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Chemotherapy and other treatment modalities in children with Neuroblastoma

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Abstract:-

Neuroblastoma is the second most common solid tumor in the first decade of life. A retrospective study reviewed (39) children treated for N.B. at Al-Mansour Teaching Hospital for children from Jan. 1st 2001 to Dec. 31st 2006, the clinical data were analyzed. Thirty nine Patients were included (23) males (59%) and (16) females (41%) , the median age at diagnosis was (48) months .The abdomen was the site of initial tumor in 31(79.4%) of patients , hypertension is found in 6 out of eleven cases (54.5%) and hepatomegaly is found in 53.8% of cases . Anemia was recorded in 26(68.4%) of patients .Stage IV was the predominant clinico-pathological stage .The median survival was 13.5 months (range 1 month – 45 months). There was significant association between the stage of the disease and event free survival. There was no statistically significant association between the age at diagnosis and the outcome because about 15 cases (38%) of the patients were lost to follow-up .The study recommends the use of the new method for early diagnosis and treatment of the disease like the use of autologous bone marrow transplant and the use of antibodies directed against the tumor cells.

العقاقير المضادة للسرطان مع طرق علاجية اخرى عند الاطفال المصابين بسرطان العقد العصبية

المستخلص:-

دراسة استرجاعية أجريت على 39 طفل مصاب بسرطان العقد العصبية تمت معالجتهم في مستشفى المنصور التعليمي خلال الفترة من الأول من كانون الثاني لسنة 2001 إلى الحادي و الثلاثين من كانون الأول لسنة 2006.. عدد الذكور كان 23 (59%) و عدد الإناث كان 16 (41%) و قد كان معدل العمر وقت التشخيص 48 شهرا . كانت البطن هي المكان الأكثر شيوعا عند التشخيص الأولي للمرض 31 حالة (79.4%) كما وجد أن ارتفاع ضغط الدم و تضخم الكبد موجودين في 54.5% و 53.8% على التوالي. فقر الدم وجد في 26 حالة (68.4%) . كانت المرحلة الرابعة من المرض هي الأكثر شيوعا بين المرضى.معدل البقاء للمرضى أحياء كان 13.5 شهر (بمعدل 1-45 شهر) . وجدت الدراسة أن هناك علاقة كبيرة بين معدل المرض و البقاء أحياء. فيما لم تجد الدراسة أن هناك أي علاقة بين وقت تشخيص المرض و مصير المرض لان 15 حالة (38%) من المرضى قد فقد الاتصال بهم . توصي الدراسة باستخدام الطرق الحديثة في التشخيص المبكر للمرض و في العلاج مثل زرع نخاع العظم و استخدام المضادات الموجهة ضد الخلية السرطانية.

Introduction:-

Neuroblastoma (N.B.) is the most common malignant tumor in infancy and is second only to brain tumors as the type of solid malignancy seen during first decade of life [1].

Pathology: -

N.B. originates from neural crest cells that normally give rise to the adrenal medulla and the sympathetic ganglia [2]. These cells called sympathogonia, are pluripotent and may develop into ganglion cells, pheochromocytes, or neurofibrous tissue. Tumors derived from this tissue reflect the different stages of maturation or differentiation of neural crest cells [1].The tumor usually extend to the surrounding tissue by local invasion and to the regional lymphnode via lymphatics. Hematogenous spread to the bone marrow, skeleton, and the liver is frequent. [3]

Clinical manifestations:

Common presentation of N.B. include a hard painless mass in the neck a localized Intrathoracic mass found accidentally on chest radiographorlarge palpable mass in the flanks or abdomen which may represent an enlarging primary adrenal or retroperitoneal tumor or hepatomegaly secondary to liver involvement. Metastasis to orbit may present with proptosis. The clinical picture may reflect tumor associated metabolic disturbances like diarrhea and acute cerebella encephalopathy. [4]Physical examination may reveal lymph node enlargement or an abdominal or flank mass. Raccon eyes or scalp masses may be present. [3]

