Original Article

I-131 MIBG MYOCARDIAL UPTAKE IN LOCALLY ADVANCED AND METASTATIC NEUROBLASTOMA PATIENTS: DOES IT CARRY A PROGNOSTIC SIGNIFICANCE?

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ABSTRACT

Introduction: Neuroblastoma is the most common solid extra cranial malignancy in children younger than 15 years. Though there are many prognostic factors for neuroblastoma, none of them is considered to provide enough additional value to be used in clinical practice. Radio-iodinated Meta-iodobenzylguanidine (MIBG) is a functioning analog of norepinephrine taken up by sympathetic neurons and considered very good radiopharmaceutical for diagnosis of neuroblastoma .

Aim of the work : In this work, we are looking for a possibly relevant correlation between myocardial I-131 MIBG extent of uptake and outcome in neuroblastoma to be further used as a prognostic value.

Patients: This study included 38 pediatric patients with pathologically proven stage III & IV neuroblastoma. Twenty one of the study patients (53.85%) were males and 18 (46.15%) were females with a ratio of 1.17 to 1.0 respectively. Their age ranged from 6 months to 12 years, with a mean of 4.8±3.3 years. All patients were treated with neoadjuvant chemotherapy according to protocols issued at the Pediatric Oncology Department, NCI (OPEC, OJEC ICE, CADO). Assessment of response to combined modality treatment was defined in terms of complete response "CR", very good partial response "VPR", partial response "PR", stable disease "SD", or progressive disease "PD". Objective response (OR) is the sum of complete plus any partial response**.** I-131 MIBG scan was done 24 and 48 hours after IV injection of 0.5-1 mCi I-131 MIBG 5 days prior to starting chemo-therapy. Myocardial I-131 MIBG uptake in the anterior image of the whole body was graded according to the following scale: grade (0): no visible uptake, grade (1): mild uptake, grade (2): moderate uptake, grade (3): prominent uptake.

Results: We found statistically significant correlation between I-131 MIBG myocardial uptake and patients outcome with P value <0.05. Eight patients showed prominent (grade 3 uptake) and all the 8 patients showed complete response to treatment and were alive at 24 months. 5 patients out of these 8 patients were stage III and 3 patients were stage IV neuroblastoma. On the other hand 9 patients showed no uptake(grade 0), 4 patients of them patients showed partial response to combined modality treatment, while three patients showed progressive disease and 2 patients showed stationary disease Fourteen patients (37%) showed moderate (grade 2) I-131 MIBG

myocardial uptake, two patients them of showed complete response (CR), 10 patients showed partial response(PR) and two patients showed stationary disease (SD). All these fourteen patients were alive at the end of 24 months. Seven patients showed mild (grade 1) I-131 MIBG myocardial uptake. Five patients (71.4%) of them showed partial response to treatment, one patient (14.2%) showed stationary disease(SD), and one patient (14.2 %) showed progressive disease(PD) with statistically significant correlation (P value <0.05) (Table 2) .Three patient of this group (42.8%) died because of their disease progression with statistically significant correlation with I-131 MIBG myocardial uptake.

Conclusion: We conclude that there is a correlation between I-131 MIBG myocardial uptake and patients outcome and survival, thus it can be used as a prognostic factor for advanced cases of neuroblastoma.

INTRODUCTION

Neuroblastoma is the most common solid extra cranial malignancy in children younger than 15 years [22]. It accounts for 8-10% of all childhood cancers and 15% of cancer deaths in children [3]. A remarkable heterogeneity observed in tumor phenotype, ranging from spontaneous regression to relentless progression. There are literally dozens of clinical and biologic makers that have been proposed as being predictive of disease outcome[3]. Children's Oncology Group (GOG) stratify neuroblastoma patients into low, intermediate-, and high risk groups based on age at diagnosis, disease stage, MYCN gene amplification status, Shimada histopathology (favorable vs. unfavorable), and tumor cell ploidy (DNA index= 1 vs. >1) [12]. Treatment which remains a significant challenge is tailored according to patient's risk; however cure rates for high-risk patients treated with intensive multimodal therapies remain suboptimal [12,14]. The currently accepted age cutoff as 365 days based on observations by Breslow and McCann that older age was associated with worse outcome [2]. Recent studies suggest that older age cutoff may improve prognostic precision [12]. There is growing evidence suggesting that the cutoff for age should be increased from the 365-days cut-off currently in use [11]. Within clinically relevant risk stratification, statistical support exists for an age cutoff of 460 days [12,22]. Though other prognosticators such as genetic alterations of the chromosomal regions 3P, 2q, and 17q, or expression levels of candidate genes (e.g., trk-A) have been proposed, none of them is considered to provide enough additional value to be used in clinical practice, leaving an urgent need for novel risk estimation tools [1]. Meta-iodobenzylguanidine (MIBG) which is a functioning analog of the neurotransmitter norepinephrine taken up by sympathetic neurons becomes a very good radiopharmaceutical for diagnosis of neuroblastoma when radio-iodated with iodine isotopes (I-131 or I-132) [7,13]. Radiolabelled MIBG scintigraphy has been established as a useful technique for the detection, staging and follow-up of catecholamine-secreting noradrenergic tumors [9,16,17,21,24]. Some reports have shown an interaction between myocardial uptake and level of catecholamine in patients with noradrenergic tumors [18,27].

