intensive treatments, or "megatherapy," combining high-dose myeloablative chemotherapy and/or total-body irradiation (TBI) with either autologous bone marrow transplantation (ABMT) or peripheral blood stem cell reinfusion are often used in advanced disease. The rationale is that if undetectable minimal residual disease can be eradicated, then the otherwise inevitable relapse is prevented. Residual cells which have survived initial chemotherapy may be resistant to drugs at conventional doses, but still sensitive to similar drugs which at higher dose levels can bypass inadequate membrane transport and saturate detoxification pathways and DNA repair mechanisms. Single-agent high-dose melphalan, which was evaluated in ENSG trial 1, is one of the more commonly used schedules **[Pritchard J et al; 1982 & Pritchard J et al; Pritchard J et al; 1986]**.

Although radiation, usually in the form of TBI, has been investigated with high-dose chemotherapy and ABMT for neuroblastoma, the results are no better than when chemotherapy alone is used, yet the acute and late side effects are greater. Allogeneic transplantation is not associated with improved results.

It is difficult to be certain of the true value of megatherapy. It certainly seems to prolong time to relapse; whether it truly improves long-term disease-free survival is less clear. The European Blood and Marrow Transplant Group has registry data on more than 1,000 patients with neuroblastoma who have received myeloablative therapy, Overall, survival at five years is 33%, but relapses may still be seen later. When patients relapsed after initial ABMT, salvage was not possible, but ABMT did salvage 15% of patients in second or subsequent relapse who had not previously undergone ABMT. The principal factor indicating a poor outcome for transplantation in stage 4 patients over the age of one year is persistent skeletal or bone marrow involvement. **[Philip T et al; 1997]**

Targeted Therapy:

Targeted radiotherapy involves the use of compounds labeled with radionuclides which preferentially localize in or around tumor deposits. Biological differences between normal and malignant cells are exploited to achieve the required differential distribution. Clinical results of radioimmunotherapy using the labeled monoclonal antibody UJ13A **[Lashford LS et al; 1988 & Kemshead JT et al; 1987]** and the anti-GD2 antibody 3F8 **[Cheung N-KV et al; 1991]** in neuroblastoma have been disappointing. Targeting with nonradiolabeled antibodies may also be used **[Cheung N-KV et al; 1994]**. While not necessarily improving bulky disease, such treatment may have a role post-megatherapy with the aim of controlling minimal residual disease and thus improving long-term event-free survival.

The pharmaceutical mIBG, an analog of the adrenergic neuron-blocking drugs guanethidine and bretylium, is taken up into neuroblastoma cells and normal tissues of sympathetic nervous origin by an active transport process **[Mairs RJ et al; 1991]** involving the epinephrine transporter molecule **[Pacholczyk T et al; 1991].** When radiolabeled, mIBG can be used for both imaging and treatment of neuroblastoma and other neural crest tumors.

The use of 131I-mIBG as part of the initial treatment of advanced neuroblastoma must still be considered experimental, although encouraging results from Holland have led to the initiation of several prospective studies of its use in this setting **[De Kraker J wt al; 1995].** The principal side effect is myelosuppression, particularly thrombocytopenia. 131I-mIBG has also been evaluated in conjunction with high-dose chemotherapy as part of myeloablative regimens prior to ABMT **[Gaze MN et al; 1995].**

Differentiating Agent:

A variety of agents have been shown to have noncytotoxic biological effects on neuroblastoma cells in vitro. For example, drugs such as interferon and retinoids **[Lucarelli E, et al; 1994 & Spengler BA et al; 1994]** may induce differentiation, and betulinic acid can cause apoptosis. These agents offer possible therapeutic pathways for control of neuroblastoma. In the randomized Children's Cancer Group study CCG-3891, 255 high-risk patients were randomized after completion of conventional therapy to receive 13-cis-retinoic acid or no further treatment. The three-year event-free survival rate for those receiving retinoids was 47% compared with only 25% ($p = 0.013$) for those receiving no treatment **[Schmidt ML et al; 1997]**.

In the ENSG trial 4, 177 patients with advanced neuroblastoma in complete or good partial remission were randomized to receive either 13-cis-retinoic acid or a placebo as maintenance therapy. This trial has now closed, and results will be analyzed in 1998 when follow-up data are more mature. Other isomers of retinoic acid may be suitable for clinical evaluation **[Lovat PE et al; 1997]**

Palliative Care:

Sadly, despite advances in treatment, the majority of patients with advanced neuroblastoma are still destined to die from their disease. While those patients who relapse after minimal initial treatment for early disease may still be salvaged, patients relapsing after intensive therapy for advanced disease are very rarely cured by second-line treatment. Nonetheless, judicious use of chemotherapy and radiotherapy can be beneficial in terms of symptom control and prolongation of life, and supportive measures can often enhance the quality of life of terminally ill children. **[Joanna K et al; 1998]**

Palliative anticancer Treatment:

The use of oral etoposide, given daily for three weeks with a seven-day interval between courses, can sometimes produce disease stabilization even in heavily pretreated patients, although the response rate is disappointing **[Davidson A et al; 1997]** . As the capsules are very large and may be difficult to administer to children, the liquid intravenous preparation is preferred, although its unpleasant taste must be disguised. The principal side effects are myelosupression and alopecia.

Some new cytotoxic drugs are always undergoing evaluation in the pediatric setting in phase I and II clinical trials. The likelihood of benefit for an individual patient is small, and these drugs are most often tried when a family, unwilling to accept the grave prognosis, is desperate for every avenue to be explored. The anti-DNA-topoisomerase I drug irinotecan is due to enter clinical studies in patients with neuroblastoma in the United Kingdom soon **[Vassal G et al; 1997].**

External beam radiotherapy can be valuable in the care of terminally ill children with recurrent or refractory neuroblastoma. It is most widely used for the relief of pain from bone metastases. A single 8Gy fraction usually results in a rapid and lasting benefit. In some cases, however, symptoms may recur at the same site, in which case retreatment can be considered. A fractionated regimen, such as 20Gy in five daily treatments, may be considered preferable in some circumstances, such as for the relief of spinal cord compression or extensive orbital disease.

Over the last decade, 131I-mIBG therapy has found a definite place in the palliation of symptoms of advanced neuroblastoma. Response rates varying between 16% and 58% have been reported **[Garaventa A. et al; 1991 & Voûte PA et al; 1991 & Lewis IJ et al, 1991].**

While many patients show no objective tumor reduction, pain relief is often dramatic, making noncurative treatment worthwhile **[Gerrard M et al, 1987].**

Prognostic Factors and Genetic Evaluation:

A number of biologic variables have been studied in children with this tumor.[Riley RD et al; 2004] Of particular importance are Shimada histology, aneuploidy of tumor DNA, and amplification of the N-MYC oncogene within tumor tissue, since treatment decisions may be based on these factors **[Cotterill SJ et al;2000 & Brodeur GM et al;1992 & Look AT et al ;1991 & Schmidt ML et al;2000 & Berthold F et al;1992 & Matthay KK et al ;1998]**

An open biopsy is usually needed to obtain adequate tissue for determination of these biological characteristics. Hyperdiploid tumor DNA is associated with a favorable prognosis, **[Ladenstein R et all; 2001**]

Especially in infants with neuroblastoma [**Look AT et al; 1991**] while N-MYC amplification is associated with a poor prognosis regardless of patient age**.[Brodeur GM et al;1992 & Look AT et al ;1991 & Tonini GP et al;1997]** . In contrast to N-MYC gene amplification, the degree of expression of the N-MYC gene in the tumor does not predict prognosis. **[Maris JM et al; 2000 & Bown N et al; 2001]**

Amplification of N-MYC is associated with deletion of chromosome 1p and gain of the long arm of chromosome 17(17q), the latter of which independently predicts a poor prognosis. **[Bown N et al; 1999 & Roberts SS et al; 2004]**

The profile of GABAergic receptors expressed in neuroblastoma is predictive of prognosis regardless of age, stage and N-MYC amplification. **[Krams M. et all; 2002]**

A higher proportion of proliferating tumor cells may independently predict poor prognosis.[Nakagawara A et al; 1993] Expression of the gene encoding one of the high-affinity neurotrophin receptors, termedTRK-A, is associated with good prognosis tumors.**[Wei JS et al; 2004]**

Gene expression profiling may prove useful for prognosis prediction**. [Poremba C et al; 1985]**. Increased levels of telomerase RNA **[Shuster JJ et al; 1992],** elevated serum ferritin **[Massaron Set al;1998],** elevated serum lactate dehydrogenase **[De Bernardi B;1992]** and the persistence of neuroblastoma cells in bone marrow during or after chemotherapy are each associated with poor prognosis**. [Berthold F et al;1992, Combaret V et al; 1996 & Reynolds CP et al; 2001 & Burchill SA et al; 2001 &**

Seeger RC et al; 2000 & Maris JM et al; 1999 & Lastowska M et al; 2001] Biologic staging consisting of N-MYC copy number and age is useful in defining prognosis and treatment of stage III neuroblastoma. **[Matthay KK et al; 1998]**

Neuroblastoma has been categorized into 3 biological groups. One type expresses the TRK-A neurotrophin receptor, is hyperdiploid, and tends to spontaneously regress. Another type expresses the TRK-B neurotrophin receptor; has gained an additional chromosome, 17q; has loss of heterozygosity of 14q; and is genomically unstable. In a third type, chromosome 1p is lost and the N-MYC gene becomes amplified. **[Sawada T et al; 1992 & Takeuchi LA et al; 1995]**

Many of the improvements in survival in childhood cancer have been made using new therapies that have attempted to improve on the best available, accepted therapy. Clinical trials in pediatrics are designed to compare potentially better therapy with therapy that is currently accepted. Further studies and evaluating a single new treatment and comparing the results with those previously obtained with standard therapy is very useful in determining the most suitable approach on evidence based.

Treatment Outcome:

Children of any age with localized neuroblastoma and infants younger than 1 year with advanced disease and favorable disease characteristics have a high likelihood of long-term, disease-free survival.**[Adams GA et al;1993 & Brodeur GM et al; 1992]**

Older children with advanced-stage disease, however, have a significantly decreased chance for cure despite intensive therapy. As an example, aggressive multiagent chemotherapy has resulted in a 2-year survival rate of approximately 20% in older children with stage IV neuroblastoma. **[Bowman LC et al; 1991 & McWilliams NB et al; 1995]**

Neuroblastoma in the adolescent or adult has a worse long-term prognosis regardless of stage or site and, in many cases, a more prolonged course when treated with standard doses of chemotherapy. **[Franks LM et al; 1997]**

Children who survive neuroblastoma may be at increased risk for second malignancies, including renal cell carcinoma. **[Fleitz JM et al; 2003]**

High-dose chemotherapy and surgery have been shown to achieve a minimal disease state in >50% of these patients. Other modalities, such as local radiation therapy and the use of agents with confirmed activity, may improve the poor prognosis. **[Kushner BH et al; 2003]**

Spontaneous regression of neuroblastoma has been well described in infants, especially in those with the 4S pattern of metastatic spread. **[Hiyama E et al; 1995 & Hiyama E et al; 2000]**

Regression generally occurs only in tumors with a near triploid number of chromosomes that also lack N-MYC amplification and loss of chromosome 1p. Features associated with spontaneous regression include the lack of expression of telomerase **[Kitanaka C et al; 2002 & Yamamoto K et al; 2002]** expression of Ha-ras,**[Okazaki T et al ; 2004]** and expression of the neurotrophin receptor TrkA, a nerve growth factor receptor. Recent studies have suggested that selected infants who appear to have asymptomatic, small, low-stage neuroblastoma detected by screening or as an incidental finding by ultrasound, often have tumors that spontaneously regress and may be observed safely without surgical intervention or tissue diagnosis. **[Fritsch P et al; 2004]**

Currently, the Children’s Oncology Group (COG) is studying whether it is safe to simply observe neonates with small adrenal masses that are presumed to be neuroblastomas (COG ANBL00P2). These masses are usually found during prenatal or incidental ultrasounds.

SCREENING :

The current data do not support neuroblastoma screening. Screening infants for neuroblastoma by assay of urinary catecholamine metabolites was initiated in Japan. **[Woods WG et al; 2002]**

A large population-based North American study in which most infants in Quebec were screened at ages 3 weeks and 6 months has shown that screening detects many neuroblastomas with favorable characteristics **[Schilling FH et al; 2002 & Reynolds CP et al, 2002]** that would never have been detected clinically, apparently because the tumors would have spontaneously regressed. Another study of infants screened at 1 year of age shows similar results. **[Ambros PF et al; 2000]** Screening at age 3 weeks, 6 months, or 1 year caused no reduction in the incidence of advanced-stage neuroblastomas with unfavorable biological characteristics in older children nor did it reduce the number of deaths from neuroblastoma in infants screened at any age. No public health benefits have been shown from screening infants for neuroblastoma at these ages. **[Reynolds CP et al; 2002, Ambros PF et al; 2000**

As the risk factors for, and causes of, neuroblastoma have not been established, it is not possible to provide information or advice for the primary prevention of this disease. It is generally thought that many neuroblastomas are present and detectable at birth, thereby allowing for detection of tumors by a single, once-in-a-lifetime screening test, such as those used for neonatal screening for noncancerous conditions, e.g., phenylketonuria. Screening is performed through biochemical tests for metabolites of norepinephrine and dopamine, i.e., vanillylmandelic acid (VMA), and homovanillic acid (HVA). Seventy-five percent to 90% of cases of neuroblastoma excrete these substances into the urine, and these can be measured in urine specimens**[Williams CM et al;1963].** There is no known optimal age for screening, but the most commonly discussed and studied age for a one-time screen has been 6 months. Screening at 12 months of age has also been evaluated in a population-based study in Germany**[Schilling FH et al;2002].** Approximately 65% of cases present before 6 months of age **[Parker L et al;1991]** Furthermore, the clinical significance of screen-detected neuroblastomas is in question since stage I and II localized tumors under 5 cm have been observed to regress without treatment in an observational study **[Yamamoto K et al;1998]**

Testing of liquid urine samples or of samples collected on filter paper for VMA and HVA is possible. **[Tuchman M et al; 1987]** The first attempts to conduct mass screening through urinary testing occurred in Japan in the early 1970s.**[Sawada T et al; 1992**] The VMA and HVA levels are usually measured by gas chromatography, thin layer chromatography, and/or high performance liquid chromatography.

There are no standard cut-off levels between positive and negative VMA and HVA tests. One recommendation is to use a VMA cut-off of 25 ug/mg creatinine and an HVA cut-off of 32 ug/mg creatinine. Alternatively, individual laboratories use a level of 2 standard deviations above that laboratory's age-specific mean to identify specimens for reanalysis. On reanalysis, a level of 3 standard deviations above the mean is used to determine the need for diagnostic evaluation**. [Chamberlain J et al; 1994]**

The sensitivity of the screening procedure used in different studies ranges from 40% to 80%.**[Woods WG et al; 1996]** False positives can be caused by dietary agents such as bananas and vanilla **[Woods WG et al; 1987**] but are rare with quantitative assays such as gas chromatography (specificity approximates 99.9%). **[Scriver CR et al; 1987]**

Because of the low prevalence of the disease, even in the Quebec Neuroblastoma Screening Project in which the specificity of the test was extremely high, the positive predictive value was only 52%, **[Woods WG et al; 1996]** i.e., for every 2 children identified by screening as being likely to have neuroblastoma, only 1 was actually affected. In the German Neuroblastoma Screening Project, the positive predictive value has been reported as only 8.5% **[Schilling FH et al; 2002].** False positive cases are generally followed for prolonged periods with serial noninvasive testing before a definitive diagnosis excluding cancer can be offered to the parents **[Bernstein ML et al; 1996]**

After approximately 8 years of follow-up (range 6-11 years), the neuroblastoma death rate in the screened population was not significantly different from rates in unscreened populations (standardized mortality ratio 1.11 (95% CI 0.64-1.92)) for the Quebec cohort compared to Ontario children). **[Woods WG et al; 2002]** Similar findings were observed in the German neuroblastoma study. **[Schilling FH et al; 2002]** Although final mortality rates are only expected in 2008, an interim analysis shows that the death rate from neuroblastoma is similar in screened and control populations (1.3 versus 1.2 deaths per 100,000 children).

Despite these results, some authors have argued that the Japanese experience shows that the number of children over 1 year of age diagnosed with neuroblastoma may have decreased since the inception of screening **[Sawada T et al; 2002]** and that overall mortality has declined during this period **[Asami T et al; 1995].**

A true reduction in neuroblastoma mortality may reflect improvements in treatment efficacy as much as a benefit of treating earlier stage disease. Mortality has decreased in other countries where screening does not occur**.[Cole M et al; 1992]** In any event, the majority of cases detected by screening at 6 months of age appear to have biologically favorable prognoses independent of stage**. [Hayashi Y et al; 1992]** Furthermore, despite the shift in stage distribution of cases detected by screening compared to those that are routinely detected, the evidence of reduction in the incidence of advanced stage cancers in the Japanese experience has been disputed,**[Bessho F et al; 1991]** and in the Quebec Project, as noted above, no such reduction is observed **[Woods WG et al; 1991].**

An increase in survival rates among screen-detected cases would be expected if screening was detecting neuroblastoma at an earlier and more curable stage. While improved survival rates after initiation of screening have been reported **[Sawada T et al; 1991],** these observations should be viewed cautiously, since improvements could be due to lead time bias, to length bias, and to identification of cases through screening which would have spontaneously regressed.

There is, as yet, no evidence from controlled studies or randomized trials of decreases in mortality associated with screening.

AIM OF WORK

Aim of Work

The aim of our study is to discuss and evaluate the role of preoperative chemotherapy in disease control via studying it's effect on:

A) The intraoperative surgical technique including :

- The accessibility and respectability of the tumor
- The frequency of visible residuals after resection.
- The frequency of intraoperative and immediate Postoperative complications

B) The Prognosis of the disease during the follow up period including:

- Prognostic Factors.
- Rate of Recurrence.
- Quality of patient's life.

PATIENTS & METHODS

Patients & Methods

Out of all cases presented to our National Cancer Institute (2003 – 2006) Diagnosed as having primary Neuroblastoma: 35 patients were selected to fulfill our selection criteria :

- No Previous treatment received for their Neuroblastoma.
- Eligible for Neo-Adjuvant Chemotherapy and fit to receive it.
- Fit for surgical intervention at the proper time for the procedure
- Primary Tumor :
    1. Adrenal
    2. Non-adrenal abdominal
    3. Non-adrenal Thoracic
    4. Non-adrenal combined abdominal and thoracic.
- All stages of the disease rather than stage I

Management Protocole :

1- All patients were subjected to Pre-treatment evaluation in the form of :

- Proper History taking for symptoms of presentations and duration of the symptoms and severity.
- Complete Medical examination.
- Local examination and clinical assessment for the site of the tumor and it's clinical effect

2- Laboratory Investigations:

-Neuron specific enolase (NSE) in plasma as a tumor marker.