Diagnosis:

The diagnosis of N.B. is confirmed by tissue biopsy. Bone marrow aspirate or biopsy must be done before any surgical procedure is done because o the possibility of bone marrow metastasis. The definitive diagnosis is made by histopathological studies of tumor tissue or documented B.M. involvement plus increased serum and urine catecholamine's. [5]

Staging system:

Several staging system available for N.B. the Pediatric Oncology Group (POG) is the most widely used. POG systems divide N.B. into 5 groups:

Stage I: grossly resected tumor.

Stage II: localized unrespectable tumor.

Stage III: metastasis to the non contagious intracavitary lymph nodes.

Age IV: metastasis beyond lymph node.

Stage IVS: infants with small adrenal tumors with metastasis limited to the skin, liver or bone marrow. [6]

Treatment:

There are three main lines of treatments, surgery, chemotherapy and radiotherapy. [3] For a localized tumor, complete surgical resection is curative .Unfortunately 70% have restively advanced disease at diagnosis. [6]Chemotherapy is the treatment of choice for unresecttable or metastatic disease including combination of Cyclophosphamide and daunurubicin. About 20-25% of children with disseminated disease are alive and disease free at 5years post diagnosis. [6]Most neuroblastoma is radiosensitive. Radiotherapy is used for local control in addition to systemic chemotherapy or for local palliative therapy. [6]

Experimental approach includes very intensive chemotherapy with or without B.M. transplant, the use of radioactive MIBG or monoclonal antibodies directed against neuroblastoma cells. [3]

Although the N.B. was first described more than a century ago, it remains the most challenging childhood cancer to the pediatric oncologist because of its unusual and unpredictable biologic behavior and its resistance to therapy .[1]

Aim: To study the different treatment modalities used in the N.B. Patients.

Objectives:

To study the clinicopathological features of the disease and its distribution according to the age and sex and to assess the stage of the disease at presentation and its relation to the survival rate of the affected patients.

Patients and Methods:-

A retrospective study reviewed (39) children treated for N.B. at Al-Mansour Teaching Hospital for children from Jan. 1st 2001 to Dec. 31st 2006, Information regarding (age , sex , clinical presentation , investigation , staging , histopathological typing , treatment modalities and outcome) were recorded .

Follow-up and outcome of treatment were taken from the records of the consultation clinic where they have been followed-up.

The staging system used was that of the Evans staging system [3].

The diagnosis was established by the following Procedures:

-Histopathological review of specimens taken by surgical exploration (complete resection or biopsy) in (15) cases.

-Fine needle aspirate (FNA) cytological examination in (12) cases only.

-B.M. aspirate in (7) cases, B.M. biopsy in (1) case and both B.M. aspirate and biopsy positive at the same time in (4) cases only.

Treatment schedules: [1, 3]

Patients with neuroblastoma were treated by a special chemotherapy schedule for neuroblastoma either ENSG-OPEC protocol, favorable risk (stage II and IVS) or high risk group (stage III and IV).

1. The ENSG-OPEC protocol (figure 1):

It is the most commonly used protocol for the treatment of patients with neuroblastoma specially the high risk group. It includes the use of Vincristine 1.5 mg / m^2 IV with Cyclophosphamide 600 mg/ m^2 IV. Prehydration 500 cc/ m^2 (0.9normal saline + 20 mmol/ m^2 + Kcl over 3 hours). Cis platinum 80 mg/ m^2 in 240 cc normal saline over 24 hours followed by hydration 3 liter / m^2 /day (0.5 normal saline+ 2.5% glucose water)followed by continuous hydration 3 liter / m^2 /day (0.5 normal saline+ 2.5% glucose water). The protocol will end by the use of VP-16 200 mg/ m^2 normal saline over 4 hours. The course repeated every 3 weeks up to 10 courses.