The aim of this study is to look for a possibly relevant correlation of myocardial I-131 MIBG extent of uptake and outcome in neuroblastoma to be used as a prognosis predictive in neuroblastoma.

PATIENTS AND METHODS

Sample Characteristics:

The study included 39 pediatric patients treated and followed up at the National Cancer Institute (NCI), Cairo University between June 2004 and Dec.

2007. All patients had a confirmed histopathology of neuroblastoma and none of them received any form of previous therapy. Ten patients (25.64%) had stage 3 disease and 29 (74.36%) were stage 4. Twenty one of the study patients (53.85%) were males and 18 (46.15%) were females with a ratio of 1.17 to 1.0 respectively. Their age ranged from 6 months to 12 years, with a mean of 4.8±3.3 years. Frequencies of the disease primary sites are shown in table (1). Lymph node spread was seen in all 9 patients of stage 3 disease. Multiple bone deposits were detected in 7 patients while 21 patients had combined bone and bone marrow lesions. Hepatic deposits were present in 2 patients and brain metastasis was present in one of them.

Table (1): Primary sites of the disease.

Site	N (%)	Grade (0)	Grade (1)	Grade (2)	Grade (3)
Suprarenal	26 (68.4%)	6	5	9	6
Retro-peritoneal	5 (13.1%)	-	1	2	2
Mediastinal	3 (7.8%)	2	-	1	-
Para-aortic	1 (2.6%)	-	1	-	-
Para-vertebral	1 (2.6%)	1	-	-	-
Pelvic	2 (5.2%)	-	-	2	-

Procedure:

***Work up*:** has included I-131 MIBG scintigraphy in addition to CT scans, ^{99m} Tc MDP bone scans, skeletal survey, bone marrow aspirates and biopsies as well as measurement of urinary levels of vanillmandelic acid (VMA) prior to therapy.

***Treatment and evaluation*:** the 39 patients were treated with neoadjuvant chemotherapy according to protocols issued at the Pediatric Oncology Department, NCI; in which chemotherapy regimens were based on different combinations per risk group (e.g. OPEC, OJEC ICE, CADO). Patients were candidates for reevaluation of their disease features following 4 cycles of chemotherapy that comprised both clinical as well as by imaging and BM studies. Out of the study group, 14 patients (40%) had been operated upon following induction chemotherapy at the aim of primary tumor resection. Patients were eligible for surgery if, they achieved "PR" with their tumors -in surgical opinion- was amenable for safe resection. Only 4 patients were candidates for local radiotherapy for stage 3 disease with post surgical residual. Assessment of response to combined modality treatment was defined in terms of complete response "CR", very good partial response "VPR", partial response "PR", stable disease "SD", or progressive disease "PD". Objective response (OR) is the sum of complete plus any partial responses.

I-131 MIBG Scintigraphy: Thyroid uptake was blocked by oral administration of 100-200 mg of saturated solution of Potassium Iodide 3 days before and 3 days after injection of I-131 MIBG. None of the drugs known to interfere with MIBG myocardial uptake (reserpine, tricyclic anti-depressants, and alpha methyl dopa) were taken by any patient. Scintigraphy was done 5 days prior to initializing chemotherapy using 0.5-1 mCi I-131 MIBG injected intra-venously. Imaging was done 24 and 48 hours post injection. Whole body Scan in the anterior and posterior projections at rate 6 cm/minute was performed followed by localized detailed spot views for 750 K count over chest and abdomen. Large field of view dual head Gamma Camera was used with high energy parallel hole collimator and energy window centered over 364 Kev. Myocardial I-131 MIBG uptake was assessed qualitatively and quantitatively. *Qualitatively*: Myocardial I-131 MIBG uptake in the anterior image of the whole body was graded according to the following scale in comparison to liver uptake : grade (0): no visible uptake,