-Tissue culture of a fresh tissue specimen (storedat - 80 C) for molecular biological studies .We tried to look for N-myc gene amplification and / or chromosome 1 p deletion.

3- Radiological studies:

-Plain chest X -ray.

-Abdominal ultra sonogaphy .

-Computed tomogaphy (CT) of the primary tumor site and masses.

-Magnetic Resonance Imaging (MRI) for tumors extending to the paravertebral or musculoskeletal structures.

- Skeletal survey (plain X - ray).

4- Radionuclide Imaging:

- 99mTc bonescintigraphy.
- 131 I-MIBG whole body scan.

Treatment Protocol

[Diagram A] illustrates treatment Protocol:

Here Add Diagram A Will Be <u>Page 76</u>

Treatment Guide lines:

1) 131 I-MIBG therapy:

Therapeutic 131 I-MIBG cycles were given for three to four courses according to response (fourth course given to patients who were still showing further evidence of tumor response after the third cycle).

With each systemic 131 I-MIBG cycle, patients received Lugol's iodine 100 mg/day (PO) starting 3 days prior to and continuing through the cycle in order to block thyroid uptake. 131IMIBG was delivered to patients over a period of 4 hours infusion in saline using a closed lead-shielded syringe infusion pump.

The dose per cycle of 13II-MIBG ranged between 100 and 200 mCi according to age and surface area.

Pulse and blood pressure were monitored during infusion and for 24 hours there after.

Patients were encouraged to drink plenty of fluids and to empty their bladders frequently in order to avoid radiation cystitis (IV fluids used for non cooperative young patients).
Cycles were repeated after 21-28 days guided by hematological recovery.

After the administration of 131 I-MIBG, Patients were hospitalized for 4 days following each course in an isolated, separate and lead shielded room that was especially prepared with safety Precautions.

A proper medical and nursing care was provided under safety precautions that allowed medical and nursing staff to use protective procedures and tools (eg; lead vest, gloves, stocks, head cover and masks). Patient-mother (or-relative) under cautious conditions were also allowed to contact on intervals.

Patient then discharged home by the fourth day. MIBG scan done after each course to evaluate response **[John, 1996]**.

By end of 131I-MIBG therapy, all patients had been reassessed for response to treatment and operability as well. Urinary VMA, MIBG scan, CT/I\4N and BM biopsy (if initially positive or MIBG evidence of infiltration) were done in addition to thorough clinical examination.

Further treatment was according to response, many investigators adopted the expression of objective response to denote a group of responders having a satisfactory treatment outcome in the form of CR+VGPR+PR **[Tepmongkol et al; 1999].**

[Diagram B]: Definitions of response to treatment.

Patients with **PR** (Partial Response) were regarded for the possibility of primary tumor resection

Patients who achieved **CR/ VGPR** with MIBG alone or with surgery in addition were indicated to receive 7 courses of first line chemotherapy as adjuvant therapy.

On the other hands, inoperable patients and those having **SD, MR** or **PD** were directly switched to receive 4 courses of first line chemotherapy.

Diagram B : Definitions of response to treatment :

Complete Response	Complete Disappearance of Tumor and Normal Catecholamine Levels
Complete clinical response	>90% decrease (sum of the products of the greatest perpendicular diameters) of the primary tumor and metastatic disease (if any) No new lesions Healing of bone lesions
Partial clinical response	□50% decrease (sum of the products of the greatest perpendicular diameters) of primary tumor and metastatic disease (if any) No new lesions Healing of bone lesions
Minor response	>25% or <50% decrease (sum of the products of the greatest perpendicular diameters) of primary tumor and metastatic disease (if any) No new lesions Healing of bone lesions
No response	<25% decrease (sum of the products of the greatest perpendicular diameters) of primary tumor or metastatic disease (if any) No new lesions
Progressive disease	>25% increase (sum of the products of the greatest perpendicular diameters) of the primary tumor or all metastatic lesions (if any) Appearance of new lesions

2) Systemic chemotherapy:

A] First Line:

First line chemotherapy was in the form of alternating cycles **OJEC/OPEC**:

OPEC

VCR (vincristine): l.5mg/m2 m day I .

CPM (cyclophosphamide): 600mg/m2 on day 1.

Cisplatin: 90mg/m2 on day 2 plus hydration and

Etoposide: 20kng/m2 on daY 4.

OJEC

VCR 1.5mg/m2 onday 1.

CPM: 600mg/n2 on daY 1.

Carto'platin: 500mg/n2 on day l.

Etoposide: 200m!m2 on daY 1.

Clinical examination, CBC, LFTs, KFTs, and urinary VMA were routinely done prior to each course.

Reassessment of tumor response was performed for all patients after the fourth cycle with VMA, US, CT, MRI, chest x-ray, bone scan, MIBG scar, and BM biopsy (if previously positive or suspected infiltration on MIBG scanning).

Patients with **CR /VGPR** (with or without prior surgery) after completion of their fourth course, would have resumed their chemotherapy again for further three courses (total of 7) to be scheduled for follow up thereafter.

Non responders (**SD, MR, PD**) at earlier stage were indicated for second line chemotherapy (4 courses maximum) followed by re-evaluation to assess the response.

Those who went into PR after the fourth cycle while have not been operated upon at an earlier stage were then assessed for operability.

Whenever feasible operation over the primary tumor was attempted and then followed by further chemotherapy (same line) for another 3 courses.

After 7 courses, patients who were still in PR would be subjected to surgery (first or second look) if feasible.

Patients were scheduled for follow up if they had either **CR** or **VGPR** (ie: no active disease) with or without surgery. Others who were still not operable till that time while in **PR** or those having further disease progression were then shifted to second line chemotherapy.

B] Second line:

Melphalan: 8 mg/day (PO) on days 1 to 5

Etoposide: 100 mg/day (PO) on days 1 to 5

monthly alternating with the following combination;

VCR: 1.4 mg/day day 1 and

CPM: 150 mg/day daily from from day 1 to 7

3) Surgery:

- Timing for surgical intervention was decided based on individual case response at different stages of therapy as described above.

- Surgical Intervention was classified into 2 categories:
  - Initial Surgical Exploration.
  - Second Look Surgery.

- Accurate data recording included: Time of intervention, clinical assessment of tumour intra-operatively, Operative techniques, success in achieving complete resection or presence of residuals, Intra-operative or immediate post-operative complications complications , The need for a second look surgery.

- Surgery over the primary tumor was indicated under conditions:
  - Partial disease remission.
  - Accepted general condition.
  - Either complete or > 90% resection is feasible.

- Second Look Surgery was undertaken :
  - For removal of residual tumours.
  - For Debulking of poorly responding tumours.

4) Radiotherapy:

Patients were subjected to radiotherapy in the certain instances:

- Active residual primary (gross/microscopic) with absence of all metastases after the end of systemic therapy and attempted local surgical resection

- In progressive disease with uncontrollable pain or a tumor compressing a vital structure (as palliation).

- On developing a neurological deficit while on treatment with a tumor compressing the spinal cord and /or intracranial metastases.

- In presence of local unresectable residuals under surgery in absence of good general conditions allowing a second look surgery.

Treatment toxicity:

Treatment induced toxicity was reported and scored according to the WHO criteria [**Miller et al, 1981].**

Several aspects as hematological (WBCs, Hb, Plt), gastrointestinal (nausea, vomiting diarrhea stomatitis),hepatic (aminotransferases, Billirubin, albumin), renal(craetinine,BUN,Metabolic(Ca,Na,K), electrolytes and infection were monitored.

Blood pressure monitoring and thyroid scanning were particularly focused on with MIBG therapy.

Follow up:

Complete reassessment was done for patients at the end of their treatment before starting follow up.

1 -Visiting schedule: The frequency of such visits was as following:

- Monthly visit for the first 6 months.
- Every 2 months during the next 6 months of their first follow up year and then;
- Every 3 months thereafter.

2-Follow-up evaluation:

-Clinical examination and measurements of any suspicious lesions

-Laboratory tess in the form of : urinary VMA and LDH in the serum

-Plain chest X-ray and abdominal ultrasound

-CT / MRI for the sites of previously known lesions every 3 months during the first year and then every 6 months.

-131 I-MIBG-scan every 3 months during the first year and then every 6 months.

Statistical analysis

-Statistical Package for social sciences (SPSS) used to compute results.

-Mean and standard deviation of the mean were used for describing quantitative data.

-Frequency and percentage were used to describe qualitative data

-Kaplan-Meier. Survival tables were used for survival analysis and Log Rank test for comparing survival data.

RESULTS

Results

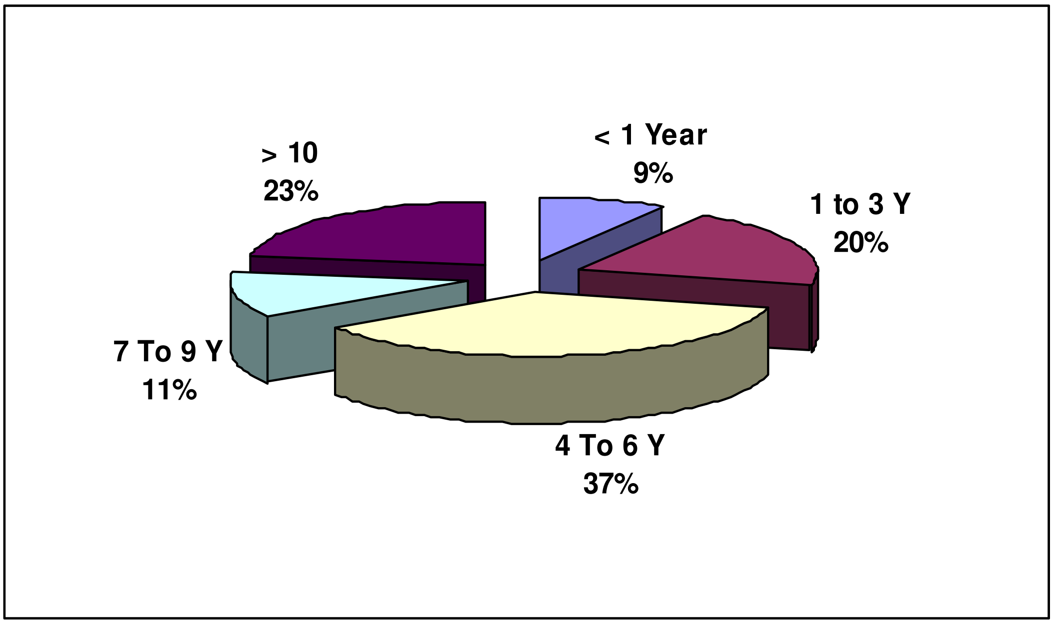
Thirty Five patients of newly diagnosed neuroblastoma were involved in this study.

Age:

Age of patients ranged between 7 months old and 16 years old with a median age of 5 years at the time of presentation.

Table (1) shows the Age distribution among the diagnosed patients:

Age	< 1 Year	1 to 3 Y	4 To 6 Y	7 To 9 Y	≥ 10
Pt. No	3	7	13	4	8
%	9%	20%	37%	11%	22%

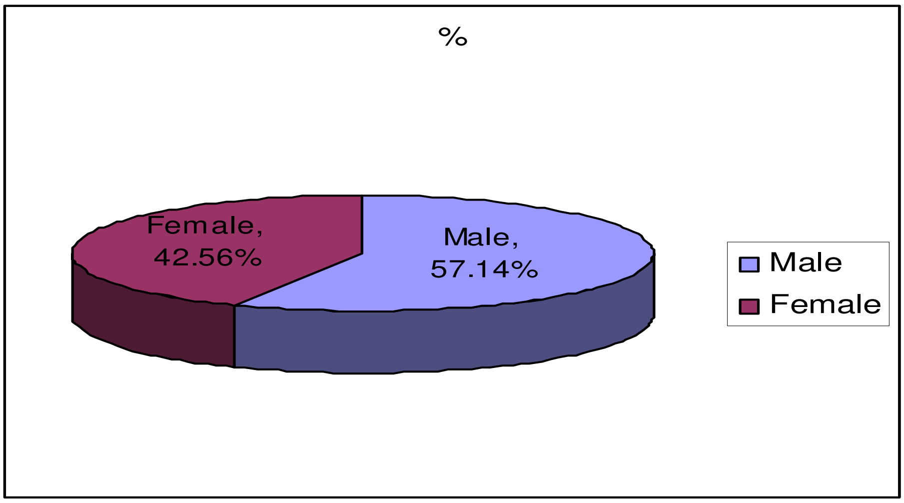


Sex :

Males constituted 57.14% (20 patients) of cases, and Females 42.56% (15 Patients) , with a male to female ration of 1.33: 1

Table (2) shows the sex distribution of the disease in the selected group:

Sex	Male	Female
%	(20 Pt.) 57.14%	(15 Pt.) 42.56%



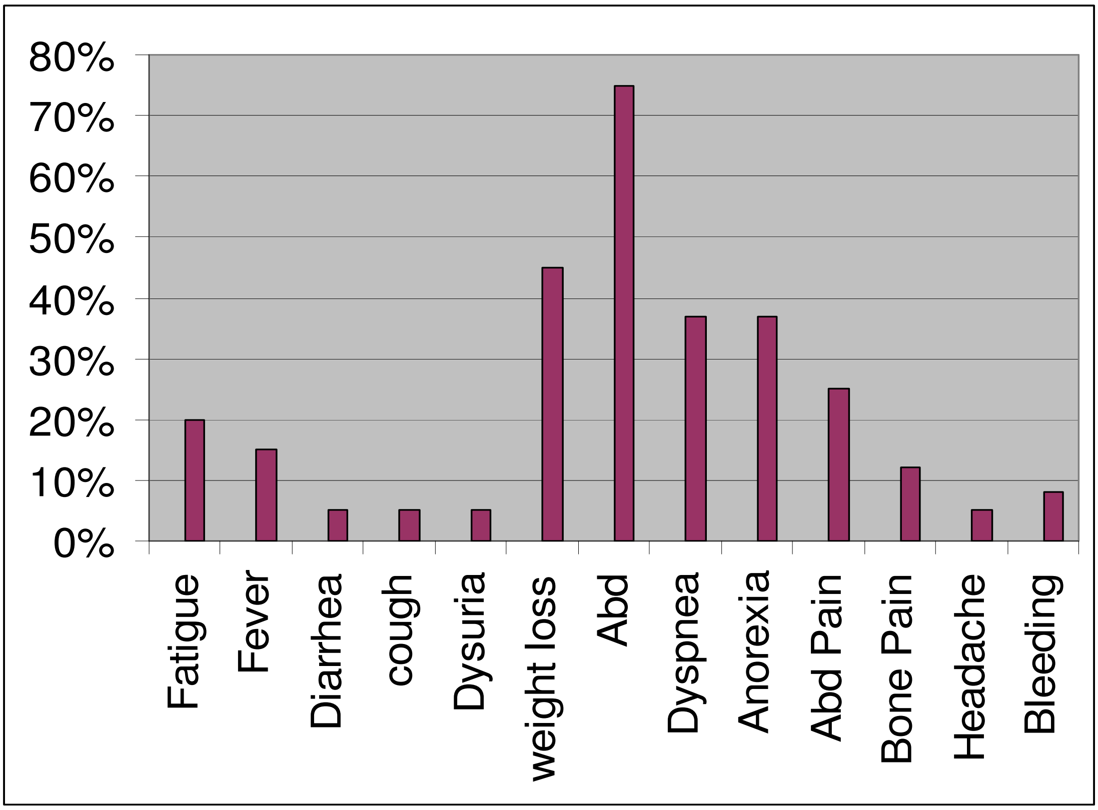
Clinical Presentation:

Symptoms:

Mode of presentation varied greatly in between children ranging from just fever and fatigue to abdominal enlargement and marked weight loss.