2. Favorable risk neuroblastoma schedule (figure 2):

This schedule include the treatment with doxorubicin 30 mg/m^2 IV with Cyclophosphamide 600 mg/ m^2 IV infusion in 100 ml 5% glucose water over 30-60 minutes every 3 weeks for five courses. Each 3 weeks the patient evaluated for: complete blood picture, lactate dehydrogenase level, and liver function test and urine analysis.

At the end of the coarse tumor evaluation id done repeating the imaging studies, bone marrow aspirate and biopsy.

3. High risk neuroblastoma (figure 3):

This schedule include the use of cisplatinum 100 mg / m^2 IV with VP-16 150 mg/ m^2 IV every 3 weeks with adding Cyclophosphamide 1.2 gm/ m^2 IV and Adriamycin 40 mg/ m^2 every 6 weeks. The duration of the course for 15 weeks.

A tumor evaluation is done at the 9th week and after the complete of the course which includes repeating the imaging study and bone marrow aspirate and biopsy.

The follow-up was scheduled every (2) months for the first (6) months of treatment, and (6) monthly thereafter for (5) years included complete physical examination, full blood count, chest X-ray and abdominal ultrasound. [1]

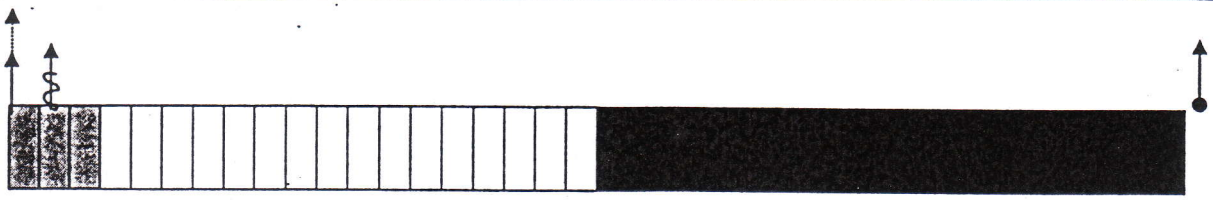


Figure (1): ENSG-OPEC Protocol for Treatments of Neuroblastoma

Vincristine 1.5mg/m^2 I.V.
Cyclophosphamide 600 mg / m^2 I.V.

Prehydration 500 cc / m^2 (0.9 N.S. + 20 mmol / m^2 + Kcl over 3 hours)

Cis-platinum 80 mg / m^2 in 240 cc N.S. over 24 hours

Hydration 3 liters / m^2 / day (0.5 N.S. / 2.5% G.W.)

Continue hydration 3 liters / m^2 / day (0.5 N.S. / 2.5% G.W.)

VP – 16 :- 200 mg / m^2 in 500 cc /m^2 N.S. over 4 hours

N.B.:- The course is to be repeated every 3 weeks up-to 10 courses

Name: - *Age: -* *SA. :-*

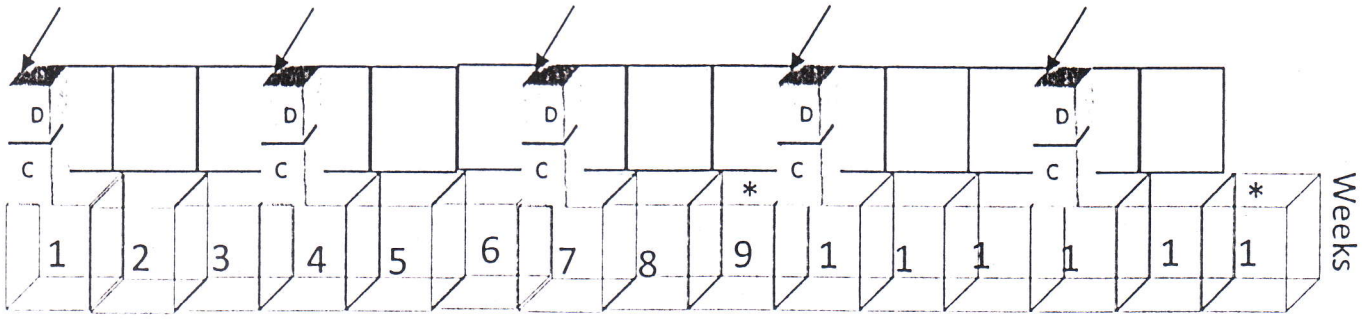
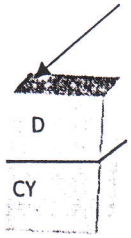