grade (1): mild uptake, grade (2): moderate uptake, grade (3): prominent uptake. Q*uantitative measurements* were also done by measuring heart to chest background uptake ratio (C/B ratio). A region of interest (ROI) was drawn over the myocardium and mirror image of this region of interest was placed over the contra-lateral side of chest. When the myocardium was poorly visualized, the size & position of the cardiac ROI was checked using the anterior view in the chest radiography. Qualitative and quantitative pre-therapy I-131 MIBG myocardial uptake was correlated with changes in post therapy levels of urinary VMA and findings of CT scan as compared to the pre-therapy results. Assessment of MIBG myocardial uptake with various clinicopathological aspects including age, sex, primary and secondary sites of disease at presentation, stage, time to disease progression "TDP", overall survival, and response to combined modality treatment was done for all patient groups.

Statistical Methods: All data were entered onto SPSS version 15 for analysis. Simple frequencies were used for data checking. Associations between categorical variables were examined using chi square fisher's exact test. A *"p*" value <0.05 was used for detection of statistical significance in all tests. Survival analysis was estimated by the Kaplan and Meier method.

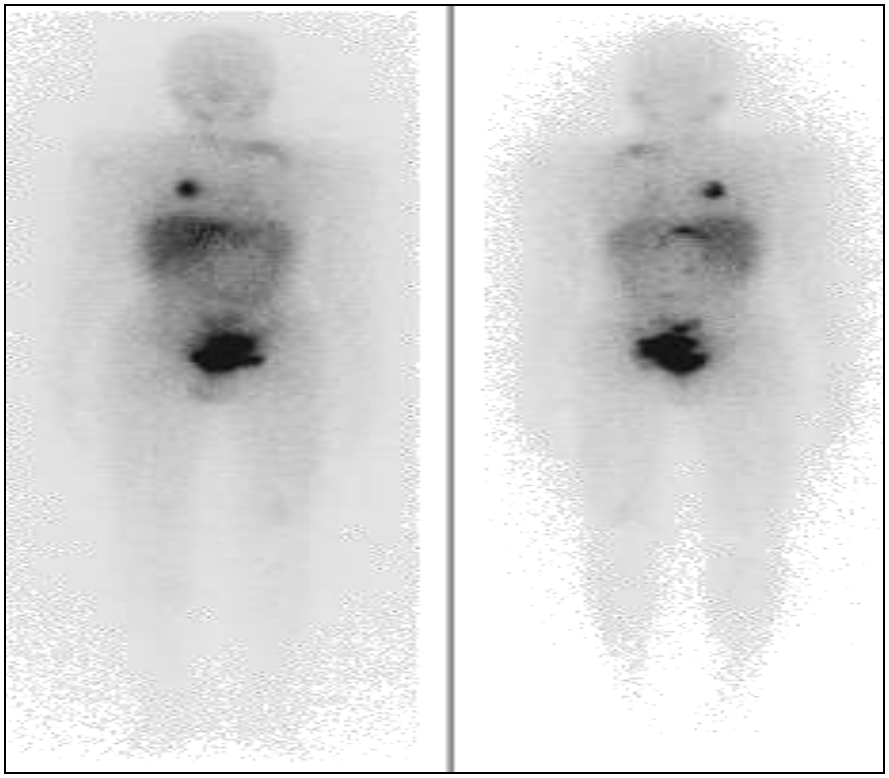
RESULTS

38 patients were included in the study. Twenty nine patients (76.4%) showed "OR" to treatment offered (10 CR and 19 PR) while 4 patients (10.5%) had "PD", and 5 (13.1%) showed "SD".

Evaluating the initial I-131 MIBG myocardial uptake prior to therapy; 9 patients (23.7%) had no (grade 0) I-131 MIBG myocardial uptake at all (Fig. 1) while 7 had only mild (grade 1) I-131 MIBG myocardial uptake with mean heart to chest uptake (C/B) ratio of 1.7. Fourteen patients showed moderate (grade 2) I-131 MIBG myocardial uptake and the mean C/B uptake ratio was quantitatively 2.4. Prominent (grade 3) I-131 MIBG myocardial uptake (Fig. 2) as seen in the remaining 8 patients with mean C/B uptake ratio of 3.1.