Table (3) shows different symptomatic patterns and the frequency of each:

Presentation	%
Fatigue	20%
Fever	15%
Diarrhea	5%
cough	5%
Dysuria	5%
weight loss	45%
Abd enlargement	75%
Dyspnea	37%
Anorexia	37%
Abd Pain	25%
Bone Pain	12%
Headache	5%
Bleeding tendancy	8%

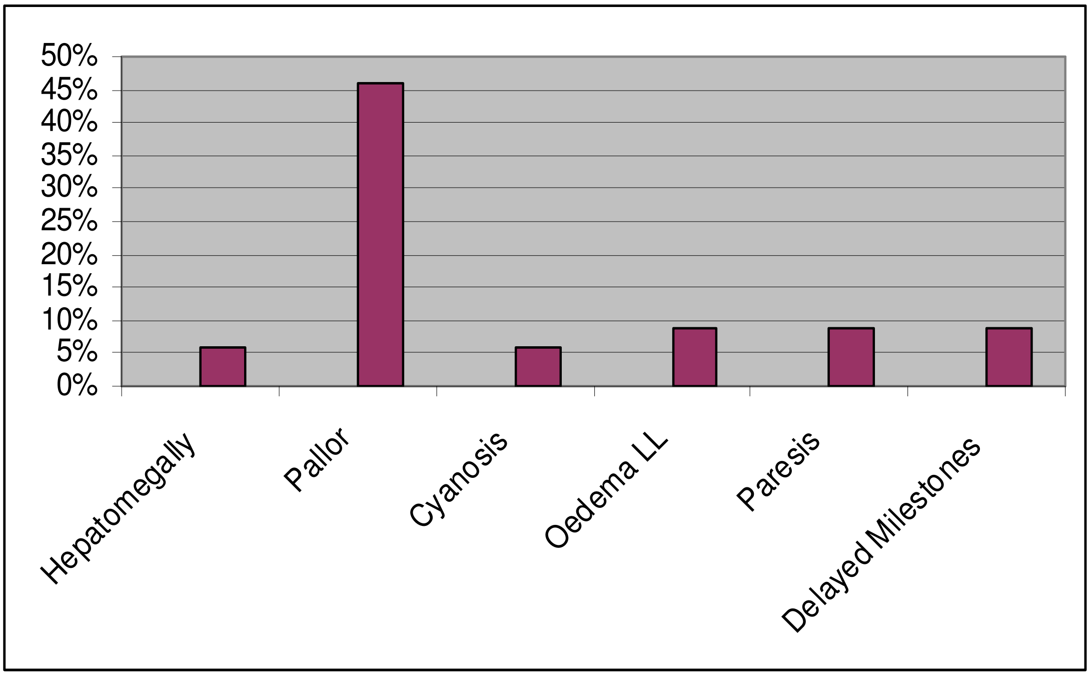


Signs:

Other signes detected during the initial examination of patients presented are demonstrated in table 4 :

Table (4) : Other Signs detected during initial Examination :

Other Signs	%
Hepatomegally	6%
Pallor	46%
Cyanosis	6%
Oedema LL	9%
Paresis	9%
Delayed Milestones	9%



Primary Tumour sites :

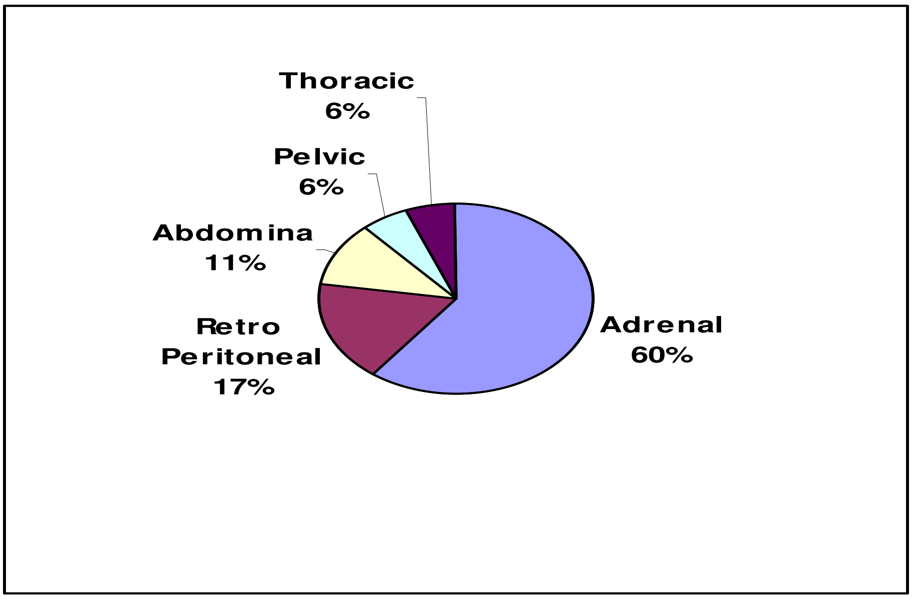
As one of our selection criteria was: Localization of the primary Tumour including: Adrenal, Non adrenal abdominal, Thoracic and combined, we had to exclude 2 patients from our cohort who presented with an intracranial primary site of the tumour as they were not eligible for evaluation of the role of surgery in this disease in our centre being transferred to another neurosurgery centre different from the National Cancer Institute to have surgical part of their treatment.

Primary Tumour sites included Supra Renal, Retro-peritoneal, Pelvic, and Thoracic, while the secondary sites of the disease varied greatly but included Lymph nodes, Bones and Bone Marrow, Liver, Lungs and Pleura and Testes.

Table 5 shows frequency of different primary sites and Table 6 shows the frequency of different secondary locations of the disease.

Table(5) : Primary Site Distribution :

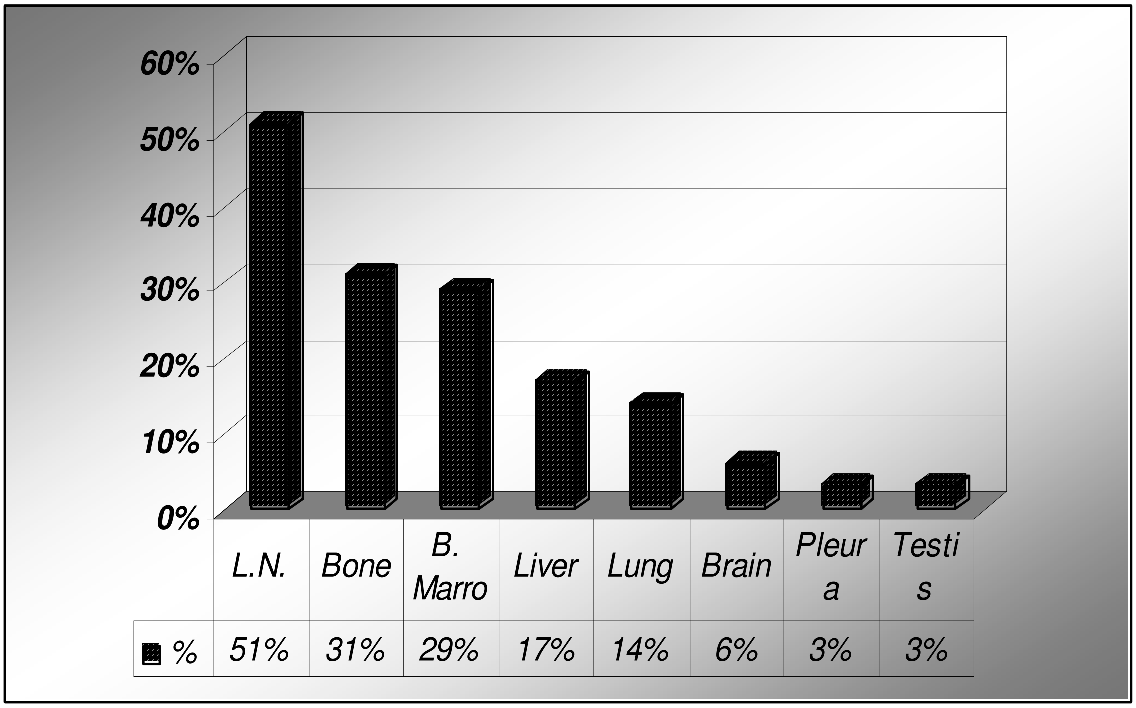
Site	No	Frequency
Adrenal	21	60%
Retro Peritoneal	6	17%
Abdominal	4	11%
Pelvic	2	6%
Thoracic	2	6%



Secondary Tumour Sites :

Table (6) :Secondary Tumour Sites:

Site	No	%
L.N.	18	51%
Bone	11	31%
Bone Marrow	10	29%
Liver	6	17%
Lung	5	14%
Brain	2	6%
Pleura	1	3%
Testis	1	3%

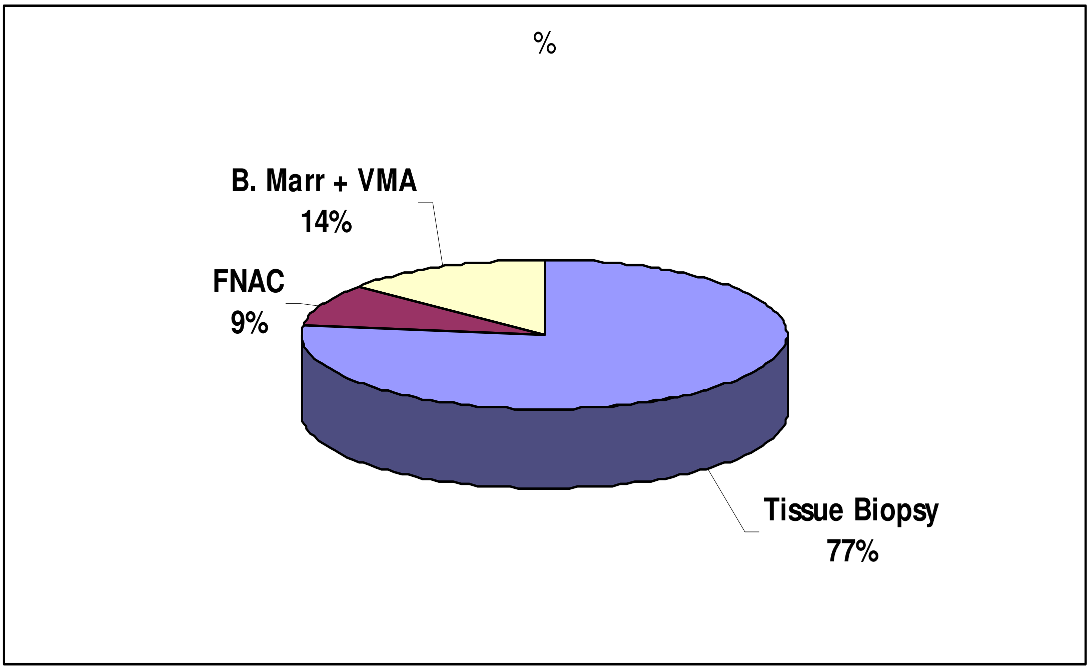


Diagnosis:

Histopathological confirmation of the neuroblastoma nature of the tumours were carried out through tissue biopsy in the majority of cases 77% (27 Patients) while 9% of patients (3 patients) were diagnosed by FNAC while 5 patients(14%) of patients have their tumours confirmed through a bone marrow biopsy for infiltration with detection of high level of VMA in their urine .

Table (7) : Confirmation of Tumour nature :

Test	No	%
Tissue Biopsy	27	77%
FNAC	3	9%
B. Marr + VMA	5	14%



Detection of Bone Metastasis and bone marrow involvement:

Bone metastasis was detected in 11 patients (31% of all patients) but (73% of stage IV patients), skeletal survey was positive in 9 patients, Bone scan in 10 patients and MIBG scan in all 11 patients . While bone marrow involvement was detected in 10 patients diagnosed by bone marrow aspiration in 7 only and bone marrow biopsy in 3 patients. MIBG scintigraphy was able to detect BM disease in all the 10 patients with Bone Marrow involvement.

Table (8) : Detection of Bone Metastasis

Detection of Bone Metastasis	No	%
Skeletal Survey	9	81%
Bone Scan	10	91%
MIBG Scan	11	100%

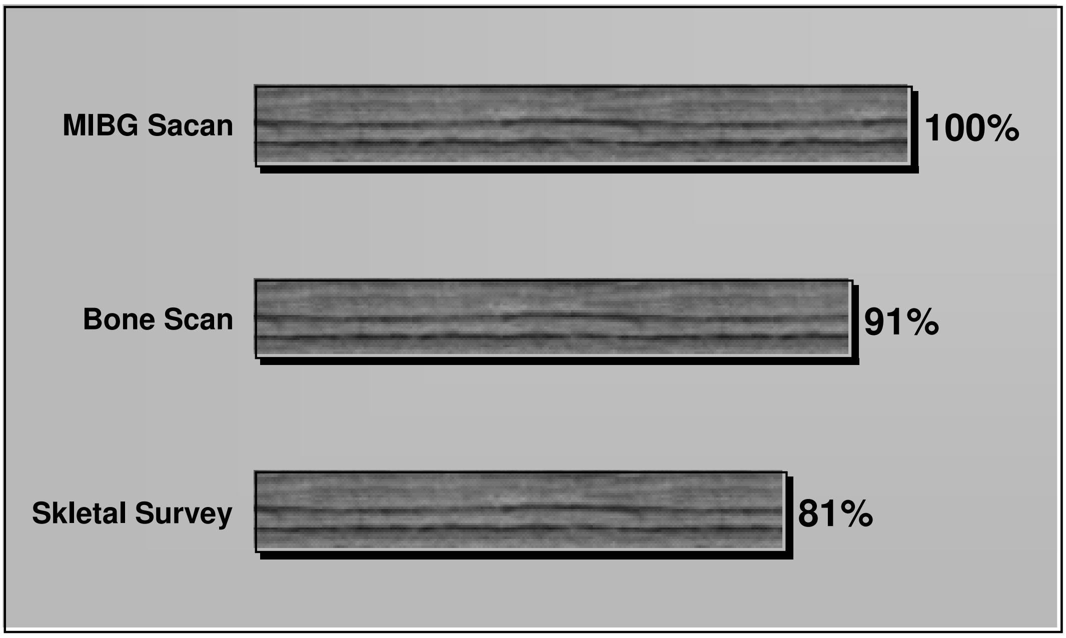
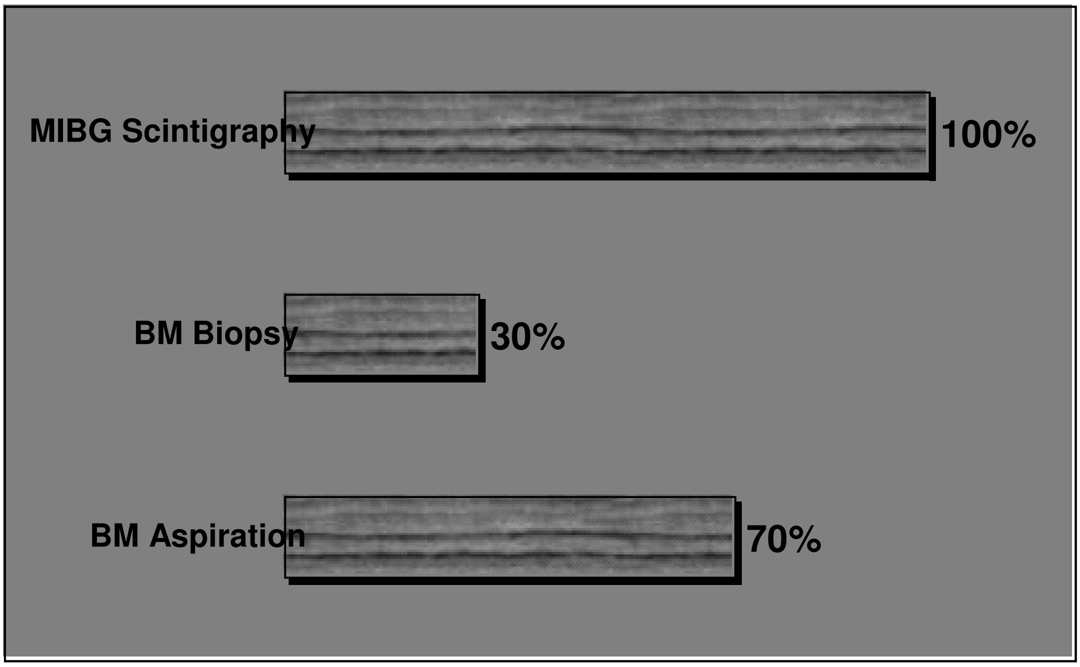


Table (9) : Detection of Bone Marrow Involvement :

Detection of BM involvement	No	%
BM Aspiration	7	70%
BM Biopsy	3	30%
MIBG Scintigraphy	10	100%



Biochemical Markers :

Recording of the biochemical levels of VMA, LDH and Serum Ferritin showed evidence of abnormally elevated values of VMA in 33 patients (94%) and abnormal levels of LDH in 27(77%) and in 23(66%) of patients an abnormal level of Serum Ferritin was recorded .

Table (10): Abnormally elevated levels of Biochemical Markers:

Biochemical Markers	No	%
VMA	33	94%
LDH	27	77%
Serum Ferritine	23	66%

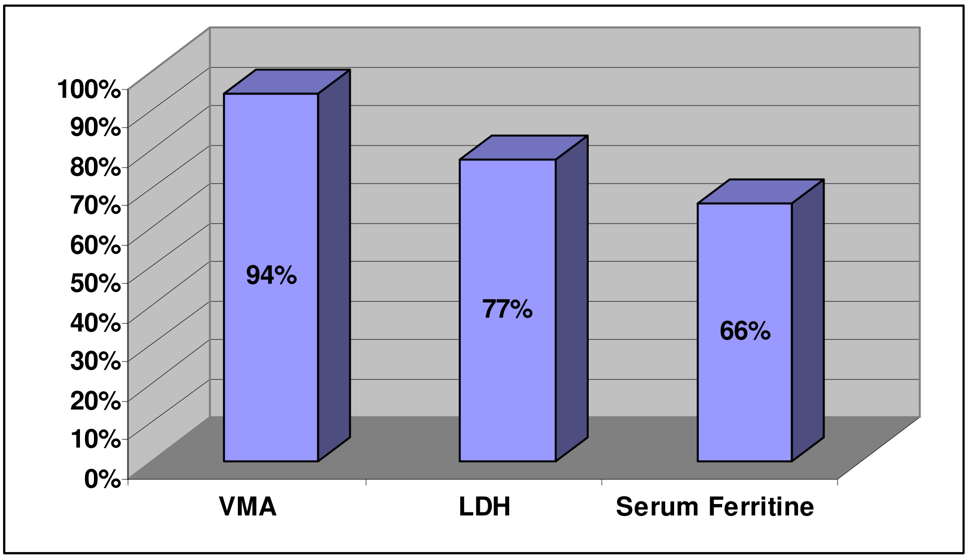


Diagram C is here

Management Protocol:

<u>[Diagram C] Illustrates management in this cohort of patients.</u>

<u>MIBG Therapeutic Induction:</u>

Following the initial diagnostic and metastatic work up, 34 patients out of the 35 found subjective to MIBG upfront treatment while the remaining 1 patient did not complete the MIBG treatment due to unsatisfactory performance and non compliance at the time of treatment as patient felt very unwell during the course of the treatment after the third cycle and did not show any evidence of improvement or desire to continue treatment despite delaying further cycles.

Response:

2 patients showed evidence of complete response (CR)

13 showed evidence of partial response (PR)

0 patients could be classified as having minor response while (MR)

19 showed evidence of progressive disease (PD)

The over-all evidence of objective response to the MIBG Therapy of 44.1 % (15 Patients)

MIBG cycles were in an average of 2-4 cycles (median: 3 Cycles) for every patient which were 3 to 4 weeks apart (Median of 3 weeks).