Figure (2): Favorable Risk NEUROBLASTOMA



C.B.C., LDH, ALT, TSB, Urinary analysis.
Doxorubicin 30mg/m^2 I.V.
Cyclophosphamide 600mg/m^2 I.V. infusion in 100ml 5% G.W. over 30-60 minutes.

* Tumor Evaluation: - repeat imaging studies showing disease at diagnosis, and BMA/B, if positive at diagnosis. Repeat echo – cardiograph.

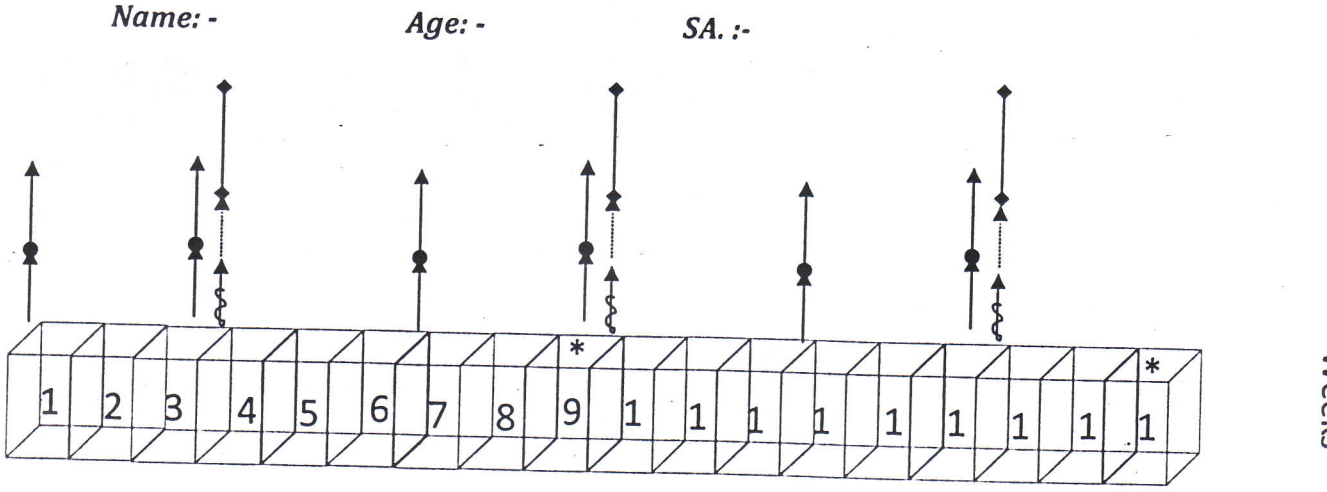


Figure (3): High Risk NEUROBLASTOMA

Cis-platinum 100mg/m^2 I.V.

VP-16 150mg/m^2 I.V. daily for 3 days

Cyclophosphamide 1.2gm/m^2 I.V.

Adriamycin 40mg/m^2 I.V.

*Tumor evaluation: - repeat imaging studies showing disease at diagnosis & BMA & B. , if positive at diagnosis . Repeat echo-cardiograph.

Results:-

A total of (39) case of N.B. was reviewed.

Table (1): shows the age and the sex distribution of the study cases. It is clearly shown that most of the cases are males (23 patients) and most of the patients are at the 1-5 years age group, 23 patients (58.98%).