Table (2): Degree of I-131 MIBG myocardial uptake in correlation to treatment response

Response	**(n)**	**Grade (0) Uptake n=9 (%)**	**Grade (1) Uptake n=7(%)**	**Grade (2) Uptake n=14(%)**	**Grade (3) Uptake n=8(%)**	**"*P*" value**
CR	(10)	-	-	2 (14.3%)	8 (100%)	0.01
PR	(19)	4 (44.4%)	5 (71.4%)	10 (71.4%)	-	<0.05
SD	(5)	2 (22.2%)	1 (14.3%)	2 (14.3%)	-	<0.05
PD	(4)	3 (33.4%)	1 (14.3%)	-	-	<0.05
Total (n)	**(38)**	**(9)**	**(7)**	**(14)**	**(8)**	



(A) (B)

Fig. 1(A, B): A case of stage 4 neuroblastoma with bone metastases showing no I-131 MIBG uptake.

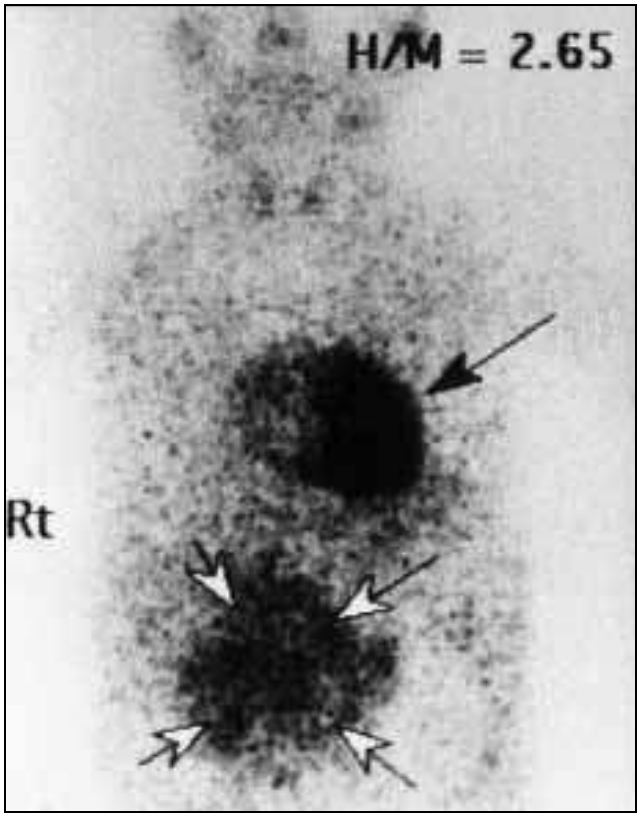


Fig. (2): A case of stage 4 neuroblastoma showing prominent (grade 3) I-131 MIBG uptake.

Response to treatment varied among different groups of I-131 MIBG myocardial uptake. Grade (0) uptake patients showed (4 "PR", 2 "SD", and 3 "PD") ,while, for grade (1) uptake sub-group (5 went into "PR", 1 had "SD", and 1 "PD"). Response as relatively better among grade (2) uptake sub-group of whom (85.7% achieved "OR" with 2 "CR" and 10 "PR") while 2 of them had "SD". Grade (3) I-131 MIBG myocardial uptake patients were having the best response among all 8 patent with 100% "CR" rate.

The correlation between the grade of I-131 MIBG myocardial uptake and disease outcome in terms of response to therapy at the end of first line was statistically significant (*P* value < 0.05), in favor of a better treatment response among those with higher grades of I-131 MIBG myocardial uptake at their initial pre-therapy evaluation than others who showed lesser uptake.

With a median follow up duration of 19.3 month (1.0-51.8 months), the median overall survival (OS) was not possible to estimate since > 50% of the cases were alive till closure of the study. However, the mean OS was computed as 45.2 month (39.9-50.6 months) (Fig. 3).