In all, 12 cycles of therapeutic MIBG were delayed for a period that ranged between a week to four weeks (Median 2 weeks) due to variable reasons:

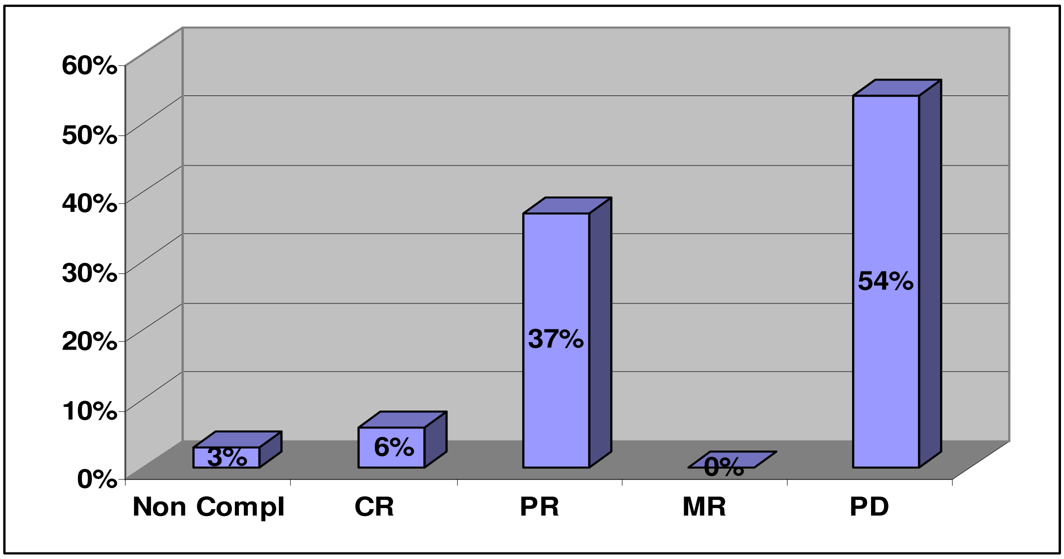
- Unsatisfactory Blood Count (4 Cycles)
- Poor patient's performance at cycle time (2 Cycles)
- Sever infections (1 Cycle)

- Others including non availability of the radio active material (1 Cycle)

Table (11) : Response to MIBG Therapy:

Response To MIBG Therapy	No	%
Non Compliance	1	3%
CR	2	6%
PR	13	37%
MR	0	0%
PD	19	54%

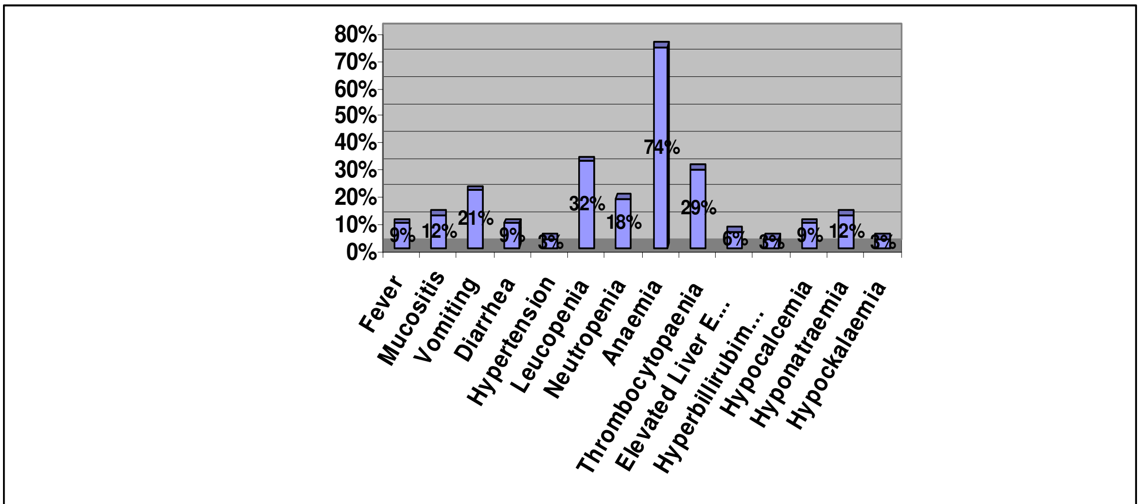
Objective response to the MIBG Therapy of 44.1 % (15 Patients)



While the side effects for the systemic MIBG Therapy included toxicities in different patterns of presentation, Anaemia, Leucopoenia, and thrombocytopenia of which were the commonest. That were generally tolerated and non fatal.

Table (12): Shows different patterns of MIBG Toxicity in this cohort of patients:

Toxicity	No	% of treated Pt.
Fever	3	9%
Mucositis	4	12%
Vomiting	7	21%
Diarrhea	3	9%
Hypertension	1	3%
Leucopenia	11	32%
Neutropenia	6	18%
Anaemia	25	74%
Thrombocytopaenia	10	29%
Elevated Liver Enzymes	2	6%
Hyperbillirubimaemia	1	3%
Hypocalcemia	3	9%
Hyponatraemia	4	12%
Hypockalaemia	1	3%



First Line Chemotherapy :

34 were subjected to receive first line chemotherapy, Only 33 patients received the treatment in the form of a total of 131 cycles . One patient died after the third cycle of 1st line chemotherapy and did not complete the treatment .

A median of 6 cycles / patient were given at intervals of 3 to 4 weeks , a median of 3 weeks .

16 cycles (15.4% of all cycles) were delayed due to variable reasons most commonly non satisfactory blood counts in 52%, and infections in 30% at the time of the Chemotherapy cycle

Assessment of patients following the first line Chemotherapy was carried out at two stages:

First Stage : at the end of the initial 4 Cycles of chemotherapy and that was available in 33 patients out of the 34 as 1 patients died through the course of the Chemotherapy as a result of developing intracranial haemorrhage and coma after the 3rd cycle of Chemotherapy.

Summarising the response to the first line chemotherapy (OPEC/OJEC) Initial 4 Cycles showed that :

- 1 Patient died following 3rd cycle of chemotherapy.
- 4 patients showed evidence of complete response :
    - 2 patients previously showed evidence of Complete Response to MIBG

- 2 Patients who previously showed partial response to MIBG therapy

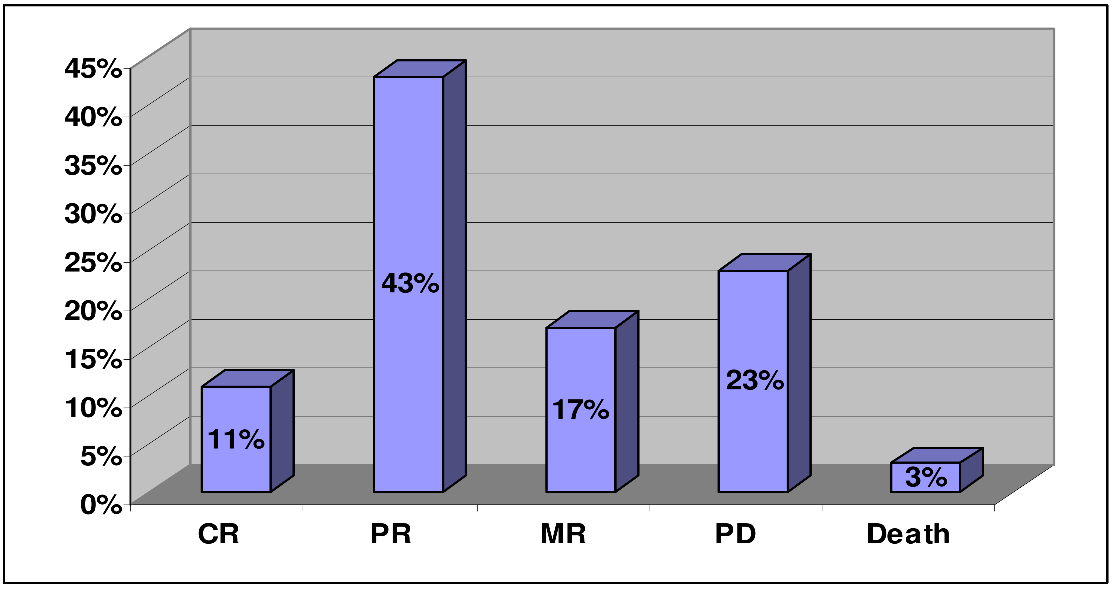
- 15 patients showed evidence of partial response
- 6 patients showed evidence of minor response.
- 8 patients showed evidence of progressive disease

The objective response to first line chemotherapy 4 cycles (was detected in 25 out of the 34 patients who were assessed following first 4 cycles of the 1st line chemotherapy which constituted (74%) of those received the initial 4 cycles of first line chemotherapy.

Table (13): Response to initial 4 cycles of Chemotherapy :

Initial 4 Cycles OPEC/OJEC	No	%
CR	4	11%
PR	15	43%
MR	6	17%
PD	8	23%
Death	1	3%

The objective response to first line chemotherapy 4 cycles was 74%



Further management of the 33 patients who completed 4 cycles of 1st line chemotherapy:

- 4 Patients who had evidence of complete response:
  - 2 Patients (who previously had MIBG and Surgical Intervention) moved to close follow up scheme
  - 2 Patients who previously showed partial response to MIBG therapy were offered completion of another 3 cycles of chemotherapy.
- 15 Patients showed evidence of partial response:
  - 4 patients offered Surgical Exploration
  - 11 patients completed another 3 courses of chemotherapy, a total of 7 courses after which they had their surgical intervention.
- 6 Patients with minor response were offered surgical exploration.
- 8 Patients showed evidence of progressive disease:
  - 7 patients offered Surgical Exploration.
  - 1 patient completed another 3 cycles of 1st line chemotherapy yet this patient died just after the last cycle of the chemotherapy of disease progression and never had any surgical attempt of resection.

A total of 14 patients completed 7 courses of 1st line chemotherapy:

- 2 Patients who had complete response (Previously partial response to the initial 4 cycles)
- 11 Patients who expressed partial response to the initial 4 cycles.
- 1 Patient who had evidence of progressive disease following the initial 4 cycles.

Further assessment of patients who complete 7 cycles showed that:

- 4 patients had complete response:
  - 2 Patients (previously showed evidence of complete response after initial 4 cycles) : moved to the close follow up scheme and never had any surgery .
  - 2 Patients expressed new complete response (Previously had Partial Response to the Initial 4 cycles and they were offered surgery)
- 10 patients showed evidence of Partial Response and they were offered surgery.

The Overall Response to 1st line Chemotherapy :

1 Patient died following 3rd cycle of chemotherapy.

6 Patients showed Evidence of Complete Response.

13 patients showed evidence of Partial Response

6 patients showed evidence of Minor Response

8 Patients showed evidence of progressive disease.

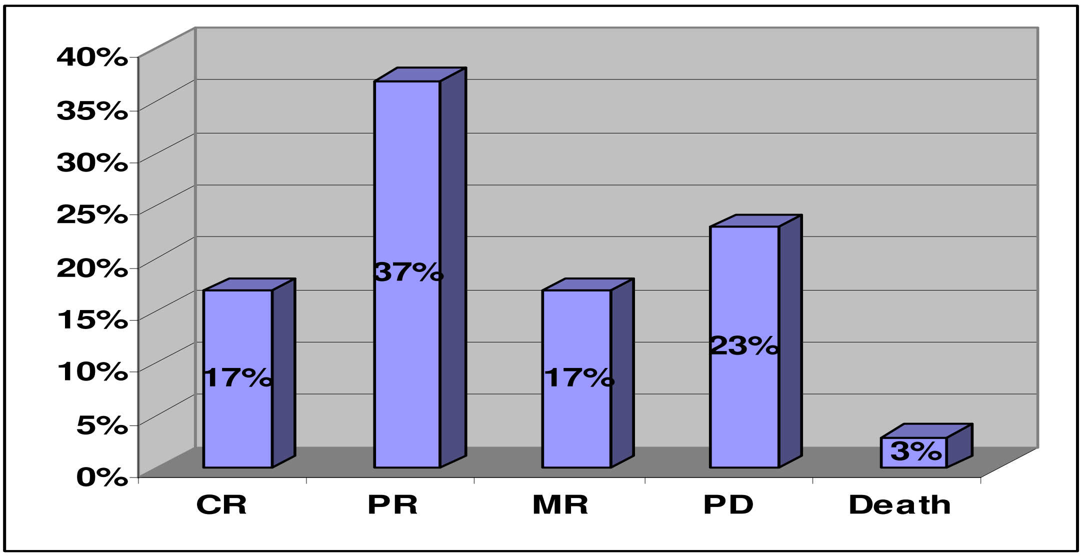
(One of these patients died while waiting for a surgery of sever disease progression immediately after the end of the last cycle of chemotherapy)

Objective response was detected in 25 out of 34 patients which constitutes to 74% of patients received 1st line chemotherapy.

Table (14) : Overall Response to 1st Line Chemotherapy + MIBG + Surgery :

Response	No	%
CR	6	17%
PR	13	37%
MR	6	17%
PD	8	23%
Death	1	3%

Objective Response: 74%



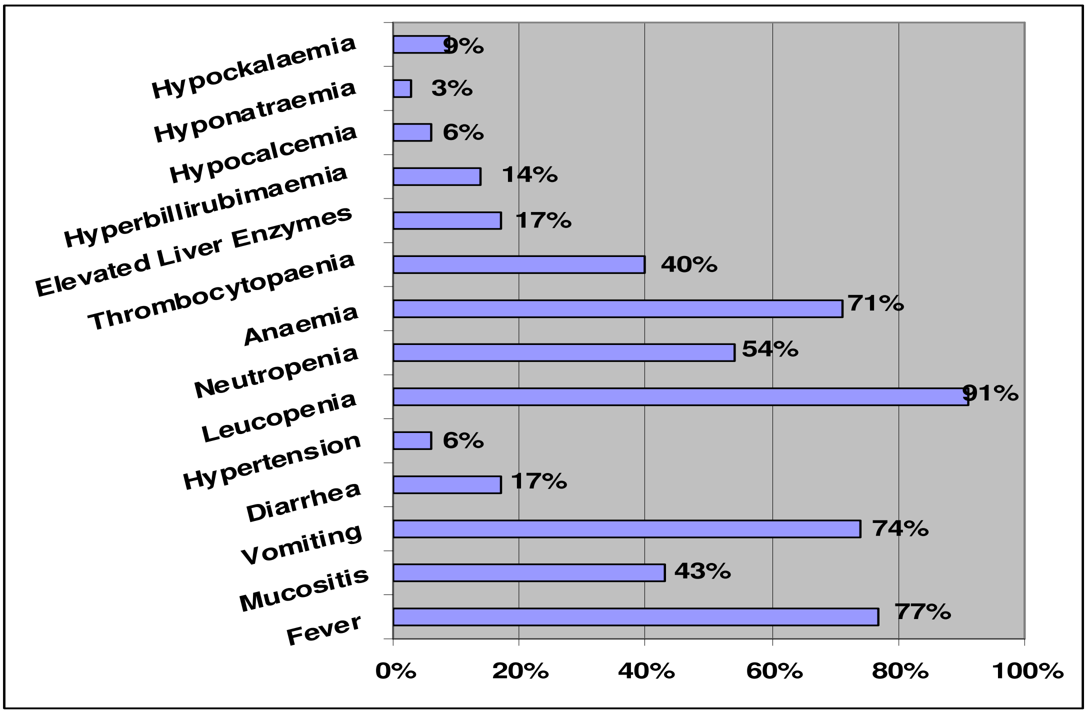
The first line Chemotherapy was not without complications: these complications were sever in one patient and these complications led to death of this patient shared with the disease progression,

Other complication of the first line chemotherapy which was not fatal to the patients and could be managed and treated successfully medically included: minor infections, Fever, diarrhoea, anaemia, Elevated Liver enzymes and hyperbilirubinemia, Hypocalcemia, Hyponatremia and Hypokalemia . Toxicities related to chemotherapy seemed to be more sever and more resistant than those related to the MIBG induction therapy.

Table (15) shows the distribution of Chemotherapy complications among assessed patients

<u>Table (15) shows the distribution of Chemotherapy complications :</u>

Toxicity	No	%
Fever	27	77%
Mucositis	15	43%
Vomiting	26	74%
Diarrhea	6	17%
Hypertension	2	6%
Leucopenia	32	91%
Neutropenia	19	54%
Anaemia	25	71%
Thrombocytopaenia	14	40%
Elevated Liver Enzymes	6	17%
Hyperbillirubimaemia	5	14%
Hypocalcemia	2	6%
Hyponatraemia	1	3%
Hypockalaemia	3	9%



Surgical Treatment:

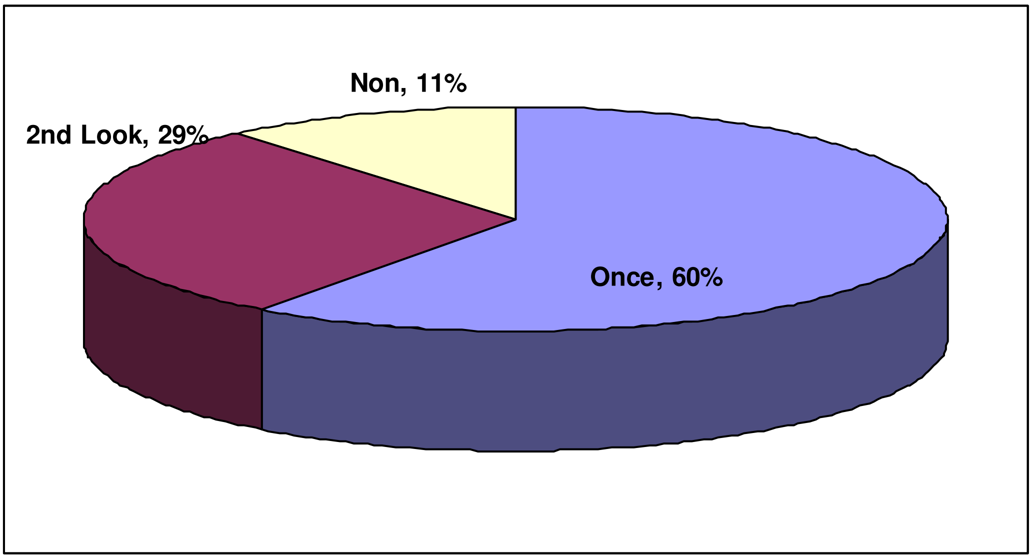
Surgical intervention was carried out in 31 patients :

21 patients had only one surgical exploration

10 patients had a second look surgery.

Table (16) Surgical Intervention :

Surgical Intervention	No	%
Once	21	60%
2nd Look	10	29%
Non	4	11%



Distribution of the surgical Intervention has shown that:

A} 2 patients who showed evidence of complete response to MIBG Therapy: had complete removal of the residual tumour . and moved to receive 1^{st} line chemotherapy (4 cycles) as an adjuvant therapy.

B} 4 patients had the surgical exploration after completion of 4 cycles of 1^{st} line chemotherapy showing evidence of partial response :

Results:

- 1 Patient had a successful complete resection of the tumour: after which he had further 3 cycles of 1^{st} line chemotherapy and scheduled for follow up.
- 2 patients had incomplete resection of the tumour
- 1 patients was found inoperable .

Further Management :

- The 2 patients who had incomplete resection of tumour plus the 1 patient who was found inoperable completed another 3 courses of 1^{st} line chemotherapy , and then they were subjected to second look operations:
  -The 2 patients who previously had incomplete resection of the tumour could have their residuals completely removed, and placed on follow up schedule.
  -The 1 inoperable case found operable but with residuals left and was classified as incomplete resection of the tumour and that was progressed to have a second line chemotherapy.