Table (2): the clinical presentation of the cases which shows that fever was the most common form of presentation (90.6%). On examination, 31.2% of patients have weight less than the 3rd percentile; hypertension was present only in 54.45% of the study cases. Neurological signs were present only in 4 cases only (10.25%).

The abdomen was the initial site of the tumor in 31 cases (79.48%). The orbit was the most common site for metastasis, 11 cases (28.2%).

Table (3): shows the results of investigations available at the time of presentation of the study cases. Anemia was present in 26 cases (68.42%). abdominal ultrasound was abnormal in 30 cases (88.23%). Skeletal survey was positive only in 17 cases (65.38%).

Table (4) shows the histopathological studies done on the study cases. Bone marrow was positive in 15 cases (44.12%) while the bone marrow biopsy was positive in 8 cases only (32%).

Table (5): shows the proportion of the staging system in the current study. It is clearly shown that most of the patients are presented at the stage IV, 22 cases (59.45%).

Table (6): shows the treatment modalities used at the current study. Chemotherapy was used in 35 cases (89.74%), surgery in 14 cases (35.89%) and radiotherapy in 1 case (2.56%).

Table (7): shows the response to treatment and outcome of disease in our study cases. Most of the patients died 16 cases (41%).

Table (8) shows the relation between the age at diagnosis and the survival. It is clearly shown that there is no relation between the age at diagnosis and the survival.

Table (9) shows the relation between the stage of the disease and the survival. There is significant association between the stage of the disease and the survival.

Table 1: Age and Sex distribution of the study cases

Age (years)	Males	Females	M : F	Total	%
< 1 year	2	4	0.5 : 1	6	15.38
1-5 years	15	8	1.8 : 1	23	58.98
> 5 years	6	4	1.5 : 1	10	25.64
Total	23	16	1.4 : 1	39	100

Table 2: Clinical presentation of the study cases

	No. of patients	%
Clinical presentation		
Fever	29/32	90.6
Pallor	25/32	78.1
Weight loss	19/32	59.4
Diarrhea	1	2.56
Clinical examination		
Weight < 3rd centile	10/32	31.2
Hypertension	6/11	54.54
LAP	11	28.20
Hepatomegaly	21	53.85
Neurological signs	4	10.25
Site of initial tumor		
Abdomen	31	79.48
Intrathoracic	6	15.38
Neck	1	2.56
Eyes	1	2.56
Evidence of metastasis		
Orbit	11	28.2
Bone	9	23.1
CNS	7	17.95
Para spinal	3	7.69
Skin nodule	3	7.69

Table 3: The results of investigations available at time of presentation of the study cases:

Investigation	No. of cases	Results (%)
Complete blood count	38	Anemia 26 (68.42) platelet count : - normal 34 (89.5) - increased 2 (5.26) - decreased 2 (5.26)
Abdominal ultrasound	34	Abnormal (suprarenal mass, central abdominal mass, Para-aortic LN or hepatic metastasis). 30 (88.23).
Skeletal survey	26	Positive 17 (65.38)
Chest X-ray	29	Abnormal (Mediastinal mass or soft tissue mass) . 10 (34.48).
IVP	6	Positive (suprarenal mass). 6 (100%)

Table 4: Histopathological studies done on the study cases

Histopathological exam.	No. of cases	Results (%)
B.M. aspirate	34	Positive 15 (44.12)
B.M. biopsy	25	Positive 8 (32)
Biopsy from a mass	15	Positive 15 (100)
FNA	14	Positive 12 (85.71)
Pleural fluid for cytology	1	Positive 1 (100)

Table 5: The proportion of staging system in the current study

Stage	No.	%
II	2	5.40
III	10	27.02
IV	22	59.45
IVS	3	8.1
Undetermined (loss of records)	2	5.40