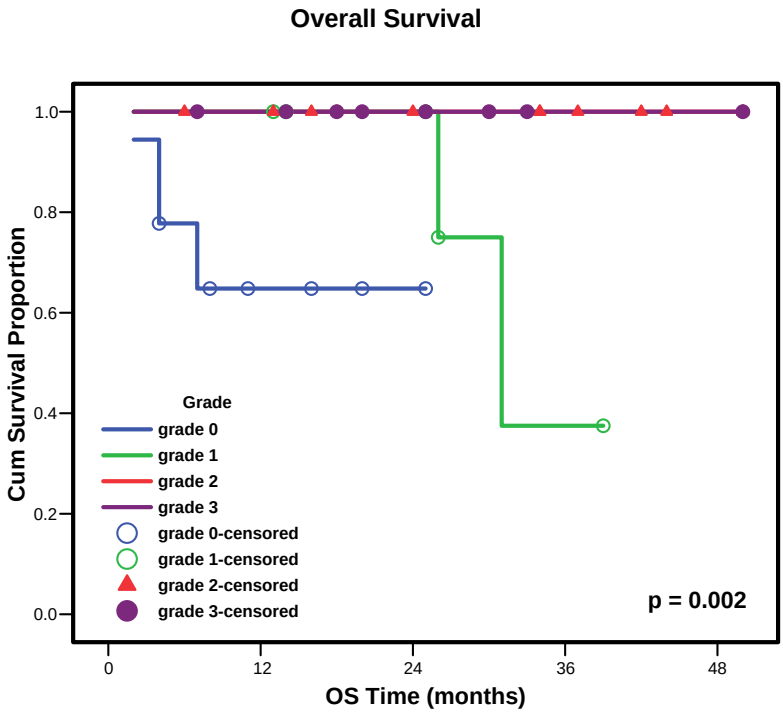


Fig. (3): Overall survival within different grades of I-131 MIBG myocardial uptake

Table (3) shows survival frequencies and their correlation with pre-therapy I-131 MIBG myocardial uptake among different groups. All patients of both grade "2" (n= 14) and "3" (n= 8) uptake were alive at the end of study. Compared to other groups of patients (i.e. grade 0&1), difference in survival found to be of statistical significance*"P"* value < 0.05.

Table (3): I-131 MIBG myocardial uptake in correlation with survival.

	Alive	**Died**
Grade 0 uptake	7	2
Grade 1 uptake	4	3
Grade 2 uptake	14	0
Grade 3 uptake	8	0
"P" value	0.01	< 0.05

As regards the relation between I-131 MIBG myocardial uptake and disease staging, 22 patients out of the 28 patients with stage 4 neuroblastoma showed myocardial uptake while 6 patients showed no uptake. 7 patients out of the 10 patients with stage 3 neuroblastoma showed myocardial uptake while 3 patients showed no I-131 MIBG myocardial uptake with no significant statistical correlation (P value 0.95)

Other parameters were additionally correlated with I-131 MIBG myocardial uptake. Primary disease site was among these parameters, table (1). 6 patients (23%) out of the 26 patients with suprarenal tumors show no myocardial I-131 MIBG uptake and the rest 20 patients (77%) show different grades of uptake with no statistically significant correlation (P: 0.49). As well the distant sites of metastases had no statistical significance on correlation with myocardial I-131 MIBG uptake.

5 patients (17.8%) out of the 28 who had bone metastases did not show myocardial I-131 MIBG uptake, and 23 (82.2%) patients showed myocardial uptake, compared to 6 patients (60%) out of 10 having no bone metastasis had MIBG uptake and 4 patients (40%) did not have uptake with no statistically significant correlation (*P* value 0.56).

15 patients (88.2%) out of 17 who had no bone marrow metastasis had MIBG uptake and 2 patients (11.8%) had no MIBG uptake compared to 14 patients (66.6%) out of 21 who had bone marrow metastases had MIBG uptake and 7 patients (33.3%) did not had uptake (*P* value 0.72)

Other metastatic sites as visceral, brain and intra spinal metastases did not reveal statistical significance in correlation with MIBG uptake (P value 0.63)

TDP time to disease progression was not significantly correlated with MIBG uptake in terms of local and distant recurrence where 6 patients (75%) out of 8 who suffered no disease progression had MIBG uptake and 2 patients (25%) had no MIBG uptake compared to 23 patients 76.6% out of 30 who suffered disease progression had MIBG uptake and 7 patients 23.3% had no MIBG uptake (*P* value 0.78) (table 4)

Table (4): I-131 MIBG myocardial uptake in correlation with disease progression.

	MIBG uptake	**NO MIBG uptake**
Disease progression	23 (76.6%)	7 (23.3 %)
No disease progression	6 (75 %)	2 (25 %)

DISCUSSION

MIBG is an analogue of guanethidine, which shares many cellular transport properties with NA; MIBG and NA enter adrenergic cells through the same uptake system, i.e. a specific, high-affinity mechanism (uptake1) as well as a

non-specific mechanism (uptake 2) which is probably due to diffusion [4,18]. Adrenergic nerves of the sympathetic nervous system play a major role in regulating cardiac function & MIBG can be of use for the evaluation of the sympathetic innervation & for exploring sympathetic neuronal NA uptake & strong function in the heart [5,16].