C}2 Patients who completed 7 cycles of 1^{st} line chemotherapy: showing evidence of complete Response .

D} 10 patients who completed 7 cycles of 1^{st} line chemotherapy: showing evidence of Partial Response :

- 7 Patients had successful complete resection
- 1 patient had incomplete resection of the tumour: Moved to receive 2^{nd} line chemotherapy, after which patient had a second look operation and a complete excision.
- 2 patients found inoperable: scheduled to receive a second line chemotherapy,

  - 1 patient died of sever disease progression after the 1^{st} cycle

  - The Other patient had a second look operation and incomplete excision of the tumour then a follow up and further assessment of tumour.

E} 6 Patients who expressed Minor Response following 4 cycles of 1^{st} line chemotherapy were subjected to surgical exploration:

- 2 had complete resection, then scheduled for follow up
- 3 had incomplete resection of the tumour then shifted to second line chemotherapy then a second look :

  -2 had completion of resection of the tumour successfully

  -1 had incomplete resection
- 1 patient found inoperable after which he had a second line chemotherapy then a second look and a successful complete resection of the tumour.

F} 7 Patients who found to show evidence of Progressive disease following 4 cycles and :

Non of the patients could have complete removal of the tumour.

- 5 had incomplete excision:

  -1 died immediately postoperative as a result of surgical complications in the form of a sever form of coagulopathy and generalised disseminated intravascular coagulopathy despite maximum care in the ITU.

  -4 patients shifted to 2nd line chemotherapy:

    2 had Partial Response and then a second look and successful complete excision .

    2 had No response and deterioration of the general condition, No further management rather than supportive treatment was offered.

- 3 Patients found Inoperable and scheduled for second line chemotherapy :

    1 had partial response and Second Look resulted in incomplete excision of the tumour.

    2 patients had No Response and deterioration of the general condition, only supportive treatment was offered.

Surgical treatment Outcome:

At the initial Surgical intervention :

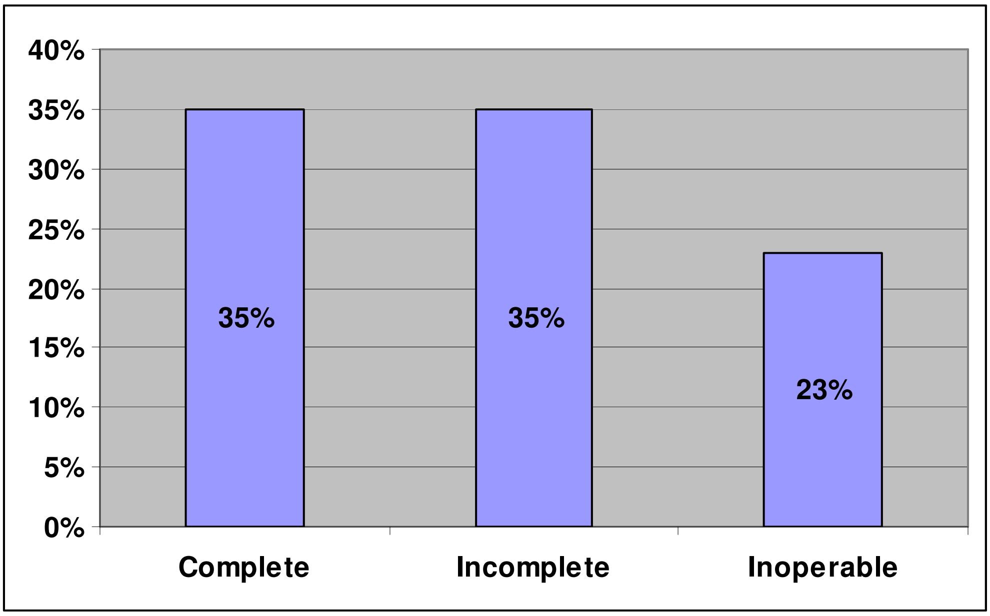
11 patients had Complete Resection of the tumour.

11 patients had incomplete resection of the tumours.

7 patients found Inoperable

Table (17) Response to Initial Surgical Intervention:

Resection	No	%
Complete	11	35%
Incomplete	11	35%
Inoperable	7	23%



At the 2^{nd} Look Surgery:

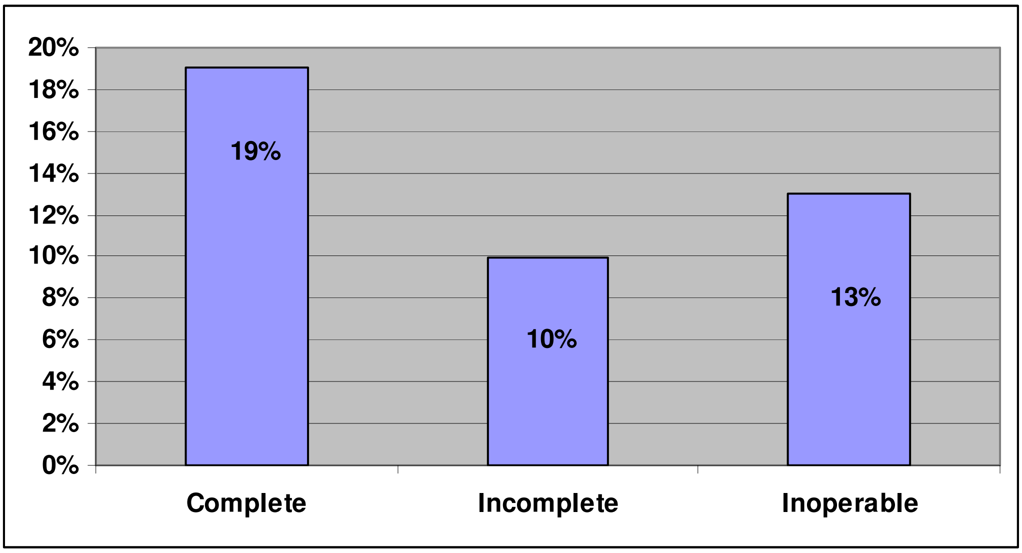
5 patients had completion of their surgical resection

1 patient out of the 7 inoperable could have complete resection.

3 patients out of the previously found 7 Inoperable could have incomplete resection

Table (18) Response following a 2^{nd} Look Surgery :

Resection	No	%
Complete	6	19%
Incomplete	9	10%
Inoperable	3	13%



Overall Surgical Treatment Showed that:

17 patients had Complete Resection

9 Patients had Incomplete Residuals

3 Patients remained Inoperable

Table(19) Overall Surgical Treatment outcome:

Resection	No	%
Complete	17	55%
Incomplete	9	29%
Inoperable	3	10%

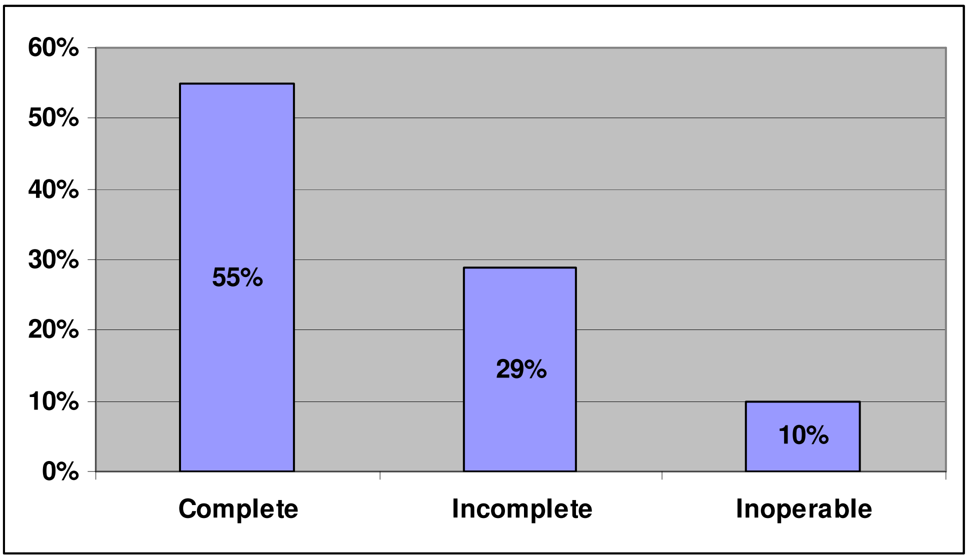
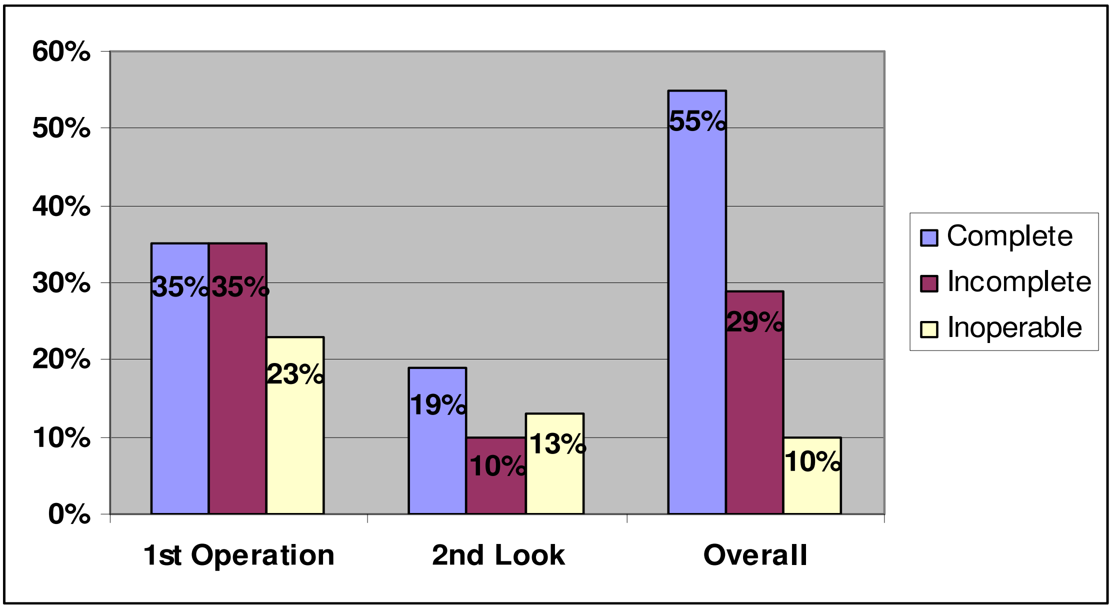


Table (20)Comparison Between the 2 Surgical Stages :

Resection	1st Operation	2nd Look	Overall
Complete	35%	19%	55%
Incomplete	35%	10%	29%
Inoperable	23%	13%	10%



Surgical treatment outcome, effect of MIBG and Chemotherapy 1st and 2nd lines on surgical intervention and the most common complications are summarized below in overall treatment outcome results.

Second Line Chemotherapy :

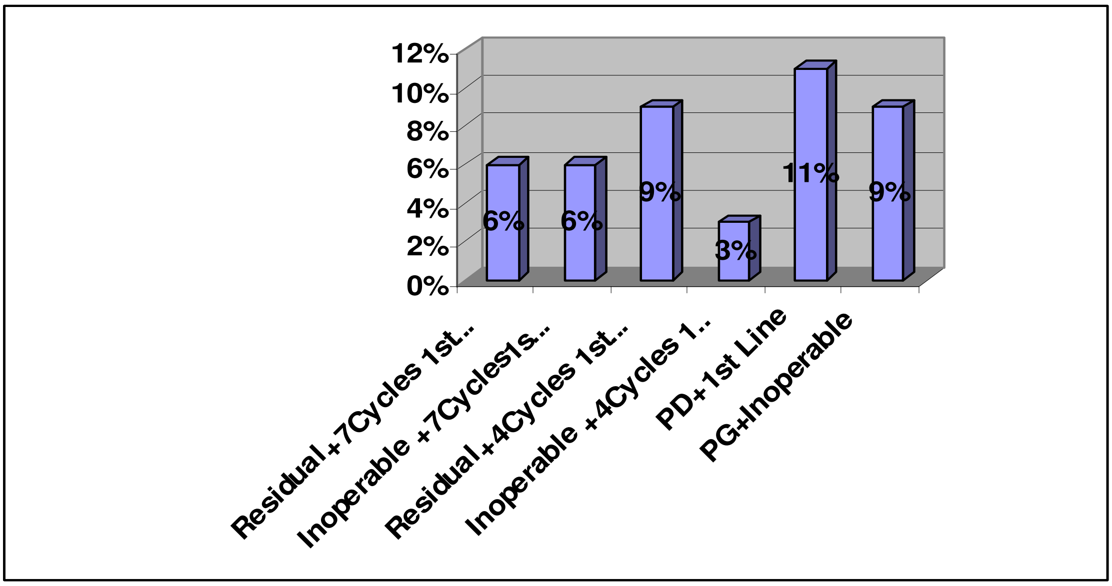
15 patients were subjected to second line salvage chemotherapy .

- 2 patients had incomplete resection of the tumour following 7 cycles of 1^{st} line chemotherapy and a second look operation.
- 2 patient who was found inoperable following 7 cycles of 1^{st} line chemotherapy
- 3 patients who had incomplete resection of the tumour following a minor response to 4 cycles of 1^{st} line chemotherapy
- 1 patient who was found inoperable following 4 cycles of 1^{st} line chemotherapy.
- 4 patients who had progressive disease under 1^{st} line chemotherapy and incomplete resection of the tumour
- 3 patients who had progressive disease and were found inoperable intraoperatively.

Objective response to 2^{nd} line chemotherapy that was detected by a change in the progress of the disease and change in the course of the surgical operability from incomplete resection to a complete one , or inoperable to respectable either complete or incomplete was detected in 8 patients out of 15, (53.3%)

Table (21) Indications for 2nd line Chemotherapy :

Indication	No	%
Residual+7Cycles 1st Line	2	6%
Inoperable+7Cycles1st Line	2	6%
Residual+4Cycles 1st Line	3	9%
Inoperable+4Cycles 1st Line	1	3%
PD+1st Line	4	11%
PG+ Inoperable	3	9%



Localized Radiation Therapy:

Localized Radiation therapy was attempt in 9 patients :

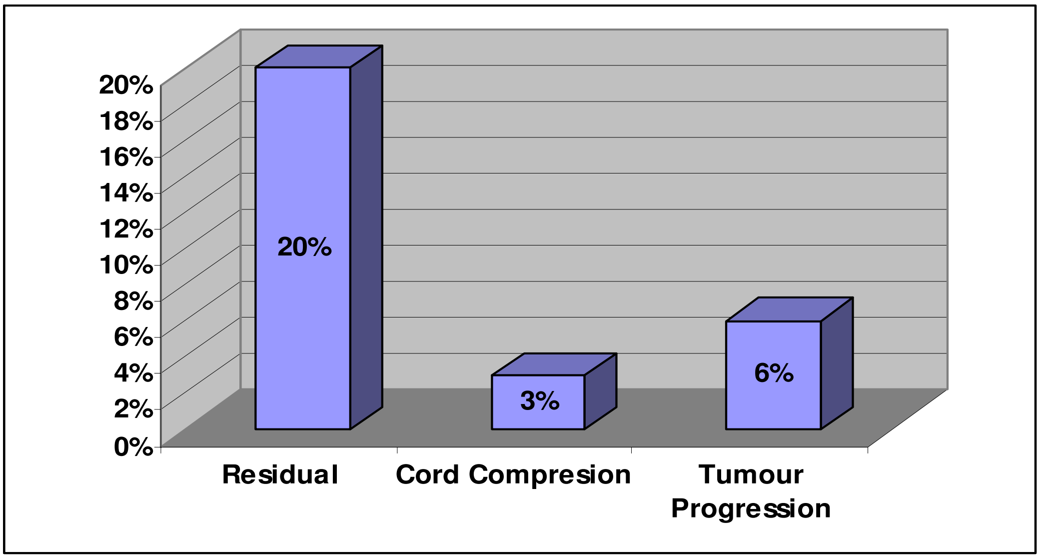
- 7 patients had Radiotherapy of residual tumours following incomplete surgical resection.
- 3 patients had palliative Radiotherapy :

  -1 patient for neurological signs following cord compression

  -2 patients for palliation of pain and sever tumour progression despite maximum treatment and care.

Table 22: Indications for Radiotherapy:

Indication for Radiotherapy	No	%
Residual	7	20%
Cord Compression	1	3%
Tumour Progression	2	6%



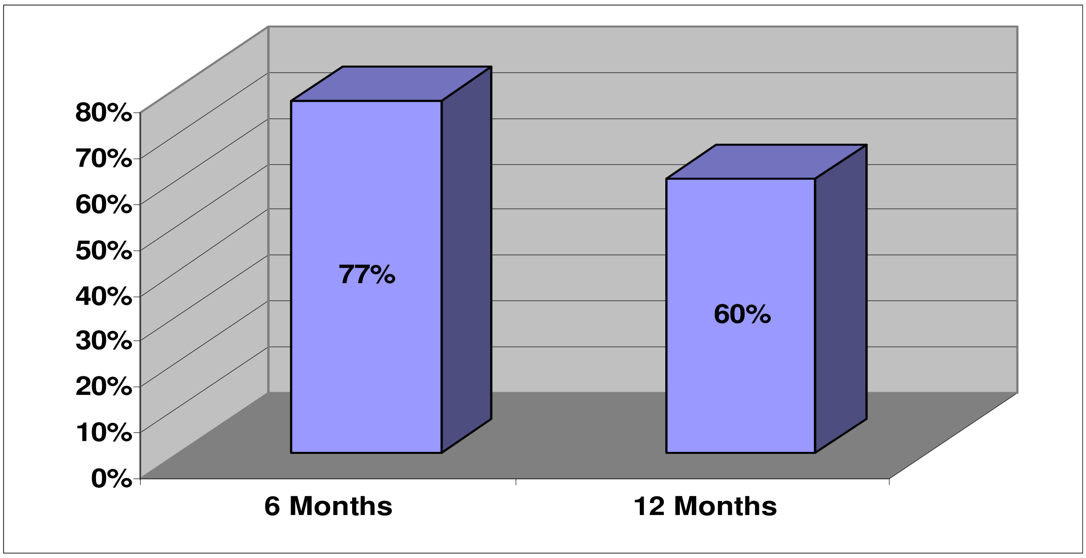
Treatment Outcome:

Evaluation of patients survival has demonstrated that :

The overall survival at the end of 6 months of active treatment and follow up was 77% and the survival rate at the end of 12 months of follow up was 60%

Table (23) Overall Survival :

Duration	No	%
6 Months	27	77%
12 Months	21	60%



Further evaluation of the prognostic factors that could have participated in this survival have shown that :

Age:

Patient's age presented a significant statistical value in survival as the survival was higher among those who were 1years old and less. (P= 0.20)

Table (24):

A)Age as a Prognostic factor affecting Survival: All Age Groups:

	<1Y	1 To 3 Y	4 To 6 Y	7 To 9 Y	>10 Y	Total
Survival	2	5	9	1	5	22
Deaths	1	2	4	3	3	13
Total	3	7	13	4	8	35

Degrees of freedom: 4
Chi-square = 2.92098126232742
The distribution is not significant.
p is less than or equal to 1.