Table 6: Treatment modalities

Treatment modality	No. of patients	%
Chemotherapy	**35**	**89.74**
ENSG-OPEC	22	62.85
High risk protocol	10	28.57
Favorable risk protocol	3	8.57
Surgery	**14**	**35.89**
Before presentation	12	30.76
After presentation	2	5.12
Radiotherapy	**1**	2.56
No treatment	**3**	**7.69**
Referred	**1**	**2.56**

Table 7: The response to treatment and outcome in our study cases:

Response treatment	No. of patients	%
Died	16	41
Lost to follow-up	15	38.5
Free of disease	6	15.38
Partial response	1	2.5
Referred to other center	1	2.5

The mean age of survival in our study is 18.5 months and the median is 13.5 months

Table 8: The relation between the age at diagnosis and survival in our study cases :

Age	No. of patients	Survival	Dead	Lost to follow-up	Partial response	Referred
< 1year	6	1 (16.6)	1 (16.6)	4 (66.6)	–	–
1-5 years	23	5(21.8)	8(34.8)	9(39.1)	–	1(4.3)
>5 years	10	–	7(70)	2(20)	1(10)	–
Total	**39**	**6(15.3)**	**16(4.1)**	**15(38.5)**	**1(2.56)**	**1(2.56)**

P value >0.5. There is no statistical significance between the age at diagnosis and the survival .

Table 9: Relationship between stage of disease and survival in the study cases

Stage	No. of patient	Dead	Survival	Lost to follow-up	Partial response	Referred
II	2	-	2 (100)	-	-	-
III	10	-	3 (30)	5 (50)	1 (10)	1 (10)
IV	22	15 (68)	1 (4.6)	6 (27.3)	-	-
IV_S	3	-	-	3 (100)	-	-

P value < 0.035 there is significant association between the stage of the disease and the survival.

Discussion:-

Neuroblastoma is one of the most common solid tumors in children with secretory and neurological manifestations. It originates from neural crest cells that normally give rise to the adrenal medulla and the sympathetic ganglia [2].

The median age at the onset of diagnosis was (48) months which is higher than (24) months reported by Victor M.Santana (1996)[3] and that of (36)months reported by the previous Iraqi study (1994)[10] . Most of the cases were between (1-5) years (58.9%) with M/F ratio of 1.4:1 similar to that reported by Garrett M.Brodeur (1997). [9]

The abdomen was the site of initial tumor in (79.5%) of cases in our study compared to slightly higher results (65%) reported by Lanzkowsky (1983).[7]

The posterior mediastinum was the primary site in (15.4%) similar to that reported by LANZKOWSKY. [7] Pallor was initially reported in (64%) of cases similar to that reported in the previous Iraqi study[10]. Weight loss was reported in (59.4%) of cases which is higher than that (35%) reported in Saudi Arabia study (1998).[11] Weight loss rarely reported by Blanka Lopez Ibor (1985)[1] .

This high figure of weight loss may be related to malnutrition in Iraqi children under the effect of sanction and to the poor socioeconomic state thereafter.

Blood pressure measurement was reported in (11) patients only in our study, (6) of them were found to be hypertensive (for age) [3] (54, 5%) compared with (19%) found in Blanca study [1] . This low figure for the measurement of blood pressure reflects that the hypertension frequently missed because B.Pr. measurement are not routinely performed in children and this reflects the high percentage of hypertension among our study cases compared with the Blanca study. [1]

Spinal cord involvement (paraplegia, urinary incontinence) was reported in (7.7%), however; it was (6.8%) in the previous Iraqi study [10] . Proptosis was reported in (28%) higher than that (20%) reported in Saudi Arabia study [11] .

Anemia (for age)[3] was reported in (68.4%) which is higher than that (57.6%) in the previous Iraqi study [10] . This high figure is probably due to malnutrition which has a major impact on most of our children during these years of embargo and to the poor socioeconomic state thereafter.

Skeletal survey was done in (26/39) of patients and was positive for lytic lesions in (65.3%) of cases higher than that (47.5%) reported in the previous Iraqi study [10] probably due to delayed diagnosis and late referral of cases.