Myocardial MIBG uptake is decreased in diseases or conditions in which NA content &/or uptake is reduced, such as myocardial infarction, congestive heart failure & cardiac denervation [18]. One of the possible explanations for the decreased myocardial MIBG uptake in patients with neuroadrenergic tumors is the competition between circulating MIBG and over-secreted NA and A in the sympathetic nerve terminals. Previous experiments using rat hearts showed that guanethidine inhibits myocardial uptake of circulating radiolabelled NA , and that prior treatment with NA prevents myocardial uptake of hydrogen-3 guanethidine[4,18].Elevated circulating NA and/or A decreases myocardial MIBG uptake even in the absence of neuroadrenergic tumors [4, 18] . Down-regulation of the uptake pathway and rapid turnover of MIBG in cardiac sympathetic neurons due to the effects of excess catecholamines can also be postulated [20] . Sequestrations of MIBG by primary tumors might also contribute to the suppression of myocardial MIBG uptake, but this effect is probably insignificant, since only 0.15%-2.0% of the administered dose of MIBG is taken up by neuroadrenergic tumors [16,23,25] .It is possible that the myocardium had been injured by the over-secreted catecholamines during the prolonged presence of the disease [18]. As a direct effect of excess NA and A on the myocardium, focal myofibril degeneration with inflammatory cellular infiltrations can occur in catecholamine-induced cardiomyopathy [6]. Myocardial injury may be the result of (a) reduced coronary perfusion and hypoxia caused by vasospasm mediated by an adrenergic receptor, (b) calcium permeability change in the cell membrane or (c) oxidized products of the catecholamines. These forms of pathological damage result in a decrease in MIBG uptake owing to a reduction in the number of sympathetic nerve endings, impaired neuronal uptake function and reduced synthesis or rapid turnover of NA in the neurons [6] .

Catecholamine-induced cardio-myopathy can be reversible after removal of primary tumors, but persistent dysfunction can occur due to long-term accumulation of myocardial damage [27]

Neuroblastoma have not only synthetic enzymes for catecholamines but also abundant metabolizing enzymes of catecholamines such as catechol -0-methyltransferase and monoamine oxidase [10, 27] .Furthermore, in Neuroblastoma as much as 60% of MIBG is taken up extra granular (19,26).

Bernardi et al, 1999 (1) studied the relation between the initial I-123 MIBG myocardial uptake and the post therapy after 24 months in 20 patients with stage III & IV neuroblastoma. they found highly statistically significant correlation between degree of I-123 MIBG myocardial uptake and outcome with *P* value <0.001. 4 patients out of his 20 patients showed normal (high grade) myocardial uptake, all these four patients showed complete remission and very good partial remission. 9 patients showed minimal poor myocardial uptake and 6 out of them died before 24 months. The remaining 7 patients showed mild and moderate degree of myocardial uptake, 6 patients of them showed stationary disease at the end of 24 months.

Similarly, this study showed statistically significant correlation between I-131 MIBG myocardial uptake and patients outcome with *P* value <0.05.in our study, 8 patients showed

prominent (grade 3 uptake) with complete response to treatment and they were alive at 24 months. 5 patients out of these 8 patients were stage 3 and 3 patients were stage 4 neuroblastoma. On the other hand, 9 patients showed no uptake(grade 0), 4 patients of them showed partial response to combined modality treatment while three patients showed progressive disease and 2 patients showed stable disease

Fourteen patients showed moderate (grade 2) I-131 MIBG myocardial uptake, two patients out of these fourteen showed complete response (CR), 10 patients showed partial response(PR) and two patients showed stationary disease (SD). All these fourteen patients were alive at the end of 24 months. Seven patients showed mild (grade 1) I-131 MIBG myocardial uptake. Five patients (71.4%) out of these seven patients showed partial response to treatment, one patient (14.2%) showed stationary disease(SD), and one patient (14.2 %)showed progressive disease(PD) with statistically significant correlation (P value <0.05) (Table 2) .Three patient out of these seven patients(42.8%) died because of their disease progression with statistically significant correlation with I-131 MIBG myocardial uptake.

CONCLUSION

We conclude that there is a correlation between I-131 MIBG myocardial uptake and patients outcome and survival, thus it can be used as a prognostic factor for advanced cases of neuroblastoma.

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