B) Age as a prognostic factor : <1Y Vs >1Y:

Age as a prognostic factor			
	Survival	**Deaths**	**Total**
< 1 Y	2	1	3
> 1 Y	20	12	32
Total	22	13	35

Degrees of freedom: 1
Chi-square = 0.0203962703962704
For significance at the .05 level, chi-square should be greater than or equal to 3.84.
The distribution is not significant.
p is less than or equal to 1.

Stage:

Disease stage has shown a statistically significant impact on a better survival for those who were diagnosed at Stage 2 of the disease while there was no significant statistical difference between stage 3 and stage 4 patients.

Table (25): Stage as a significant prognostic factor :

	Stage II	Stage III	Stage IV	Total
Survival	11	6	4	21
Deaths	1	7	6	14
Total	12	13	10	35

Degrees of freedom: 2
Chi-square = 7.71901709401709
p is less than or equal to 0.025.
The distribution is significant.

Primary Tumour Sites :

The primary tumour site had been evaluated as of no statistically significant value (*p* is less than or equal to 1) when the adrenal versus extra-adrenal tumour sites were evaluated as parameters of survival.

Table (26) Site of the Primary Tumour and Survival :

	Adrenal	Retro-Peritonea	Abdominal	Pelvic	Thoracic	Total
Survival	12	4	3	1	1	21
Death	9	2	1	1	1	14
Total	21	6	4	2	2	35

Degrees of freedom: 4
Chi-square = 0.724206349206349 .
The distribution is not significant.
p is less than or equal to 1.

Response to different Lines of Treatment :

The response to the initial MIBG induction therapy was of valuable significant value in prognoses (*p* is less than or equal to 0.05) as well as the response to 1st Line chemotherapy (P less than or equal to 0.001) while the response to 2nd line chemotherapy was not of statistically significant value (P less than or equal to 0.20)

Table (27): Significant Response to MIBG:

	Objective Response	No Resp / Prog D	Total
Survival	14	7	21
Death	2	12	14
Total	16	19	35

Degrees of freedom: 1
Chi-square = 9.28728070175439
p is less than or equal to 0.01.
The distribution is significant.

Table (28): Significant Response to 1st Line Chemotherapy :

	CR	PR	MR	PD	Total
Survival	6	11	1	1	19
Death	0	2	5	7	14
Total	6	13	6	8	33

Degrees of freedom: 3
Chi-square = 19.0778267784847
p is less than or equal to 0.001.
The distribution is significant.

P.S. There is one patient who died following 3 Cycle of 1st Line Chemotherapy and could not be evaluated properly for the Significance of the cohort.

Table (29): Non Significant Response to 2nd Line Chemotherapy :

	Objective Respn	No Resp/Prog D	Total
Survival	4	1	5
Death	4	6	10
Total	8	7	15

Degrees of freedom: 1
Chi-square = 2.14285714285714
For significance at the .05 level, chi-square should be greater than or equal to 3.84.
The distribution is not significant.
p is less than or equal to 0.20.

Response To Surgical Treatment :

Surgical Treatment was an important statistically significant factor in survival of the patients, those who had respectable tumours showed statistically higher evidence of survival, while those who had non respectable tumours had shown a significant low rate of survival .

The degree of respectability and the presence of residuals during initial surgical exploration or after a second look surgery also expressed a statistically significant value (*p* is less than or equal to 0.01) in comparing those who had a complete surgical resection of the tumour versus those who had residuals after resection.

Table (30):Significant Relation between Respectability and Survival:

	Complete Resection	**Incomplete Resection**	**Inoperable**	**Total**
Survival	15	2	0	17
Death	5	3	6	14
Total	20	5	6	31

Degrees of freedom: 2
Chi-square = 11.0128151260504
p is less than or equal to 0.01.
The distribution is significant.

The response to MIBG induction therapy in the determining the accessibility respectability of the tumours have expressed a statistically significant value (*p* is less than or equal to 0.05)

<u>Table (31):Sinificant Relation between Respectability and Response to MIBG :</u>

	CR to MIBG	PR to MIBG	PG with MIBG	Total
Complete Resection	2	12	6	20
Incomplete Resection	0	1	4	5
Inoperable	0	0	6	6
Total	2	13	16	31

Degrees of freedom: 4
Chi-square = 11.0586538461538
p is less than or equal to 0.05.
The distribution is significant.

The response to the 1st line chemotherapy as well showed a significant statistical value (*p* is less than or equal to 0.025) when studied as a factor that may play a role in determining the intraoperative technique as respectability and accessibility of the tumour.

Table (32): Significant Relation between Respectability and Response To Chemotherapy:

A)Resectability in response to therapy :

A)Surgical resectability in relation to response to therapy				
MIBG+Chemo Response	**Complete Resect**	**Incomplete Rese**	**Inoperable**	**Total**
Objective Respo	14	6	4	24
PD	0	4	3	7
Total	14	10	7	31

Degrees of freedom: 2
Chi-square = 7.46530612244898
p is less than or equal to 0.025.
The distribution is significant.

B) Objective Response Vs. Progressive Disease :

B)Surgical resectability in relation to response to therapy				
MIBG+Chemo Response	**Complete Resect**	**Incomplete Rese**	**Inoperable**	**Total**
CR+PR	12	3	3	18
MR+PD	2	7	4	13
Total	14	10	7	31

Degrees of freedom: 2
Chi-square = 8.29505494505495
p is less than or equal to 0.025.
The distribution is significant.

While 2^{nd} line chemotherapy was not of a statistically significant factor in determining the intraoperative progress as respectability and accessibility of the tumour. (*p* is less than or equal to 1)

Table (33): Insignificant Relation between Resectability and Response to 2^{nd} Line Chemotherapy:

	Objective respo	**No Response**	**Total**
Complete Resection	1	0	1
Incomplete Resection	3	5	8
Inoperable	4	2	6
Total	8	7	15

Degrees of freedom: 2
Chi-square = 2.109375
For significance at the .05 level, chi-square should be greater than or equal to 5.99.
The distribution is not significant.
p is less than or equal to 1.

Table (34): Effect of response to Pre operative ttt on 2nd Look Surgery:

Effect of response to Pre operative ttt on 2nd Look Surgery			
	Complete Exc	**Incomplete Exc.**	**Total**
Objective respo	7	2	9
PD	2	1	3
Total	9	3	12

Degrees of freedom: 1
Chi-square = 0.148148148148148
For significance at the .05 level, chi-square should be greater than or equal to 3.84.
The distribution is not significant.
p is less than or equal to 1

Biochemical Markers as Prognostic Factors:

VMA:

Evaluation of the survival rate in correlation with the initial VMA level as a possible prognostic factor at the time of presentation showed no statistical significant value between the level of the VMA and the survival rate .

Table (35): VMA High Level effect on Survival :

	High VMA	Normal VMA	Total
Survival	21	0	21
Death	12	2	14
Total	33	2	35

Degrees of freedom: 1
Chi-square = 3.18181818181818
For significance at the .05 level, chi-square should be greater than or equal to 3.84.
The distribution is not significant.
p is less than or equal to 0.10.

LDH:

While the high serum level of LDH more than 1000 U/L at the time of presentation expressed a poor significant correlation on survival in comparison to those who expressed lesser values (P=0.025)

Table (36) LDH and Survival:

	High LDH	Normal LDH	Total
Survival	14	8	22
Death	13	0	13
Total	27	8	35

Degrees of freedom: 1
Chi-square = 6.12794612794613
p is less than or equal to 0.025.
The distribution is significant

Serum Ferritin:

Serum Ferritin was found of no significant statistical value in anticipating a good prognosis and a higher survival when the high and low levels were evaluated as prognostic parameters. (*p* is less than or equal to 1)

Table (37): Serum Ferritine and Survival:

	High Serum Ferritine	Normal S Ferritine	Total
Survival	13	8	21
Death	10	4	14
Total	23	12	35

Degrees of freedom: 1
Chi-square = 0.33816425120773
For significance at the .05 level, chi-square should be greater than or equal to 3.84.
The distribution is not significant.
p is less than or equal to 1.

Non of the previous markers had a significant correlation with the disease stage either stage 3 or stage 4 of the disease.

Neuron Specific Enolase:

Neuron Specific Enolase was evaluated in 23 patients and the levels ranged between 9 and 71 ng/L a significant statistical value (*p* is less than or equal to 0.05) could be detected on survival when this factor was studied as prognostic indicator.

Table (38): Significant Values of Neurone Specific Enolase :

	9 to 20	21 to 40	41 to 60	61 to 80	Total
Survival	5	4	2	0	11
Death	0	1	3	2	6
Total	5	5	5	2	17

Degrees of freedom: 3
Chi-square = 8.24242424242424
p is less than or equal to 0.05.
The distribution is significant.

And finally : the immediate clinical picture on evaluation of the patient during follow up of the patients has shown a statistically significant impact on survival as those who were tumour free by the end of active treatment had definitely had a higher survival rate than those who had residuals or secondaries at the end of active treatment (*p* is less than or equal to 0.025)

Table (39): Overall Survival and Tumour Clearance :

	Tumour Free	Residual	Inoperable + Secondaries	Total
Survival	14	1	1	16
Death	6	4	5	15
Total	20	5	6	31

Degrees of freedom: 2
Chi-square = 7.64236111111111
p is less than or equal to 0.025.
The distribution is significant.

Results Summary

Table (40): Epidemiology and survival :

Epidemiology and Prognostic Factors :						Effect on Survival	Chi-square	Significance
Age	**<1Y**	**1-3Y**	**4-6**	**7-9**	**≥10**			
	(9%)	(20%)	(37%)	(11%)	(22%)	$p \leq 1$	0.020396	-Ve
Sex	**Male**		**Female**					
	(57.14%)		(42.56%)					
Stage	**II**	**III**	**IV**					
	(34.3%)	(37.1)	(28.6%)			$p \leq 0.025$	7.719017	**+Ve**
Primary Site	**Adrenal**	**Retro-per**	**Abd Paras**	**Pelvic Paras**	**Thoracic**			
	(60%)	(17.1%)	(11.5%)	(5.7%)	(5.7%)	$p \leq 1$	0.724206	-Ve
Secondary Sites	**L.N.**	**Bone**	**BM**	**Liver**				
	(51%)	(31%)	(29%)	(6%)		$p \leq 0.001$		**+Ve**
	Lungs	**Brain**	**Pleura**	**Testis**				
	(14%	(6%)	(3%)	(3%)				
Bone Metastasis (31%) Detection Method			**Skl Surv**	**Bone Scan**	**MIBG Scan**			
			.(81%)	(91%)	(100%)			
BM Involvment			**Aspiration**	**BM Biopsy**	**MIBG cintig**			
			(70%)	(30%)	(100%)			
Biochemical Markers								
		High	**Low**					
VMA		(94.28%)	(5.72%)			$p \leq 0.10$	3.181818	-Ve
		High	**Low**					
LDH		(77.14%)	(22.86%)			$p \leq 0.025$	6.127946	**+Ve**
		High	**Low**					
Ferritine		(65.71%)	(34.29%)			$p \leq 1$	0.338164	-Ve
		9-20	**21-40**	**41-60**	**61-80**			
NSE		(14.29%)	(14.29%)	(14.29%)	(5.71%)	$p \leq 0.05$	8.242424	**+Ve**
Level of Parents' Education						$p \leq 0.001$		**+Ve**

Table (41): Clinical Presentation and Toxicity to treatment :

Symptoms	**Fatigue**	**Fever**	**Diarrhea**	**Cough**	**Dysuria**	**Wt. Loss**	**Bleeding**
	(20%)	(15%)	(5%)	(5%)	(5%)	(45%)	(8%)
	Abd Enlarg	**Dyspnea**	**Anorexia**	**Abd Pain**	**Bone Pain**		**Headach**
	(75%	37%	(37%)	(25%)	(12%)		(5%)
Signs	**Hepatomegally**	**Pallor**	**Cyanosis**	**Oedema LL**	**Paresis**		**Dela Mil**
	(6%)	(46%)	(6%)	(9%)	(9%)		(9%)
Toxicity	**Fever**	**Mucositis**	**Vomiting**	**Diarrhea**	**Hypertension**		
MIBG	9%	12%	21%	9%	3%		
Chemotherapy	27%	43%	74%	6%	6%		
	Leucopenia	**Neutropenia**	**Anaemia**	**Thrombocytopenia**	**Elevated LFTs**		
MIBG	32%	18%	74%	29%	6%		
Chemotherapy	91%	54%	71%	40%	17%		
	Hypocalcemia	**Hyponatremia**	**Hypokalemia**		**Hyper Bilirub.**		
MIBG	9%	12%	3%	3%			
Chemotherapy	6%	3%	9%	14%			

Table (42): Response to different lines of treatment and Survival:

						Impact on Resectability			Impact on Survival		
	CR	**PR**	**MR**	**PD**	**OR**	**P Value**	**Chi Square**	**Significance**	**P Value**	**Chi-square**	**Significance**
MIBG	6%	37%	0%	54%	44.10%	≤0.05	11.058653	**+Ve**	≤0.01	9.287280	**+Ve**
1st L Chemo	17%	37%	17%	23%	74%	≤0.025	8.295054	**+Ve**	≤0.001	19.07782	**+Ve**
2nd Line Chemo					53.30%	≤1	2.109375	-Ve	≤0.20	2.142857	-Ve
Surgery	Complete	Incomplete	Inoperable								
1st Interv.	35%	35%	23%								
2nd Look	19%	10%	13%								
Resectability &	**Clearance**								≤0.01	11.012815	**+Ve**
Overall response to Treatment											
	17%	37%	17%	23%	74%						
Overall Survival	**6 Mo.** (77%)		**12 Mo.** (60%)								

DISCUSSION

Discussion

History of the Procedure:

Virchow first described neuroblastoma in 1864, and, at that time, it was referred to as a glioma. In 1891, **Marchand** histologically linked neuroblastoma to sympathetic ganglia. More substantial evidence of the neural origins of neuroblastoma became apparent in 1914 when **Herxheimer** showed that fibrils of the tumor stained positively with special neural silver stains.

Further characterization of neuroblastoma was reported in 1927, when **Cushing and Wolbach** first described the transformation of malignant neuroblastoma into its benign counterpart, ganglioneuroma. **Everson and Cole** reported that this type of transformation rarely is observed in children older than 6 months. In 1957, **Mason** published a report of a child with neuroblastoma whose urine contained pressor amines. This discovery further contributed to the understanding of neuroblastoma and its possible sympathetic neural origin.

Spontaneous regression of microscopic clusters of neuroblastoma cells, called neuroblastoma in situ, was noted to occur quite commonly.

According to Beckwith and Perrin in 1963, regression occurs nearly 40 times more often than the actual number of clinically apparent neuroblastoma cases. **[Homsy YL et al; 1998]**

Epidemiology of Neuroblastoma :

Our Epidemiological review showed an increase of the male predominance among our patients with a ratio of 1:33 : 1 Male to Female . This is comparable to the international records which stated the existence of a modest difference in incidence rates by sex (boy: girl rate ratio = 1.2). **[Brodeur GM et al; 2006 & Gurney JG et al; 1995]**

The highest incidence rate, 55.2 per 1 million, occurs in children in the first year of life. Neuroblastoma is extremely rare in children older than 5 years of age. White children have a slightly higher incidence (25%) than black children **[Gurney JG et al; 1995].** Prior to screening, highest rates for neuroblastoma were reported in the United States (whites), Israel (Jews), New Zealand (Maori), and France (range, 11–14 per million); intermediate rates occurred in Japan, the United States (blacks), and the United Kingdom (range, 7–9 per million); and lowest rates were reported in India and China (range, 3–5 per million; Ref.). There has been a notable change in incidence rates in countries that have implemented screening. **[Stiller CA et al; 1992]**

Age at diagnosis remains the only other independent clinical prognostic factor. For all stages of disease beyond localized tumors, infants less than

1 year of age have significantly better disease-free survival rates than older children with equivalent stages of disease **[Breslow N et al; 1971 & Evans AE et al 1971]** Additional studies suggest that 1- to 2-year-old children with disseminated disease have a better outcome than children over 2 years of age **[Look AT et al; 1991]**

Clinical Presentation:

Our selected group of patients who were found suitable to be employed in this study had a different pattern of distribution: Only 9% were aged less than 1 year, majority 67 % were found five or less years old while 33 % were found more than five years old. The difference in distribution could be related to the lack of organized screening programs in comparison to the countries of the implemented screening, added to that the expected delay in diagnosis that could be related to the general lack of knowledge and education about the possible symptoms of presentation and the clinical picture of the disease among population.

Neuroblastoma has been called the great mimicker because of its myriad clinical presentations related to the site of the primary tumor, metastatic disease, and its metabolic tumor by-products. Sixty-five percent of primary neuroblastomas occur in the abdomen, with a majority of these occurring in the adrenal gland. As a result, most children present with abdominal complaints, such as fullness or distension **[Homsy YL et al; 1998]**.

Abdominal distention, weight loss, dyspnea and anorexia were the commonest modes of presentation. Approximately two thirds of patients with neuroblastoma have abdominal primaries. In these circumstances, patients can present with an asymptomatic abdominal mass that usually is discovered by the parents or a caregiver **[Brodeur GM et al; 1993]**, 75% of our patients were presented by abdominal distention, while 37% with dyspnea which could be explained on base of presence of the mass causing airway obstruction or chronic cough (In 5% of our patients) , leading to a chest radiograph **[Powell JE et l; 1998].**

Because more than 50% of patients present with advanced-stage disease, usually to the bone and bone marrow, common presentation includes bone pain and a limp (12% in our cohort). However, patients may also present with weight loss (45% in our study), Fatigue (20%), unexplained fever (15% in our study), irritability (and headache 5% in our study), and periorbital ecchymosis secondary to metastatic disease to the orbits. The presence of bone metastases can lead to pathologic fractures **[Brodeur GM et al; 1993]**.