Intravenous pyelogram and myelogram were done in minority of patients due to lack of dye material and VMA study done to one patient only due to lack of necessary lab material. CT scan and MRI were not done to any patient. The entire above are essential for proper staging as well as proper assessment.

Bone marrow aspirate was done at time of presentation in (34/39) patients and was positive in (44%) of cases lower than that (50.8%) in the previous Iraqi study [10] , whereas BM biopsy was done in (25/39) patients in our study , and was positive in (32%) compared with (44.2) in the previous study [10] .

The comparison between the proportion of staging system in the current study with that of previous Iraqi study and the Saudi Arabia study is shown in the table-10.

Our study shows higher incidence of stage IV and lower incidence of stage II. This is due to delay in the diagnosis and their referral in advanced stages.

Chemotherapy was used in (34) cases. ENSG-OPEC protocol (figure 1) was used in some patients and the N.B. high risk and favorable risk protocol was used in the others (figure 2 and 3 respectively). Radiotherapy was used only in one patient wrongly diagnosed as NHL.

Radiotherapy is an important treatment modality, however rarely used for our patients due to widespread systemic disease in addition to lack of adequate and proper machines for irradiation of these patients and a very long waiting list.

Table (11) shows the relation between stage of disease and disease free survival compared with the previous Iraqi study and Saudi Arabia study [11] and table (12) shows the relation between disease free survival and the age of the patients compared with the previous Iraqi study and Lanzkowsky study. [8]

The low survival rate compared with other studies is due to lack of chemotherapy and delay in referral of most patients and presentation in advanced stages. In addition (38%) of our cases were lost to follow up probably because of difficulty in transport , shortage of chemotherapy ,poor socioeconomic status of families or may be ignorance and poor concept about the disease , recurrence and long term complication . All these factors contribute to lower disease free survival in our study.

Table 10: The comparison between the proportion of staging system in the current study with that of previous Iraqi study and the Saudi Arabia study.

Stage	Current study %	Previous Iraqi study % [10]	Saudi Arabia study % [11]
I	0 %	1.7%	0 %
II	5.4 %	3.4%	30 %
III	27 %	27.1%	30 %
IV	59.5 %	59.3%	35 %
IVs	8 %	8.5%	5 %

*Two cases with undetermined staging

Table 11: The relation between stage of disease and disease free survival compared with the previous Iraqi study and Saudi Arabia study.

Stage	Disease free survival		
	Current study %	Previous Iraqi study % [10]	Saudi Arabian study % [11]
II	100	50	100
III	30	31	66
IV	4.5	2.8	14
IVs	-	80	100

Unrecorded survival rate in stage IVS is due to lost of follow-up of all patients.

Table 12: The relation between disease free survival and the age of the patients compared with the previous Iraqi study and Lanzkowsky study.

Age	Disease free survival		
	Current study %	Previous Iraqi study % [10]	Ph. Lanzkowsky study % [8]
< 1 year	16.6	50	74
> 1 year	21.8	37	38

Conclusions;-

Neuroblastoma in Iraqi children has higher incidence in males and those between (1-5) years of age . Higher incidence of anemia and weight loss reflecting underlying malnutrition .Majority of the cases presented in advanced stage due to delay in diagnosis and late referral and this reflects the lower survival rates at our current study.

Recommendations:-

The use of more intensive chemotherapy with other treatment modalities like surgery, radiotherapy with or without autologous BM transplantation for better response and survival in poor prognostic groups .Establishment of mass screening programs for early detection of N.B. in infants using measurement of urinary catecholamine's metabolites .The use of biologic and genetic markers such as tumor cells karyotype , DNA content (ploidy) or N-myc copy number further refine risk – directed therapy .Insight into the recent advances in treatment of N.B. by the use of radioactive (MIBG) and monoclonal antibodies directed against N.B. cell surface protein .

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