Diagnostic Markers:

Most neuroblastomas produce catecholamines as metabolic by-products, which result in some of the most interesting presentations observed as Kerner-Morrison syndrome causing intractable diarrhea reported in 5% of our cases is a rare paraneoplastic symptom and is surprisingly associated with more differentiated tumors and a good prognosis. **[Nitschke R et al; 1988]** this diarrhea is secondary to vasoactive intestinal peptide (VIP) tumor secretion and can be result in hypovolemia, hypokalemia, and prostration. This syndrome, more commonly associated with ganglioneuroblastoma or ganglioneuroma, typically resolves with the complete removal of the tumor. **[Grosfeld JL et al; 1998]**.

On running further clinical examinations and investigations , other signs for the disease could be observed , 46% of patients had anemia while cyanosis, oedema, paresis and paralysis possibly caused by neuroblastomas invading through neural foramina and compress the spinal cord extradurally, also noted **[Jennings RW et al; 1993]** , Other signs including delayed milestone and hypertension were occasionally found.

Origin and migration pattern of neuroblasts during fetal development explains the multiple anatomic sites as during the fifth week of embryogenesis, primitive sympathetic neuroblasts migrate from the neural crest to the site where the adrenal anlage eventuates into the developing embryo. These neuroblasts migrate along the entire sympathetic chain; therefore, neuroblastoma can arise anywhere along the sympathetic nervous system. The name neuroblastoma is derived from the fact that the cells resemble primitive neuroblasts **[Beckwith JB et al; 1963]** and where these tumors occur; location of tumors appears to vary with age. Tumors can occur in the abdominal cavity (40% adrenal compared to 60% in our study , 25% paraspinal ganglia comparable to 18% in our study) or involve other sites (15% thoracic but only 6% in our records , 5% pelvic comparable to 6% in our study , 3% cervical tumors, 12% miscellaneous). Infants more frequently present with thoracic and cervical tumors, whereas older children more frequently have abdominal tumors. **[Brodeur GM et al; 1997]**.

More than 50% of patients presenting with neuroblastoma have metastatic disease. The fact that many other syndromes related to metastatic neuroblastoma also commonly occur in these patients is not surprising **[Brodeur GM et al; 1988]**.

Our study has shown different varieties regarding the secondary metastatic site of the disease, LNs had the highest share among all in a percentage of 51% followed by bone and bone marrow metastasis at percentages of 31 and 29 %, this is of a unique value in managing and treating neuroblastoma, Investigators at St. Jude Children's Research Hospital developed a clinical, surgical, and pathologic staging system that places major emphasis on the presence of regional lymph node metastases**[Hayes FA et al; 1983]**. From this system evolved the Pediatric Oncology Group (POG) staging system outlined below. The prognostic significance of the POG staging system has been documented in several studies. **[Castleberry RP et al; 1991]** The major differences between the CCG and POG systems are in the staging of patients with involved ipsilateral lymph nodes (stages I and II in CCG, stage C in POG), and in patients with tumors that cross the midline and who have negative nodes (POG stage A or B, CCG stage III).

It is also of value to realize that Regardless of the staging system used, a thorough evaluation for metastatic disease is important. The following investigations are recommended before therapy is initiated. **[Brodeur GM et al; 1993]**

1) Bone marrow should be assessed by bilateral posterior iliac crest marrow aspirates and trephine (core) bone marrow biopsies to exclude bone marrow involvement which was successful in confirming the bone marrow involvevment in 10 patients in our study and this biopsy to be

considered adequate, core biopsy specimens must contain at least 1 cm of marrow (excluding cartilage).

2) Bone should be assessed by MIBG (meta-iodobenzylguanidine) scan (applicable to all sites of disease) (which succeeded in detecting bone marrow disease in all of the 10 patients with bone marrow involvement)and by technetium 99 scan if the results of the MIBG scan are negative or unavailable. Plain radiographs of positive lesions are recommended.

3) Palpable lymph nodes should be clinically examined and histologically confirmed. Nonpalpable lymph nodes should be assessed by computerized tomography (CT) scan with three-dimensional (3D) measurements.

4) The abdomen and liver should be assessed by CT scan and/or magnetic resonance imaging (MRI). Ultrasound is considered suboptimal for accurate 3D measurements.

5) The chest should be examined by anteroposterior and lateral chest radiography. CT scans and/or MRI are necessary if the results are positive or if abdominal disease extends into the chest.

The gold standard for the diagnosis of neuroblastoma is examination of tumor tissue by histopathology and immunohistochemistry. Diagnostic tools for our cohort of patients followed The International Neuroblastoma

Staging System (INSS), which was initially developed in 1986 and subsequently revised in 1993 , **[Brodeur GM et al; 1993].**

According to INSS criteria, the diagnosis of NB can be made by either characteristic histolopathologic evaluation of tumor tissue i.e. 77% of our patients had tissue biopsy and 9% had FNAC .; or by the presence of tumor cells in a bone marrow aspirate/biopsy and elevated levels of urinary catecholamines 14% of our patients .

On evaluation of Biochemical markers , 94% of our patients had raised levels of VMA , which is of great value in performing diagnostic and screening programs . The first attempts to conduct mass screening through urinary testing occurred in Japan in the early 1970s. **[Sawada T et al; 1992]** Unfortunately, screening programs cannot be recommended as they have not led to a reduction in neuroblastoma mortality **[Murphy SB et al; 1991 & Woods WG et al; 1997].**

The diagnostic value of increased levels of urine or serum catecholamines or metabolites including dopamine, homovanillic acid (HVA), and/or vanillylmandelic acid (VMA) as the majority of neuroblastomas secrete catecholamines, and elevated levels of the metabolites VMA and HVA can be detected in urine, allowing for easy and relatively inexpensive screening assays . Urinary HVA and VMA have been assayed by a number of different techniques including the spot test, TLC, HPLC, GC-MS, and EIA **[Tuchman M et al; 1987 & Takeda T et al; 1997 & Nishi M et al; 1991 & Sawada T et al; 1988 & Yokomori K et al; 1989 & Sawada T et al; 1984 & Kerbi R et al; 1996 & Sevious JA et al; 1992]** but simpler by gas chromatography, thin layer chromatography, and/or high performance liquid chromatography and to be considered increased, levels must be greater than 3.0 SD above the mean per milligram creatinine for age, and at least two of these must be measured **[Brodeur GM et al; 1993] .**

The European Neuroblastoma Study Group has reported that 87% of stage III and IV tumors excrete elevated levels of HVA and/or VMA, compared to 64% of stage I and II tumors **[Pritchard J et ak; 1989]** . Tumors that do not excrete VMA/HVA (30–40% of low-stage tumors and 20% of high-stage tumors) will not be detected by current screening strategies.

And to evaluate the statistical significance of the high level of VMA in our cohort of patients, we evaluated survivals among those who had a high level of VMA; the distribution was insignificant and reflected the absence of a considerable effect of VMA level on prognosis. (Table 35)

Serum and tumor tissue of a patient with neuroblastoma contained an abnormal isoenzyme of lactate dehydrogenase (LDH; EC 1.1.1.27), which, on agarose gel electrophoresis, migrated between LDH-2 and LDH-3 with a mobility the same as that of the extra LDH isoenzyme found in normal human erythrocytes. On surgical removal of the tumor, the high total LDH activity (775 U/L) in the serum of the patient rapidly decreased to normal (70-220 U/L), and the abnormal LDH isoenzyme was no longer detected. The total LDH activity of the abnormal LDH isoenzyme per gram of hemoglobin in the tumor tissue was 26 times that of erythrocytes, suggesting that the abnormal isoenzyme originated mainly from the tumor cells themselves rather than the erythrocytes contained in the tumor tissue. This first report on the appearance of the abnormal LDH isoenzyme in a patient with neuroblastoma suggests that this abnormal LDH isoenzyme may have some significance as a marker enzyme for neurogenic tumors. **[Otsu N et al; 1985]**.

In our cohort of patient , high LDH level had a significant impact on prognosis and the p value reflecting impact on prognosis was less than or equal to 0.025 reflecting a poor significant distribution and even though the fact that some references included LDH level among the Prognostic factors in metastatic neuroblastoma **[Berthold F et al; 1992]** yet LDH alone is a very poor prognostic index in Neuroblastoma. The value of which may be more appreciated in combination with neuroblastoma cells detected by reverse transcriptase polymerase chain reaction (RT-PCR) for tyrosine hydroxylase (TH) mRNA when it was found that: TH mRNA in peripheral blood of children with neuroblastoma is alone a poor prognostic indictor, reflecting the propensity for dissemination via the bloodstream. When combined with a serum LDH > 1500 IU/L, this is the most powerful poor prognostic model at diagnosis for children > 1 year old with stage 4 disease. The detection of TH mRNA in peripheral blood from clinically disease-free children is related to increased risk of relapse and death **[Susan A et al; 2001].**

66% of our patients had elevated level of serum ferritine suggestive of poor outcome and required more effective therapy, while 34% with normal ferritin (63% of patients) expected to have a good outcome **[Hann HW et al; 1985]** yet on evaluation of the impact on prognosis in our patients , the statistical significance found to be negative dening a strong impact on survival (Table 37) ***Imashuku S. et all 1998***, denied the value of using Serum Ferritine as a as a sole indicator of tumor activity in neuroblastoma **[Imashuku S et al; 1988]**. Eventhough determination of the level of ferritin in serum at diagnosis is useful for selecting appropriate therapy for patients especially with Stage III neuroblastoma **[Hann HW et al; 1985]**.

Neorone Specific Enolase recorded among our patients expressed a significant impact on survival, a p value less than or equal to 0.05 was estimated. **[Simon T et all; 2003]** had a similar experience and concluded that "Sensitivity of all markers was higher for metastatic compared with local recurrence. NSE was the best, being able to detect 42% of the localised relapses, 77% of the combined local/metastatic relapses, and 69% of the metastatic recurrences. Relapse or progression in neuroblastoma cannot be detected reliably by monitoring tumour markers alone. Therefore, follow-up of neuroblastoma patients must include clinical assessment and imaging studies".

The adverse significance of elevated serum levels (when compared with the normal value for a particular age) of the markers ferritin **[Evans AE et al; 1987 & Hann HL et al;1985]** neuron-specific enolase **[Zeltzer PM et al; 1986 & Labenstein R et al; 1995]** and lactate dehydrogenase **[Shuster JJ et al; 1992 & Joshi W et al; 1993]** has been recognized for some years, their clinical use is currently waning because of the increasing interest in more specific molecular markers, histology, and INSS staging. Advances in molecular biology have shown that factors such as *N-myc* amplification **[Matthay KK et al; 1998 & Brodeur GM et al; 1984]** and deletion [**Martinsson T et al; 2001 & Rubie H et al; 1997]** correlate with a poor prognosis. Tumor cell ploidy is a powerful discriminating factor, but only in children under two years of age. Patients with aneuploid tumors usually do well, whereas those with diploid tumors are likely to fare badly **[Look AT et al; 1984 & Look AT et al; 1991 & Joshi W et al; 1993].**

Recently, the significance of the family of tyrosine kinase receptors for nerve growth factor and other neurotrophic factors has been recognized. mRNA expression of trk-A, trk-B, and trk-C, among others, can be quantified and correlated with outcome **[Nakagawara A et al; 1994 & 1997 & Yamashiro DJ et al; 1997]** trk-A and trk-C expression is more common in infants and low-stage patients, and is related to a favorable outcome. In contrast, trk-B expression is associated with *N-myc* amplification, and related to a poor outcome.

Management :

Radiolabelled MIBG has been used to target delivery of radiotherapy, and responses have been observed **[Matthay KK et al; 1998 & Garayenta A et al; 1999]**. Metaiodobenzylguanidine (MIBG) is a guanethidine derivative with specific affinity for neural crest tissues **[Wieland DM et al; 1980]** MIBG labeled with iodine-131 (^{131}I-MIBG) has been shown to be active against neuroblastoma, with one third to one half of patients with refractory or relapsed disease having some response **[Matthay KK et al; 1988 & Mastrangelo R et al; 1988 & Garayenta A et al; 1999]** Although ^{131}I-MIBG typically has been used as a single agent for patients with refractory or relapsed disease, several groups have used ^{131}I-MIBG combined with chemotherapy earlier in the course of disease **[Garayenta A et al; 1999 & Mastrangelo S et al; 2001 & Yanik GA et al; 2002].**

The response to MIBG Therapy varied, 6% of patients had complete response, while 37% experienced partial response, **[Howard M et al; 2004]** stated that early response to therapy is highly prognostic in NB. This is comparable to results published by **[Garaventa A et all; 1999]** which showed evidence of complete response in 3% and partial response in 30% of patients over 1 years old , while no response or progressive disease was detected in 67% of patients . 54% of our cohort showed evidence of progressive disease.

Among the complications recorded in our patients as a result of MIBG up-front treatment anaemia (74%), leucopenia (32%) and Thrombocytopenia (29%) of patients were recorded as a result of Hematologic toxicity comparable to results in 43 patients published by [**Dominique Valteau-Couanet et all; 2005 & Steven G. 2004]** concluded that the substantial hematotoxicity associated with high-dose ^{131}I-MIBG therapy, with severe thrombocytopenia an early and nearly universal finding. Bone marrow tumor at time of treatment was the most useful predictor of hematotoxicity, whereas whole-body radiation dose was the most useful predictor of failure to recover platelets after AHSCT (autologous hematopoietic stem-cell transplantation).

Many authors concluded that MIBG therapy at diagnosis is well tolerated, with objective response up to 70% [**Hoefnagel CA et al; 1994]** It`s toxicity is limited to minor haematologic side effects and patients generally recover spontaneously **[Troncone L et al; 1997]** with increased risk of pancytopenia among those with bone or BM metastasis **[Steven G et al; 2004].** Encouraging results have been reported with 131 I-MIBG used alone in patients resistant to conventional therapy and at diagnosis.

[Mastrangelo S et al; 1995] and new protocol to use 131I-MIBG therapy in newly diagnosed patients instead of combination chemotherapy prior to surgery has been raisin **[Troncone L et al; 1995]**.

Even in cases of advanced untreated, inoperable cases of neuroblastoma, 131 I-MIBG therapy combined with Cisplatin as a "radiosensitizer" was tried, A very good partial response was obtained and further surgery (of the primary NB) and multi-drug chemotherapy was then possible. In conclusion, 131 I-MIBG therapy at diagnosis appears to be effective, low toxic treatment of NB; when integrated with Cisplatin its efficacy seems to improve even more **[Hoefnagel CA et al; 1991]** MIBG is a promising novel radiotherapeutic agent for neuroblastoma **[He Y et al; 2004]** .

33 patients completed the initial four cycles of 1st line chemotherapy in the form of alternating cycles of OPEC / OJEC while only one patient died after the third cycle as a result of intracranial hemorrhage and coma.

The Objective Response to the initial four cycles of treatment was 74%, similar results were recorded by **[Sun XF et all; 2003]** in his study of efficacy of treatment for 30 children with neuroblastoma , the response in that study was 76.7% by chemotherapy alone with tolerated toxicity .

Complete response was achieved in 4(11%) patients and this improved to 6(17%) patients following completion of another 3 cycles , two of them had the complete response with no surgical intervention but following MIBG while 2 patients achieved the complete response following complementary surgical intervention to a partial response and completed another 3 cycles of chemotherapy before scheduling for a scheme of follow up, the remaining 2 patients who expressed the complete response following completion of the 7 cycles previously expressed partial response following the initial 4 cycles.

8 patients showed evidence of progressive disease and even though they were subjected to completion of another 3 cycles no obvious change in response was detected. Results are comparable to various studies which recorded reassuring figures **[Kushner BH et al; 1994 & Tweddle DA et al; 2001 & Rubie H et al; 2003].**

Literature review demonstrates various regimes of 1st line chemotherapy practiced in different centres, while the main stem of treatment protocol still contain Vinristine, cyclohosphamide, Cisplatin , and Etoposide , Sun **XF et all; 2003** used a similar protocol to ours , while **Rubie H et all; 2003** described a low-dose chemotherapy in infants with localised and unresectable neuroblastoma and concluded that primary low-dose chemotherapy without anthracyclines is efficient in about half of the infants presenting with an unresectable NB allowing excellent survival rates without jeopardising their long-term outcome even for nonresponding patients who received standard regimen. **Tang SQ et all; *2004*** and **Laprie A et all; *2004*** both used a very high dose chemotherapy in conjunction with autologous peripheral blood stem cell transplantation and 13-cis-retinoic acid , his conclusion was that this strategy might be a good option for patients with advance neuroblastoma. **Cheung NV et all; 1991**, concluded that maximal dose intensification of selective drugs over a short duration may improve the outcome of patients with poor-risk neuroblastoma.

We concluded that cases which express good response to initial 4 cycles will continue to respond properly for the completion of 7 cycles , and surgical intervention is best employed either the initial 4 cycles or following completion of the 7 cycles depending on the volume of residual during reassessment folloeing the 4^{th} cycle of 1^{st} line chemotherapy. While cases that don`t express any response or even show evidence of progression of the disease should switch to another line of treatment possibly via offering surgical exploration for possibility of debulking of the tumor as a preparatory stage for further adjuvant therapy.

One patient died following the third cycle of 1st line chemotherapy as a result of intractable intracranial hemorrhage and coma, **Packer RJ et al ; 1985** ; concluded that cerebrovascular accidents are a relatively frequent cause of acute neurologic compromise in children with cancer and that certain types of malignancies including neuroblastoma and their treatment predispose patients to this complication added to that the suppressive effect of chemotherapy on bone marrow, **Aronson MR et all; 1995** recorded a similar complication of the disease and concluded that Metastatic neuroblastoma should be included in the differential diagnosis of multiple hemorrhagic parenchymal brain lesions in the pediatric population.

Surgical Treatment :

The role of surgical intervention in the multimodality approach to Neuroblastoma is un debatable, and even though the fact that Improvement of treatment results for neuroblastoma which has been achieved during recent years is especially related to intensifying therapy for advanced disease and Surgery has not contributed very much to this progress **[Von Schweinitz D et al; 2002]** yet The surgical role remains significant in staging, diagnosis, and therapeutic management of different types of neuroblastoma **[Smith EI et al;1989]** and there is still controversy regarding the best surgical approach particularly for high-risk disease. The time of surgical intervention, extent of surgery to include primary and or secondary, radicality or resection and the immediate end result of the surgical intervention have always been topics for further exploration.

Some authors recommended early surgical intervention to debulk the tumour but **Sawaguchi S et all; 1989** denied that approach and advised that Initial surgery for reduction of the tumor burden has no advantages for the ultimate survival of the patients with advanced diseases which then became universal fact in all management protocols for Neuroblastoma.

Out of our 35 patients employed in this study, 31 (89%) patients had surgical intervention, 21(60%) of them had only one surgical exploration and resection while the remaining 10(29%) underwent a second look surgery and sometimes an attempt for further resection.

Further analysis of surgical intervention and intra-operative surgical techniques has shown that the 2 patients who showed evidence of complete response to initial MIBG therapy had a fairly straight forward surgical intervention with relative easy surgical technique and complete resection of the residual tumor.

On evaluation of the co-relation between the response to MIBG alone therapy and the surgical respectability, a p value less than or equal to 0.05 was estimated (Table 31) suggesting a significant impact of MIBG therapy on surgical technique.

And on implication of further lines of treatment it was observed that among the patients who expressed partial response to the initial MIBG therapy and were subjected to first line chemotherapy with evidence of partial response to the initial 4 cycles, the resection was easy, successful and complete in one patient, relatively successful with resection of the majority of the primary in 2 patients and the complete resection of the residual was successful following completion of another 3 cycles of 1st line chemotherapy while one patient found inoperable and the surgical attempt failed to resect the tumor at the first attempt and succeeded to resect the tumor incompletely in the second look surgery following completion of the remaining 3 cycles of chemotherapy . **Kaneko M et all**; **1997** proved that Systematic extensive surgery for advanced or metastatic neuroblastoma is no longer required if supplemented with intensive pre and postoperative chemotherapy.

Further analysis of the results while challenging the operative results against the response to the initial pre-surgical multi modality treatment , It has shown clearly that initial surgical intervention, was successful and complete in 14 out of 24 patients who had objective response to pre-surgical treatment while was successful and complete in 0 only out of 7 patients who expressed no response or progressive disease despite pre surgical element of multimodality treatment, a *p* is less than or equal to 0.025 **(Table 32-B).**

And on classifying patients into 2 groups, one group include those who expressed complete and partial response we and the other includes those who had minor or no response , the *p* value found less than or equal to 0.025. Suggesting a significant distribution. (Table 32 +1).

Sawaguchi S et all; 1989 had a similar experience, and concluded that the principle of the treatment for children more than 1 year of age with advanced neuroblastoma consists of intensive anticancer chemotherapy followed by delayed surgery for complete resection of the original tumor and the regional lymph nodes. Complete response of the remote metastases to the chemotherapy at surgery has been proved to be a clue for cure of the diseases. Initial surgery for reduction of the tumor burden has no advantages for the ultimate survival of the patients with advanced diseases.

2nd line chemotherapy expressed a non significant impact on surgical respectability (p is less than or equal to 1).

We concluded that preoperative response to MIBG therapy and 1st line chemotherapy plays a great role in determining the course of surgical maneuver and those patients who express objective response are more likely to have a successful complete surgical intervention while 2nd line chemotherapy expressed no valuable effect on intraoperative surgical technique.

While following the 2nd look surgery , 7 patients had completion of excision and 2 had incomplete excision among those with objective response, out of those who expressed progressive disease the second look surgery was successful in complete removal of the tumour in 2 and incomplete removal of tumour in 1, A *p* is less than or equal to 1 suggesting a non significant effect of the initial response to pre-operative treatment on 2nd Look Surgery (Table (33 +1), **O'Neill JA et all; 1985** concluded that Patients who had more complete surgical resection had better disease-free survival and even more recently , **Martinez Ibanez V et all;2000** addressed that The total resection of the tumor keeps being essential for a more favorable prognostic.

And in a trial to evaluate the role of second look surgery among those who didn't have the tumor completely resected at the first surgical intervention, 6 patients had incomplete resection at the 1st operation, and 6 found inoperable but after the second look surgery 9 had complete resection and 1 incomplete. Table expresses the value of the 2nd Look surgery and explains the significant distribution suggesting the great value of 2nd Look surgery in offering the patient a complete resection of the tumor, **Grosfeld JL et al; 1984** expressed another value of 2nd Look surgery when demonstrated the value of 2nd Look Surgery in assessing the effectiveness of treatment and for sampling of retroperitoneal lymph nodes as a prognostic indicator.

7 of our patients had localized radiation to residuals following incomplete surgical resections, **Simon T et all; 2006** proved the value of External Beam Radiation Therapy that appeared effective in high-intensive treatment of stage 4 neuroblastoma. It seems to compensate the disadvantage of incomplete response to induction chemotherapy.

In an over all evaluation for the treatment outcome , the overall survival after 6 month of treatment was 77% and after 12 months 60%, our research didn`t include 5 years survival results, in a similar Chinese experience **Sun XF et all; 2003** reported a 2-year overall survival rate of 47.8% for all patients; 100% for Stage II/IVS, 34% for stage III, 22% for stage IV, respectively but **Spix C, et all; 2006** reported better figures among European children who were diagnosed with Neuroblastoma as he reported an Overall 5-year survival of 59% (1993-1997) but also mentioned marked improvement in comparative with previous values reported (1978-1982) which were 37% , Differences in outcome is strongly related to screening programs , early detection, family awareness and level of education as well as to the treatment protocols and medical resources.

Evaluation of prognostic indices in our patients have shown that survival in relation to age distribution was insignificant, P value of less than or equal to 1 was estimated, International reports have discussed an approved better prognosis of the disease in younger age group , less than 1 years old, **Losty P et all; 1993** , considered age at presentation as one of two major factors affecting prognosis, as he reported that patients who presented < 1 years of age achieved 80% 2 years Disease Free Survival DFS , > 1 year and < 2 years, 33%, and > 2 years 13%. We could not report similar results as possibly due to the low number of our patients who were less than 1 Year old (3 Patients) and despite the fact that 2 survived yet the figures are still too small to get a conclusion from . It is also valuavale to address the current changes in the "cut-off for age" changes , **London WB et all; 2005** suggested following separate cooperative group analyses performed by German and Italian groups and two analyses by the Children's Oncology Group (North America, Australia, New Zealand, Switzerland, Netherlands) that in general, the results are in agreement regarding the prognostic contribution of age.

There is strong evidence to support an increase in the age cut-off to a value in the range of 15-18 months based on the results from the German analysis and two COG analyses. However, Italian results in INSS stage 4 patients show that outcome in patients 12-17 months is not better than that of older patients

The Stage of the disease was a prominent prognostic indicator for survival, **Martinez Ibanez V; et all 2000,** has pointed to the fact that one with biggest prognostic efficacy is the stage INSS of the disease at the time of presentation , patients who presented at stage 2 of the disease had a far significant survival distribution than those who presented at stage 3 and 4 of the disease, The p value recorded was less than or equal to 0.025 suggesting a significant impact for the stage of the disease on survival and prognosis.

While the primary site of the disease didn`t have a direct strong impact on prognosis (P is less than or equal to 1), it is still related to the treatment outcome, as many authors **[Adkins ES et al; 2004 & Chamberlaine RS et al; 1995 & Koh CC et al; 2005]** have reported the value of complete resection of the tumour on prognosis which in turn is affected by the primary tumour site.

The initial objective responses to first lines of treatment have shown a great impact on the overall survival, P value of less than or equal to 0.01 was reported on evaluation of the objective response to initial MIBG therapy, and a P value less than or equal to 0.001 was reported in estimating the impact of objective response to first line chemotherapy on survival.

On the other hand, the response to 2nd line chemotherapy on the overall all survival was limited and expressed a non significant relation.
Part of this effect can be related to direct effect on the Neuroblastoma itself and another part could be related also to the effect on surgical intervention rendering the non respectable tumours more amenable to complete surgical resection which in turn plays a great role on treatment outcome as discussed.

And in an evaluation of the impact of the overall tumour clearance on survival , **Tokiwa K et all; 2000** addressed that Complete excision of the primary tumor and retroperitoneal lymphadenectomy provides excellent locoregional control for patients with abdominal neuroblastoma . This is comparable to our results which reflected that the overall clearance of the tumour had a significant impact on survival, A significant p value was estimated and similar results were achieved by **Lange R et all; 1996** concluded that Complete tumor resection produced a better survival rate. If there is any doubt in the primary possibility of complete tumor resection a reduction of the tumor mass can be achieved by chemotherapy. This allows radical surgery can be achieved in significantly more cases.

SUMMARY

Neuroblastoma is almost exclusively a disease of children. It is the third most common childhood cancer after leukaemia and brain tumours, and the most common solid extra-cranial tumour in children. More than 600 cases are diagnosed in the United States each year and about 100 in UK which accounts for approximately 15 percent of all paediatric cancer fatalities; The incidence of Neuroblastoma is greater among white than black infants (ratio of 1.7 and 1.9 to 1 for males and females, respectively), but little if any racial difference is apparent among older children

In this study the impact of up-front 131 I-MIBG and preoperative chemotherapy on intra-operative surgical technique was accurately monitored. Recording of intra-operative data at different stages of surgical intervention including accessibility and respectability of the tumour, success in achieving a complete resection and frequency of presence of visible residuals after resection, intra-operative and immediate postoperative complications, disease free survival and prognosis was completed. Finally data were analysed to anticipate impact and best time for planning surgical resection.

Out of all Neuroblastoma patients presented to our institute (2001 – 2006), 35 patients fulfilled the selection criteria of having no previous treatment received, primary tumour site of adrenal, non adrenal abdominal, thoracic, abdomin-othoracic, of any stage rather than stage I and finally eligible and fit to receive preoperative 131 I-MIBG up-front therapy, preoperative chemotherapy and surgical intervention at the proper planned time.

Response to treatment was recorded and classified, defines different responses to treatment as classified; many investigators adopted the expression of objective response to denote a group of responders having a satisfactory treatment outcome in the form of CR to PR**.**

Follow up was through complete reassessment for patients at the end of their treatment and during the scheduled follow up period (24 – 60 months) , CT/MRI for the sites of previously known lesions and 1311-MIBG-scan were planned every 3 months during the first year and then every 6 months.

Statistical Package for social sciences (SPSS) used to compute results. Mean and standard deviation of the mean were used for describing quantitative data. Frequency and percentage were used to describe qualitative data. Kaplan-Meier Survival tables were used for survival analysis and Log Rank test for comparing survival data.

Epidemiological review showed an increase of the male predominance with a ratio of 1:33:1 Male to Female, literature records stated the existence of a modest difference in incidence rates by sex (boy : girl rate ratio = 1.2). Age distribution expressed a different pattern: only 9% were less than 1 year, majority (67 %) were found five or less years old while 33 % were found more than five years old. Evaluation of age as a prognostic index has shown that impact on survival is insignificant.

Primary sites of tumour varied greatly, this included abdominal cavity in 60%, 18% in paraspinal ganglia or involved other sites (6% thoracic, 6% pelvic, 3% cervical and 7% miscellaneous).
75% of patients were presented by abdominal distension, while 37% with dyspnoea that could be explained on base of presence of a mass causing airway obstruction or chronic cough (reported in 5%) , leading to a chest radiograph. Because more than 50% of patients present with advanced-stage disease, usually to the bone and bone marrow, common presentation symptoms included bone pain and a limp (12% in this cohort), the presence of bone metastases can lead to pathologic fractures . However, patients may also present with weight loss (45%), fatigue (20%), unexplained fever (15%), irritability and headache (5%), other symptoms recorded in literature include periorbital ecchymosis secondary to metastatic disease to the orbits.

On further clinical examinations and investigations, other signs could be observed, 46% of patients had anaemia while cyanosis, oedema, delayed milestone, hypertension, paresis and paralysis caused by tumour invading through neural foramina and compressing the spinal cord extradurally were reported by some authors.

Our study has shown different secondary metastatic sites of the disease , LNs had the highest share among all in a percentage of 51% followed by bone and bone marrow metastasis at percentages of 31% and 29 %, this is of a unique value in managing and treating neuroblastoma as presence of metastasis should be taken in consideration on planning treatment protocols due to their impact on prognosis

Diagnostic tools for this cohort of patients followed the International Neuroblastoma Staging System (INSS) by either characteristic histolopathologic evaluation of tumour tissue through tissue biopsy (77%), FNAC in 9%; or by the presence of tumour cells in a bone marrow aspirate/biopsy and elevated levels of urinary catecholamines in 14% of patients.

Eventhough ferritin level in serum at diagnosis is useful for selecting appropriate therapy especially in Stage III of the disease we did not find it useful in anticipating prognosis. 66% of patients had elevated level of serum Ferritine suggestive of poor outcome and reflecting the possible requirement of a more aggressive therapy, while 34% had normal levels expected to have a good outcome yet on real evaluation of the impact on prognosis, the statistical significance found to be negative denying any impact on survival. Other authors as well denied the value of using Serum Ferritine as a sole indicator of tumour activity in neuroblastoma While Neorone Specific Enolase recorded among our patients expressed a significant impact on survival ($p \leq 0.05$) and found useful to detect disease relapse and metastatic recurrence.

On review of the treatment results, encouraging results have been reported with 131-IMIBG used alone in patients resistant to conventional therapy and at diagnosis and new protocol to use 131I-MIBG therapy in newly diagnosed patients instead of combination chemotherapy prior to surgery has been raisin. We have experienced a complete response to MIBG therapy in 2 patients (2.71%) and partial response in(37.14%), these patients had a fairly straight forward surgical intervention with relative easy surgical technique and complete resection of the residual tumour, and on evaluation of the impact of this objective response on surgical resectability, a ($p \leq 0.025$) was estimated suggesting a significant impact of MIBG therapy response on surgical technique.

Among the complications recorded in our patients as a result of MIBG up-front treatment anaemia(74%), leucopenia(32%) and Thrombocytopenia(29%) were recorded as a result of hematologic toxicity suggesting that substantial hematotoxicity associated with high-dose ^{131}I-MIBG therapy, with severe thrombocytopenia is an early and nearly universal finding. Bone marrow tumour at time of treatment was the most useful predictor of hematotoxicity.

In our study 33 patients completed the initial four cycles of 1st line chemotherapy in the form of alternating cycles of OPEC / OJEC while only one patient died after the third cycle as a result of intracranial haemorrhage and coma. The Objective Response was 74% with tolerable toxicity and their surgical resection was relatively easy, successful and complete in the majority of cases who expressed objective response to treatment. Authors demonstrated the efficacy of that treatment recorded reassuring figures **.**

While further analysis showed that cases which express good response to initial 4 cycles will continue to respond properly to the completion of 7 cycles, and surgical intervention is best employed either following the initial 4 cycles or better following completion of the 7 cycles depending on the volume of residual during reassessment following the 4th cycle of 1st line chemotherapy as statistical analysis of intra-operative data has shown maximum success in completion of resection of the primary among those who had their planned surgical interventions following completion of 7 cycles of 1st line Chemotherapy while cases that express minor response or even show evidence of progression of the disease should switch to another line of treatment possibly via offering early surgical exploration for possibility of debulking of the tumor to allow better response to further adjuvant therapy.

The role of surgical intervention in the multimodality approach to neuroblastoma is undebatable, however there is still much controversy regarding the best surgical approach particularly for high-risk disease. The time of surgical intervention, extent of surgery to include primary and or secondary tumour sites, radicality and outcome of resection are yet still to be explores.

Further analysis of our results challenging the operative results against response to initial pre-surgical multi-modality treatment has shown clearly that initial surgical intervention, was successful and complete in 14 out of 24 patients who had objective response to pre-surgical treatment while was neither successful nor complete in all patients who expressed minor response or progressive disease despite pre-surgical element of multimodality treatment ($p \leq 0.025$) suggesting a significant correlation. On the other hand 2nd line chemotherapy expressed a non significant impact on surgical resectability, i.e. $p \leq 1$.

Though Second Look surgery implemented a great impact and had a significant role ($p<0.01$) in achieving complete clearance for those who had incomplete resection at the initial session, there was no significant impact of the initial response to pre operative treatment ($p \leq 1$) on results of 2nd Look Surgery. Some authors used 2nd look surgery for assessing the effectiveness of treatment and for sampling of retroperitoneal lymph nodes as a prognostic indicator However this value is of less important now due to the prominent progress in radiological techniques and investigations.

7 of our patients had localized radiation to residuals following incomplete surgical resections, The value of External beam radiation therapy that appeared effective in high-intensive treatment of stage 4 neuroblastoma has been recorded, it seems to compensate the disadvantage of incomplete response to induction chemotherapy

In an over all evaluation for the treatment outcome, the overall survival after 6 month of treatment was 77% and after 12 months 60%, 2 years overall survival was 54%.

In addition to the previously discussed impact of biochemical levels as prognostic factors , we experienced that disease Stage at time of presentation was a prominent prognostic indicator for survival, patients who presented at stage 2 of the disease had a far better survival than those who presented at stage 3 and 4 of the disease, ($p \leq 0.025$), this is confirmed by other authors who have pointed to the fact that one with biggest prognostic efficacy is the stage of the disease at the time of presentation , suggesting a significant impact for the stage of the disease on survival and prognosis.
And though primary site of the disease didn't have a direct impact on prognosis ($P \leq 1$) , it is still affects treatment outcome as many authors have reported the value of complete resection of the tumour on prognosis which in turn is affected by the primary tumour site

Evaluation of the impact of the overall tumour clearance on survival, a significant impact was calculated, Complete resection of the primary tumour and retroperitoneal lymphadenectomy provides excellent locoregional control for patients with abdominal neuroblastoma and produces a better survival rate. If there is any doubt in the primary possibility of complete tumour resection a reduction of the tumour mass can be achieved by chemotherapy. This allows radical surgery achievable in significantly more cases. _On the other hand, the response to 2nd line chemotherapy on the overall all survival was limited and expressed a non significant relation.

Finally, another important factor that has played a great role in providing our patients with a better survival was the level of family awareness and health education, children of parents who had a reasonable level of education had a better chance of having a better follow up, more close contact and early hospital admission and treatment on suspecting complication by parents during the follow up period. Teaching parents about the nature of the disease, symptoms and signs and possible complications is a cornerstone in fighting the disease.

CONCLUSION

Conclusion

We have concluded that:

- Objective use of 131 I-MIBG upfront therapy and completion of 7 cycles of Chemotherapy provide the optimum preparation for planned surgical clearance and of great impact in improving surgical clearance and hence survival.

- Early surgical intervention should only be implicated on those who express disease progression despite adjuvant therapy and should aim only at tumour debulking rather than complete surgical clearance.

- Factors Carrying important Prognostic Values:
  - Disease stage
  - Initial response to adjuvant treatment,
  - LDH Levels
  - NSE levels.

- Parent's education and raising awareness of the nature of the disease and possible complications during treatment forms a cornerstone in planning management and provides early intervention and improved survival.

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